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Contents

Semimonthly Volume 7 Number 17 September 6, 2019

MINIREVIEWS

ORIGINAL ARTICLE

Case Control Study

Retrospective Study

Observational Study

Prospective Study

SYSTEMATIC REVIEW

CASE REPORT

Contents

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MINIREVIEWS

Multifocal G1-G2 gastric neuroendocrine tumors: Differentiating between Type I, II and III, a clinicopathologic review

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Abstract

Gastric neuroendocrine tumors (gNETs) are a rare entity that is increasing in incidence. Different pathophysiological processes can lead to the development of these tumors, appropriate histological analysis is necessary to differentiate between grade 1 (G1) and grade 2 (G2) tumors as this will impact the management of these patients based on their increased risk of lymph node and distant metastases. To provide a comprehensive clinicopathologic review of multifocal gastric neuroendocrine tumors, with particular emphasis on G1 and G2 tumors and differentiating between types I, II and II and risk stratification based upon immunohistochemical profile. This review is based on peer-reviewed literature and the authors' experience. gNETs are a heterogenous group of tumors that is rising in incidence. These lesions while arise from the same cell type, they have different etiologies. Identifying the type of gNETs is a collective effort of clinical and pathologic correlation. The correct grading and staging of these lesions are of paramount significance, due its impact on patient management and prognosis.

Key words: Gastric neuroendocrine tumors; Enterochromaffin like cells; Histopathological features; Immunohistochemistry; Diagnosis; Treatment

Core tip: Gastric neuroendocrine tumors are a rare entity with increasing incidence. Different pathophysiological processes can lead to the development of these tumors, appropriate histological analysis is necessary to differentiate between grade 1 (G1) and grade 2 (G2) tumors as this will impact the management of these patients based on their increased risk of lymph node and distant metastases. In this mini-review article, we aim to provide a comprehensive clinicopathologic review of multifocal gastric neuroendocrine tumors, with particular emphasis on G1 and G2 tumors and differentiating between types I, II and II and risk stratification based upon

immunohistochemical profile. We have based this review on peer-reviewed literature and the authors' experience.

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INTRODUCTION

Neuroendocrine tumors (NETs) of the gastrointestinal (GI) and pancreaticobiliary tracts are a heterogeneous group of tumors that have a diverse biologic and clinical profile that varies according to the primary tumor site of origin, and its histopathologic features[1-4]. Gastric neuroendocrine tumors (gNETs), which are the product of the neoplastic transformation of the enterochromaffin like cells (ECL) of the gastric mucosa, are a rare and indolent category of neuroendocrine tumors that has witnessed a rise in incidence due to the widespread use of upper digestive endoscopy and the technical refinement of endoscopists[5]. In this article we will review the histopathological features, immunohistochemistry, differential diagnosis, treatment, prognosis and outcome of these lesions.

HISTOPATHOLOGICAL FEATURES

The ECL cells play a fundamental role in the regulation of acid secretion, which is essential to understand the gNET classification into subtypes, each with distinct management and prognosis. Following food intake, the G cells of the antrum secrete gastrin which in turn stimulates the ECL cells along with the histamine-producing parietal cells to secrete hydrochloric acid (HCL), this phase is inhibited through a negative feedback mechanism that comes from the D cells, which through HCL acid stimulation secrete somatostatin reducing the secretion of gastrin[6].

Gastric neuroendocrine tumors are classified based on their location, syndromic association, clinical behavior and demographic profile, as follows. (Table 1).

Type I

These lesions correspond to the majority of gNETs found in the stomach (70%-80%), they are usually multiple small nodules/polyps in the gastric body and are limited to the mucosa and submucosa. These lesions are usually found in association with autoimmune chronic atrophic gastritis. The presence of anti-parietal cell or anti-intrinsic factor antibodies leads to the destruction of the parietal cells reducing the level of hydrochloric acid (achlorhydria), which in turn eliminates the negative feedback inhibition of gastrin production by G cells leading to hypergastrinemia, this excess hormone production favors the appearance of multiple small lesions that are generally indolent and may regress. Lymph node metastases are very rare and occur only when the tumors are large (greater than 2 cm) and infiltrate the muscularis propria. These characteristics give these tumors a little aggressive behavior; however, they have an overall good prognosis[7]. They are clinically associated with pernicious or megaloblastic anemia due to the body's inability to absorb vitamin B12 secondary to a decrease in intrinsic factor[8]. The findings on upper GI endoscopy include soft yellowish and transparent vasculature seen in the antral mucosa, contrasting with the smooth, erythematous looking mucosa of normal areas. The neuroendocrine tumors are seen as minute (less than 1-2 cm) and frequently multiple polyps (Figure 1). Histologic examination shows atrophied gastric oxyntic mucosa with occasional intestinal, pseudopyloric or pancreatic acinar metaplasia with nodules that are composed of sheets or nests of neuroendocrine cells. When these nodules measure less than 5 mm in greatest linear dimension, they should be named neuroendocrine microadenomas, rather than neuroendocrine tumors. These tumors usually exhibit nil mitotic activity and a low Ki67 proliferation index of less than 3%, compatible with well differentiated neuroendocrine tumors, grade 1 (G1) (Figure 1 and Figure 2).

Type II

Table 1 Features of Types I, II and III gastric neuroendocrine tumors

	Location	Clinical association	Metastasis	Ki67 proliferation index	Prognosis	Size
Type I	Body	Pernicious anemia; Atrophic Gastritis	Rare	< 3%	Good	Variable < 1-2 cm
Type II	Body	Multiple Endocrine Neoplasia type 1, Zollinger-Ellison syndrome	10%-30% metastasize	< 3%; Rarely 3%-20%	Variable prognosis but overall benign behavior	< 2cm
Type III	Any part of stomach	No clinical association	Very common	3%-20%; Rarely >20%	Aggressive behavior	> 2cm

These lesions account for 7% of gNETS, they are usually small, multiple tumors and have a bimodal age distribution affecting young adults with multiple endocrine neoplasia type 1 (*MEN1*), Zollinger-Ellison syndrome and older adults. *MEN1* is a tumor suppressor gene present at 11q13 locus, the transcription product of *MEN1* gene is the Menin protein[9-13]. Biallelic inactivation through a mutation in 1 allele of MEN1, coupled with the loss of the remaining wild type allele is identified in about 90% of gNETS of this type[14]. Upper GI endoscopy reveals multiple tumors measuring less than 2 cm noted in the body or fundus of the stomach and an adjacent normal or hypertrophic gastric mucosa with clinical findings of hypergastrinemia and low gastric PH (hyperchlorhydria)[15]. Serial measurements of serum gastrin levels following intravenous administration of secretin can be performed and show an increase in gastrin levels for patients with gastrinoma, while a decrease in gastrin levels is seen in healthy individuals. Histopathologic examination demonstrates a gastric oxyntic mucosa with increased oxyntic cell mass due to uninhibited gastrin stimulation along with nodules of neuroendocrine tumor nests that have negligible mitotic activity, absent necrosis and typically a low Ki67 proliferation index (less than 3%) compatible with a well differentiated neuroendocrine tumor, G1 and rarely a G2 in the advent of a Ki67proliferation index between 3% to 20%. In contrast to type I tumors, 10%-30% metastasize. Neuroendocrine microadenomatosis is a common feature of *MEN1*.Tumors greater than 2 cm that invade the muscularis propria and exhibit vascular invasion are more likely to metastasize.

Type III

These lesions are sporadic tumors and are the second most common gNET. They occur in the absence of ECL cell hyperplasia and are not associated with hypergastrinemia, chronic atrophic gastritis, *MEN1* or Zollinger- Ellison syndrome. Upper endoscopy reveals a single solitary lesion, greater than 2 cm, that can be located in any part of the stomach. Histopathologic examination shows cords and nests of tumor cells. Many cases show intermediate cytological atypia characterized by abundant amphophilic cytoplasm, enlarged nuclei with open chromatin and prominent nucleoli, single cell apoptosis or extensive necrosis can be identified along with a Ki67 proliferation index in excess of 3%, thereby making these tumors G2 or in rare occasions G3 when the Ki67 index exceeds the 20% threshold. Metastases are common and are associated with larger size, angioinvasion, and invasion of the muscularis propria.

IMMUNOHISTOCHEMISTRY

Endocrine cells of the GI and pancreaticobiliary tracts and NETs are labelled by neuroendocrine markers, including *CD56/NCAM1*, *leu7/B3GAT1*, protein gene product 9.5 (*PGP9.5*), neuron specific enolase, synaptophysin and chromogranin A. It is considered that synaptophysin is the most sensitive, and chromogranin A is the most specific of the neuroendocrine markers. Therefore, in the majority of practices those two markers are used to determine neuroendocrine differentiation. The other stains mentioned are not commonly used, due to their low sensitivity and specificity[16]. Grading of NETs is done using the Ki67 proliferation index, as recommended by the World Health Organization (WHO) classification of neuroendocrine tumors (2010 and most recently in 2017), the labelling index should be measured in 500-2000 cells in the most proliferative "hot spot" areas[17]. Indices that are less than 3% are considered a G1 tumor, indices that are between 3% and 20% are considered G2 tumors and those that have a Ki67 proliferation index higher than 20%

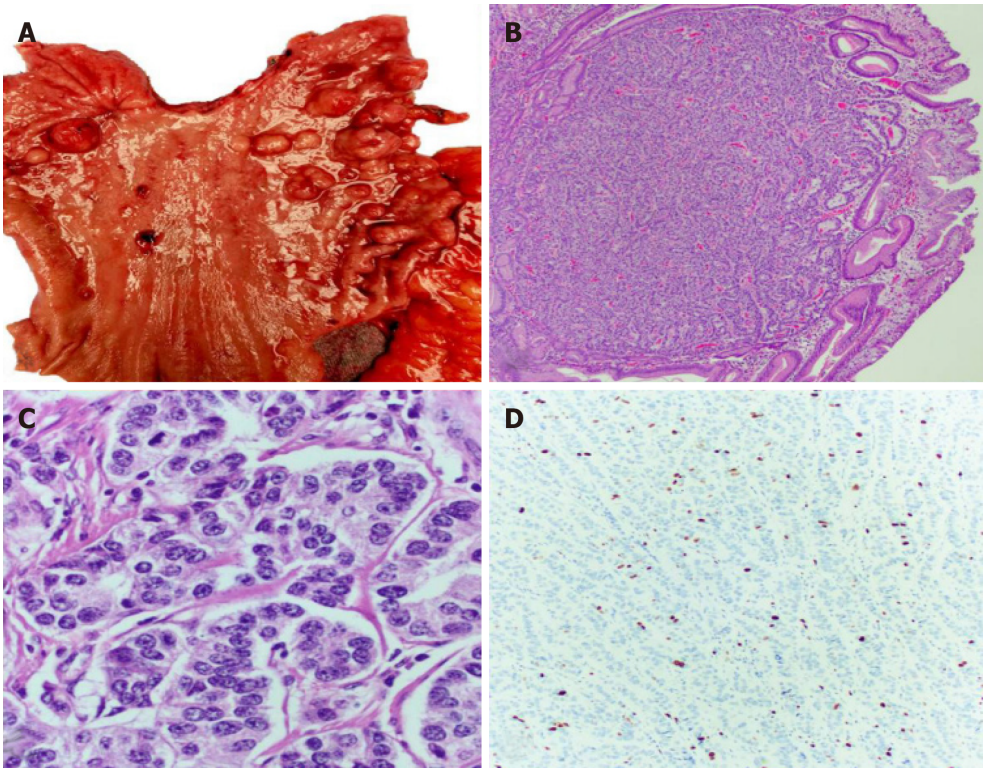

Figure 1 The neuroendocrine tumors are seen as minute (less than 1-2 cm) and frequently multiple polyps. A: Gastrectomy specimen with multiple nodules/polyps, ranging in size from 0.5 mm to 2 cm; B: Gastric mucosa showing a neuroendocrine tumor (HE, 40×); C: Nested groups of cells with nuclei showing "salt and pepper" chromatin and no mitotic activity (HE, 400×); D: Ki67 proliferation index of less than 3%, consistent with a well differentiated neuroendocrine tumor G1 (Ki67 immunostain, 200×).

are considered to be G3 lesions, based on the latest (2017) WHO recommendation. The mitotic count is also used in the grading of these tumors, grade 1 tumors have less than 2/10 HPF, grade 2 tumors have 2-20/10 HPF, and grade 3 tumors have more than 20/10 HPF (based on 2017 WHO recommendation, Table 2).Cases with discrepancies between the Ki67 proliferation index and the mitotic count comprise one third of the cases; and in these cases, the higher grade should be selected[18]. Combined, these two features have been shown to reflect the clinical behavior and prognosis of these tumors[19,20].

PROGNOSIS AND PREDICTIVE FACTORS

The prognosis of patients with gNETs is highly variable. According to the WHO, these neoplasms are classified into different grades with distinct prognosis. Histologic features that correlate with a favorable prognosis include the following: (a) Growth within the mucosa-submucosa interface; (b) Bbsence of angioinvasion; (c) Lesion size less than 1 cm; (d) Absence of endocrine syndrome on clinical evaluation; and (e) Low mitotic activity[21,22]. Tumor related deaths in Type I lesions are only observed in exceptional situations, while 1 out of 10 patients have died from Type II lesions. On the other hand, type III lesions carried a mortality rate of 27% with a mean survival of 28 mo[23].

STAGING AND TREATMENT

CT scan is recommended for type I and type II lesions that are larger than 2 cm and for all type III lesions. The use of magnetic resonance imaging of the abdomen, octreotide scintigraphy and PET-CT is limited for specific cases[24]. According to the AJCC (8th edition), lymph node metastases (N1) are detected in about 5% of type I, 30% of type II and 71% of type III, while distant (liver) metastases (M1) are found in 2.5%, 10% and 69% of cases of type I, II and III, respectively[25]. Therefore, the majority of ECL cell NETs of type I and II are considered to be stage I, *i.e.*, T1 N0 M0, and only a selected few would be stage IIa or T2 N0 M0. On the other hand, most type III

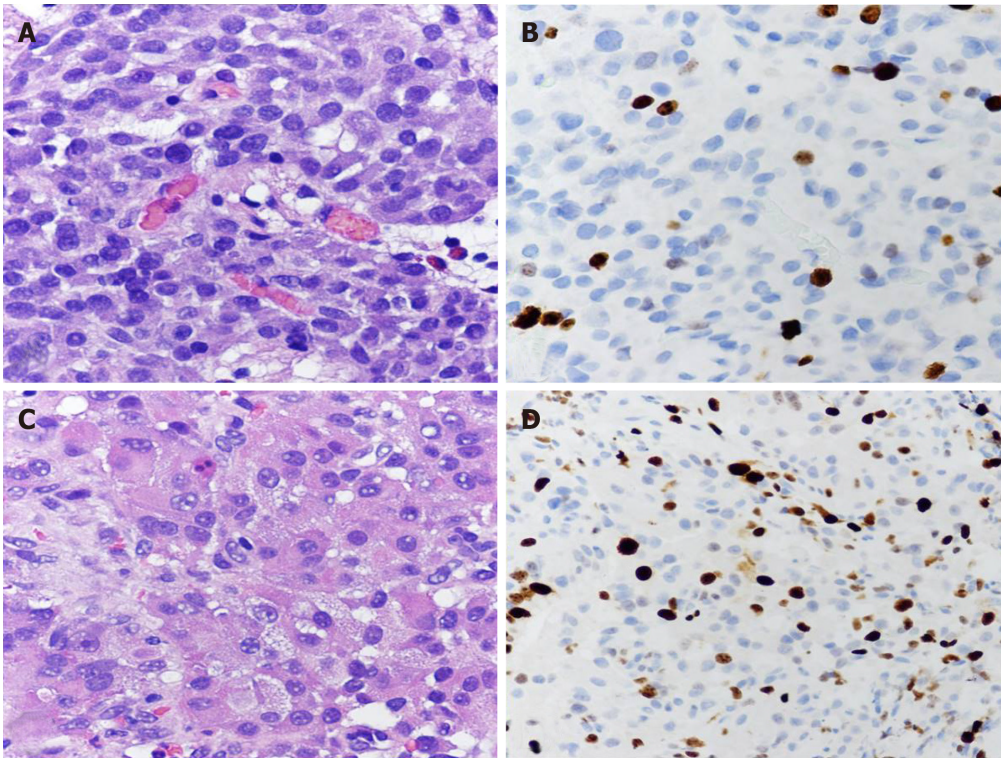

Figure 2 Tumors usually exhibit nil mitotic activity and a low Ki67 proliferation index of less than 3%, compatible with well differentiated neuroendocrine tumors, grade 1. A: A nodule of neuroendocrine tumor nest of cells with nuclei showing "salt and pepper" chromatin with negligible mitotic activity and absent necrosis (HE, 400×); B: Ki67 proliferation index of 5%, consistent with a well differentiated neuroendocrine tumor G2 (Ki67 immunostain, 400×); C: Nest of tumors cells, arranged in nodules, showing intermediate grade cytological atypia characterized by abundant amphophilic cytoplasm, enlarged nuclei with open chromatin and nucleoli; D: Ki67 proliferation index of more than 20%, consistent with a well differentiated neuroendocrine tumor G3 (Ki67 immunostain, 400×).

lesions fit stages IIa, IIb (T3 N0 M0), IIIa (T4 N0 M0), IIIb (T1 N1 M0) or even IV (any T, any N, M0)[26].

Treatment of gNETs is a multifaceted approach, depending on the clinical type, disease extent, degree of differentiation of the lesion and the presence or absence of poor prognostic indicators. Type I lesions are treated by endoscopic mucosal resection as most of these lesions are small, well differentiated and exhibits excellent prognosis[27]. Supplementing Vit B12 is also recommended. Surgical treatment of type I gNETs is reserved for cases in which endoscopic resection is not feasible or when poor prognostic indicators are present. The choice of the best surgery (*i.e.*, antrectomy, subtotal or total gastrectomy) for these lesions is also controversial[28]. Antrectomy has been proposed to remove the gastrin producing G cells; however, failure may occur due to improper removal of those cells or because the ECL cells have become autonomous. This led to the suggestion of subtotal gastrectomy to allow adequate removal of the G cells while reserving total gastrectomy for those cases with substantial disease in the gastric fundus[29]. Clinical management for type I gNETs while available, is hardly an effective option for long term management. The use of somatostatin analogue (octreotide) has been attempted by some authors; however, following discontinuation of the treatment it was noted that follow-up serum gastrin levels increased, and the tumor progressed[30,31]. Type II lesions are usually treated by localizing and resecting the gastrinoma. Type III lesions are treated more aggressively with treatments including but not limited to subtotal, or total gastrectomies (depending on the location) with associated lymphadenectomy. The presence of metastatic disease in the liver is treated by resection if present in a resectable location otherwise arterial embolization or radioablation have a success rate of 50%[32]. In cases of type III lesions with extrahepatic metastasis or recurrent disease, systemic cytotoxic chemotherapy or molecular targeted agents can be introduced.

CONCLUSION

gNETs are a group of tumors that are witnessing a rise in incidence of diagnosis due to an increase in upper GI endoscopy, and refinement of the endoscopic techniques. Those lesions while arise from the same group of cells, are different in etiology and

Table 2 Grading system of well-differentiated neuroendocrine tumors according to the 2017 World Health Organization classification

Neuroendocrine tumor	Mitotic index	Ki67 proliferation index
Neuroendocrine tumor (G1) (well differentiated)	< 2	< 3%
Neuroendocrine tumor (G2) (well differentiated)	2-20	3%-20%
Neuroendocrine tumor (G3) (well	> 20	> 20%

therefore differ in the natural disease progression. Identifying the type of gNETs is a collective effort of clinical and pathologic correlation, the correct grading and staging of these lesions is of paramount significance, due its impact on patient management and prognosis. Finally, it is worth noting that this area of digestive pathology is an active area of research and studies that will clarify the disease biology and improve its management.

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MINIREVIEWS

Attention deficit hyperactivity disorder and comorbidity: A review of literature

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with onset in early childhood. It is a clinically heterogenous condition with comorbidity posing a distinct challenge to diagnosing and managing these children and adolescents. This review aims to provide an overview of comorbidity with ADHD including other neurodevelopmental disorders, learning disorders, externalising and internalising disorders. Challenges in screening for, diagnosing and managing comorbidity with ADHD are summarised. Also, methodological challenges and future directions in research in this interesting field are highlighted.

Key words: Attention deficit hyperactivity disorder; Comorbidity; Review

Core tip: Attention deficit hyperactivity disorder (ADHD) is a clinically heterogenous condition that is typically complicated by extensive comorbid conditions. Screening for comorbidity is imperative for appropriately managing these children and adolescents presenting with complex difficulties. Further research is required for elucidating the implications of comorbidity in terms of diagnosing and managing children with ADHD.

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is characterized by pervasive and impairing symptoms of inattention, hyperactivity, and impulsivity according to Diagnostic and Statistical Manual of Mental Diseases (DSM-V)[1]. It is a common childhood onset mental disorders with reported prevalence rates of 5%-8% in school children[2]. ADHD has been identified as an extremely clinically heterogenous disorder with one of the reasons being high rates of comorbidity with other childhood onset disorders. It is estimated that around 60%–100% of children with ADHD also exhibit one or more comorbid disorders that often continue into adulthood[3,4], This narrative review aims to provide an overview of current research (including recent research findings) on comorbidity with ADHD, methodological issues with such studies and implications for nosological systems, clinical management as well as future research. The scope of this review includes comorbid mental health disorders but not physical illnesses. The review also highlights the need for a dimensional construct, particularly after release of DSM V diagnostic criteria[1].

ADHD AND COMORBIDITY

Autism spectrum and other neurodevelopmental disorders

Autism spectrum disorder: While DSM IV precluded a dual diagnosis of ADHD and autism spectrum disorder (ASD), DSM V allows for the dual diagnosis if appropriate diagnostic criteria are met. In a recent nationally representative sample from United States, in children diagnosed with ASD, the rate of comorbidity with ADHD was 42% and the rate of comorbidity with ADHD and learning disability (LD) was 17%, resulting in a 59% total comorbidity rate of ADHD and ASD[5]. In terms of symptomatology, it is widely believed that there is good degree of overlap between symptoms of ADHD and ASD. However, a recent study demonstrated that it was possible to discriminate symptom profiles of ASD and ADHD in children[6]. Another study demonstrated that children and adolescents with combined ADHD and ASD have more severe symptoms across all domains and an additive severity of sleep-related difficulties in this group[7].

Novel neuroimaging techniques including diffusion tensor imaging (DTI) have been utilised to demonstrate neurobiological changes that correspond with clinical severity in neurodevelopmental disorders and this might be a future tool to assess for additive severity of comorbid conditions in this regard[8].

Learning disorders: There is a wide variation in reports of comorbidity between ADHD and learning disorders, ranging from 10%-92%[9]. This is possibly due to differences in diagnosis and discriminating between both the conditions in individual studies[8]. A recent study demonstrated the relationship between learning difficulties and ADHD symptoms, predominantly in the inattentive type[10]. In an earlier study, a LD was present in 70% of the children with ADHD. A LD in writing was two times more common (65%) than a LD in reading, math, or spelling[11].

Tic disorders: In an international study on tic disorders and ADHD, the reported prevalence of ADHD in Tourette's syndrome (TS) was 55%[12]. Previous studies have cited similar numbers as well[13]. The other salient findings from the study were ADHD was associated with earlier diagnosis of TS and a much higher rate of other difficulties including anger management, insomnia, learning difficulties, Obsessive compulsive disorder (OCD), Oppositional defiant disorder (ODD), mood disorder, and self-injurious behaviour[14].

ADHD and internalizing disorders

Depressive disorder: The rate of major depression in youth with ADHD ranges from 12% to 50% which is more than five times higher than in youth without ADHD[13]. It is also shown that this comorbidity is higher in clinical sample than in the community sample[14]. Depressive disorders with ADHD typically occur several years after the onset of ADHD and is independent of other comorbidities[15]. Co-morbid depression is regarded as an outcome of ADHD-related impairments and negative environmental circumstances also called as ADHD-related demoralization by many authors[15-17].

However, ADHD and depression have independent and distinct courses. This proves that ADHD-associated depression reflects a depressive disorder and not merely demoralization[17].

Bipolar disorder: The rates of comorbidity between pediatric bipolar disorder and ADHD have been greater than the chance findings but are dramatically different across studies[18-20]. Evidence suggests some mechanisms for comorbidity including shared risk factors, distinct subtypes and weak causal relationships[21]. However, the clinical diagnosis of ADHD is not a reliable antecedent in the developmental trajectory toward bipolar disorder[22]. The association between these disorders appears more co-incidental than a causal relationship /predictive association. But when these two disorders co-occur the patient will have poorer global functioning, greater symptom severity, and more additional comorbidity than for either of these disorders[23].

Anxiety disorders: The prevalence of anxiety symptoms in ADHD patients range from 15% to 35%[24,25]. The rates of comorbidity may be affected by the symptom overlap and the diagnostic systems[13]. The relationship between ADHD and anxiety appears to be robust, existing in all populations and in children seen by primary care pediatricians as well[24,25]. This co-existence has been described by different psychological as well as biological models[26,27]. In terms of neurophysiology, anxiety in ADHD may partially inhibit the impulsivity and response inhibition deficits, make working memory deficits worse, and may be qualitatively different from pure anxiety. The co-morbid condition has more negative affectivity and disruptive social behaviour and less fearful/phobic behaviour. The anxiety in ADHD may substantially change the presentation and course of the disorder[17]. The co-morbid condition is associated with more attentional problems, school phobia and mood disorders and lower levels of social competence than either ADHD or anxiety alone[14]. However, when the moderation effect of ADHD in anxiety was studied it was seen that ADHD had a limited impact on the manifestation of anxiety disorder giving an evidence that ADHD and anxiety disorders are independently expressed in children[28]. It is widely suggested that due importance be given to assessment of anxiety symptoms while assessing and treating ADHD[29,30].

ADHD and externalizing disorders: Common externalizing disorders comorbid with ADHD include ODD and Conduct disorder (CD). Newer diagnostic categories like Disruptive Mood Dysregulation Disorder (DMDD) and Intermittent Explosive Disorder (IED) have also been shown to exist comorbidly with ADHD[31,32]. It is demonstrated that 30%-50% children with ADHD also fulfill criteria for CD or ODD. Population-based studies usually identify occurrence of comorbidity more in boys than girls[33].

The strikingly high rates of comorbidity could at least be partially attributed to shared genetic origin[34]. Longitudinal studies suggest that the correlation between ADHD-like and externalizing traits increases across age (from childhood to adulthood) and ADHD-like traits may exacerbate externalizing tendencies in the transition from adolescence into adult life[35]. With regard to predictive environmental factors, researchers have found that children with ADHD suffering from neuropsychological dysfunction, early aggressive behaviour, and adverse family circumstances are at increased risk for comorbid externalizing disorders[36].

CD and oppositional defiant disorder: The combined impact of ADHD with other externalizing disorders on functioning can be profound. Higher rate of academic problems in children with above comorbidity like reading disorder, impaired verbal skills, visual motor integration and visuospatial skills on neuropsychological measures is well documented when compared with children without such comorbidity[36]. Furthermore, ADHD/CD children are more likely to abuse drugs, engage in criminal behaviour, have driving-related outcomes and are more likely to adult antisocial personality disorder than children with ADHD alone[37-39]. ADHD/CD has also been found to be associated with higher expulsion and dropout rates in school than in children with ADHD alone[40] (Table 1).

Apart from impact on clinical course and symptomatology, such comorbidities also pose a diagnostic challenge for clinicians. With several overlapping clinical features, distinction between ADHD and CD can sometimes be unclear. Thus, a hybrid disorder hyperactive CD with an earlier onset and an outcome worse than of either disorder alone is now recognized[41]. Similarly, most of the patients who have been diagnosed as DMDD also fulfilled the diagnostic criteria for ODD/CD with ADHD and it becomes difficult to diagnose them as comorbid disorders[41].

Disruptive mood dysregulation disorder and IED: Sagar-Ouriaghli *et al*[31] thus

Table 1 Summary of some key studies on comorbidity with attention deficit hyperactivity disorder in children and adolescents

Comorbidity with attention deficit hyperactivity disorder	Incidence (%)	Ref.
Autism spectrum disorder	59	Stevens *et al*[5]
Learning disorders	10-92 70	Biederman *et al*[9] Mayes *et al*[11]
Tic disorders	55	Freeman *et al*[12]
Depressive disorder	12-50	Angold *et al*[13]
Bipolar disorder	5-47	Galanter *et al*[18]
Anxiety disorders	15-35	Jensen *et al*[25]
Conduct disorder	3.5-10	Barkley *et al*[40]
Oppositional defiant disorder	30-50	August *et al*[37]

postulated that DMDD appears to be an alternative way of describing the presence of ODD/CD with either anxiety or ADHD. Symptoms of aggression, anger and impulsivity are also seen in IED and high rate of comorbidity are reported in literature. An early onset and common core clinical features of both these disorders suggest a strong association between these disorders[42].

IMPLICATIONS

Phenotypes and endophenotypes of ADHD

Genetic studies on ADHD and comorbid disorders is one of the key methods to investigate the putative ADHD phenotypes based on comorbidities. For example, the study addressed the question of how the association between ADHD and reading disability (RD) might arise. The clear conclusion from subsequent studies investigating their co-occurrence is that there is a common genetic aetiology[43-49]. This raises two possibilities: either that RD and ADHD in general are influenced by the same genes or when they co-occur this comorbid group have a distinct genetic origin from those acting on RD and ADHD in isolation[50].

Studies focusing on dimensional constructs of ADHD like executive dysfunction in "pure" cases *vs* comorbid cases is another method to disentangle the association. For example, in a recent study comorbid problems including autistic traits, motor coordination problems and reading problems were just associated phenotypically, were also related to the executive function (EF) and motor ADHD-endophenotypes after correction for ADHD[51]. These findings may point towards a shared underlying neuropsychological dysfunction that may give rise to both ADHD and comorbid disorders. These familial and shared neuropsychological endophenotypes appear to have multiple behavioural consequences (pleiotropy)[52].

This gives rise to the question whether ADHD with comorbidity is viewed as a distinct phenotype or simply accentuates the severity of ADHD symptoms. A number of studies suggest that the combination of ADHD with a comorbid problem may not be best conceptualized as a distinct phenotype since the interaction between ADHD and the comorbid condition did not have predictive value on the core deficits (*e.g.*, EF) over and beyond the independent effects of ADHD and the comorbid condition[13,53-56].

Response to treatment

Comorbid conditions with ADHD have a definite bearing on selection of treatment modality as well as treatment response. For example, the landmark Multimodal treatment of ADHD study demonstrated that subjects with both ADHD and anxiety disorders are particularly responsive to behavioural therapy, compared with subjects in other comorbidity groups including those with ODD/CD[25,52]. Patients with ADHD, anxiety disorders and ODD/CD subjects were preferentially responsive to combination interventions with both medication and behavioural therapy. In children with only ADHD, and ADHD with ODD/CD behavioural intervention in isolation didn't appear beneficial[25,54].

Nosological systems

Evaluating the presence of comorbidity between different psychiatric conditions offers a method of both correcting and validating psychiatric nosology[13]. The co-occurrence of ADHD and comorbidity is partly due to shared familial/heritable neuropsychological deficits and motor dysfunction[56]. This implies that these symptoms cannot be diagnosed or treated independently of one another. This has

definite theoretical implications in future nosological systems, particularly when we consider this in the framework of RDoC (research domain criteria) of NIMH (National institute of mental health) that postulates linking basic dimensions of functioning to behaviour[57].

Methodological issues in research on ADHD and comorbidity

For an accurate interpretation of studies on ADHD and comorbidity in relation to implications in clinical management as well as future research, it is important that we consider the results in light of certain methodological limitations. The choice of information sources (*e.g.*, clinician, parent, teachers self-report, behavioural observation) as well as method of arriving at a diagnosis (*e.g.*, Standardized scales or clinical interview) were heterogenous across different studies[58]. A combination of information from different sources might sometimes lead to overdiagnosis of comorbidity and vice versa. There is also a possibility of Berkesonian bias in referred clinical population with typically more severe symptomatology, more comorbid disorders or more severe comorbid disorders[14]. In addition to this, use of different classificatory systems may lead to differences as well *e.g.*, ASD can be co-diagnosed with ADHD in DSM V but not in DSM IV[1,59].

CONCLUSION

Cross-disciplinary research combining genetics, symptom dimensions, core deficits, choice of treatment and treatment response on a large sample size is likely to shed more light on this complex but exciting area[60]. This would aid in more personalized and precise matching of patients to treatment modality using patients' comorbidity profiles and result in much better treatment gains for individual patients. A comprehensive screening for comorbidity in cases diagnosed with ADHD should be mandatory to achieve the above objectives.

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ORIGINAL ARTICLE

Case Control Study

Dietary manipulation and testosterone replacement therapy may explain changes in body composition after spinal cord injury: A retrospective case report

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Abstract

BACKGROUND

Reduced level of physical activity, high-fat diet and skeletal muscle atrophy are key factors that are likely to contribute to deleterious changes in body composition and metabolic following spinal cord injury (SCI). Reduced caloric intake with lowering percentage macronutrients of fat and increasing protein intake may likely to improve body composition parameters and decrease ectopic adiposity after SCI.

AIM

To highlight the effects of dietary manipulation and testosterone replacement therapy (TRT) on body composition after SCI

METHODS

A 31-year-old male with T5 SCI was administered transdermal TRT daily for 16 wk. Caloric intake and percentage macronutrients were analyzed using dietary recalls. Magnetic resonance imaging and dual-energy x-ray absorptiometry were used to measure changes in body composition.

RESULTS

Caloric intake and fat percentage were reduced by 445 kcal/d and 6.5%, respectively. Total body weight decreased by 8%, body fat decreased by 29%, and lean mass increased by 7%. Thigh subcutaneous adipose tissue cross-sectional

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area was reduced by 31%.

CONCLUSION
Manipulation of caloric intake, fat percentage, and protein percentage may have influenced body composition after SCI.

Key words: Spinal cord injury; Diet; High-protein; Low-fat; Nutrients; Basal metabolic rate; Case report

Core tip: Reduction in caloric intake with low-fat and high-protein diet may appear as a reasonable strategy to effectively lose weight and fat mass in persons with spinal cord injury. The supplement of testosterone replacement therapy (TRT) may offset for potential loss in lean mass and reduction in basal metabolic rate that is commonly observed in weight loss program. The combination of dietary manipulation and TRT is a feasible approach and does not appear to be accompanied with any side effects.

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INTRODUCTION

Individuals with spinal cord injury (SCI) are at heightened risk for developing obesity because of loss in lean mass, reduced basal metabolic rate (BMR) and decreased level of physical activity[1-3]. Prevalence of obesity is primarily attributed to disruption in energy balance following SCI. Disruption in energy balance is a function of decreased BMR and often leads to increased accumulation of total, regional fat and visceral adipose tissue (VAT)[4-6]. Reduction in leisure time physical activity, reliance primarily on wheelchairs for mobility, and poor dietary habits are major factors that contribute to the prevalence of obesity after SCI[7]. Therefore, providing an effective exercise regimen or dietary management plan may protect against disruptions in energy homeostasis. Moreover, it may reduce the heightened risk for developing secondary complications similar to glucose intolerance, insulin resistance, hyperlipidemia, and cardiovascular disease after SCI[2-5,7].

Persons with SCI often consume a high-fat diet of 35%-40% fat, well above the recommended level of 30% which is typical of the standard American diet[7-9]. Poor dietary habits were attributed to a lack of knowledge surrounding nutrition, solitary living, smoking, and socioeconomic status following SCI[9]. Moreover, studies involving human and animal models revealed associations between high fat consumption and increased VAT, serum leptin levels, pro-inflammatory cytokines, and insulin resistance[3,10]. To circumvent the aforementioned profile, implementation of a Mediterranean-style diet resulted in a 7% reduction in total body weight in three males with SCI[10]. These results are promising, however, a full account of the changes in total or regional lean and fat masses were not provided. Regional changes in body composition have been considered a major determinant of cardiometabolic profile in persons with SCI[2,3]. Furthermore, it is well established that loss in body weight has been accompanied with a reduction in lean mass in elderly individuals[11]; therefore, accounting for the changes in lean mass is highly important with dietary manipulation in men with SCI. Maintenance of lean mass may protect against further reduction in BMR and further increase in the prevalence of obesity after SCI.

Different rehabilitation approaches have been recommended for maintenance of lean mass including exercise, electrical stimulation and testosterone replacement therapy (TRT). Transdermal TRT has been administered in hypogonadal persons with SCI with testosterone level less than 325 ng/dL. A previous work showed that 43.3% of men with SCI had serum testosterone levels < 325 ng/dL[12]. Reduced circulating testosterone level may be a contributing factor to the loss in lean mass after SCI[13,14]. Furthermore, circulating serum testosterone is negatively linked with total and

regional body fatness, VAT and positively linked to lean mass and thigh muscle cross-sectional area (CSA)[14]. A 1-year small scale clinical trial demonstrated the efficacy of TRT in restoring total and regional lean mass as well as increasing BMR in hypogonadal men with SCI[15]. A recent randomized clinical trial showed that 16 wk of TRT accompanied with surface neuromuscular electrical stimulation-resistance training (TRT+RT) resulted in 43% increase in muscle CSA, 2.7 kg increase in total body lean mass and a trend of 14%-17% increase in basal metabolic rate compare to TRT only in men with SCI[16].

Therefore, dietary manipulation with TRT may serve as a potential rehabilitation approach to reduce body fatness, maintain lean mass and BMR in persons with SCI. We, retrospectively, tracked the dietary habits of individual and eight additional participants for the purpose of comparing caloric and macronutrient intakes during participating in a 16 wk clinical trial. The current case report highlighted the significance of reducing caloric intake and manipulating macronutrients with TRT on the changes in total and regional body composition in a male with SCI.

MATERIALS AND METHODS

The physical characteristics and demographics of one male participant as well as a comparative cohort of eight men are presented in Table 1. Each participant received a daily testosterone dose (2-6 mg/d) *via* transdermal patch (Androderm; Watson Laboratories, Inc, Corona, Canada) placed on the shoulders and alternated daily for 16 wk[16]. The initial TRT dose was determined based on the circulating level of serum testosterone and then adjusted according to participant's response in a blinded fashion. A 4 mg/d of TRT was administered on a daily basis for our participant. Data from one participant of the original cohort (n = 8) was excluded due to frequent missing data points and non-compliance with dietary records. Each participant signed an informed consent prior to enrollment in the clinical trial and all study procedures were approved by the local ethics committee.

Prior to enrollment in the 16 wk clinical trial, each participant completed 4 wk, a pre-trial-phase, as a control period to stabilize body weight and to record their standard dietary habits. At the beginning of this phase, body composition assessment was completed using dual energy x-ray absorptiometry (DXA) and participants did not receive any feedback to adjust or manipulate their dietary habits[16].

At the beginning of the 16 wk intervention, a registered dietitian encouraged compliance to a standard daily diet plan (45% carbohydrate, 30% fat, and 25% protein). Caloric allowances were estimated based on each participant's BMR[7].

Each participant completed weekly 5 d dietary recalls and monthly feedback from the dietician was provided, *via* phone interview or emails[7]. Dietary records were evaluated using Nutrition Data System for Research (NDSR; 2016 Regents of the University of Minnesota). The following dietary variables were quantified: Total caloric intake (kcal), percentage calories from carbohydrates, percentage calories from fats, percentage calories from proteins, and total soluble fiber. Retrospective analysis revealed that the dietary habits of the case report began to change at the end of week 8. Therefore, dietary data were split into phase I (weeks 1-8) and phase II (weeks 9-16). Splitting the data allowed for the comparison in caloric intake and percentage macronutrients between phase I when the participant closely followed the recommended dietary habits and phase II, when the case report deviated from the recommended caloric intake and macronutrients. The differences in percentages carbohydrate, fat, and protein intakes were calculated between phases I and II. Data from the case report was also compared to the average consumption of the cohort to demonstrate the deviation in the dietary habits in phase II of the study.

T1-weighted MRIs were obtained from a total body General Electric Signa 1.5-T MRI located within the McGuire VAMC Radiology Department at baseline and post-intervention. 12 to 15 trans-axial images (slice thickness, 0.8 cm; interslice space, 1.6 cm) were captured from hip to knee joints of the right thigh to quantify muscle and fat CSAs[17]. Four regions of interest were manually isolated using X-Vessel (Version 2.011; Michigan State University, Lansing, United States) including thigh subcutaneous adipose tissue (SAT) CSA, whole muscle CSA, absolute muscle CSA, and absolute intramuscular fat (IMF) CSA (Figure 1), as well as trunk VAT and SAT. Whole muscle CSA refers to the total muscle area of the thigh including IMF and excluding tissues of the femoral bone. Absolute muscle CSA refers to thigh muscle after accounting for IMF. IMF refers to the fat infiltrated within and between muscle fibers and is presented as an absolute value and percentage relative to the whole thigh muscle CSA[17]. To calculate CSA, the sum of pixels within a region of interest was multiplied by (FOV/matrix size)[2].

Table 1 Case individual (*n* = 1) and cohort (*n* = 8) physical characteristics, cohort values are presented as mean ± SD

Characteristics	Case Participant (*n* = 1)	Cohort (*n* = 8)	Total (*n* = 9)
Age (yr)	31	36 ± 9	36 ± 8
Sex	Male (*n* = 1)	Male (*n* = 8)	Male (*n* = 9)
Ethnicity	Caucasian (*n* = 1)	African American (*n* = 3)	African American (*n* = 3)
		Caucasian (*n* = 5)	Caucasian (*n* = 6)
Weight (kg)	77	77 ± 11	77 ± 10
Height (m)	1.8	1.8 ± 5	1.8 ± 5
BMI (kg/m^2)	24.8	24 ± 4	24 ± 4
Level of injury	T5-T6	C6-T11	C6-T11
Time since injury (yr)	7	7 ± 7	7 ± 7
AIS classification	A	A (*n* = 5)	A (*n* = 6)
		B (*n* = 3)	B (*n* = 3)
Level of Paralysis	Paraplegia	Paraplegia (*n* = 3)	Paraplegia (*n* = 4)
		Tetraplegia (*n* = 5)	Tetraplegia (*n* = 5)

AIS: American Spinal Injury Association Impairment Scale; BMI: Body mass index.

For trunk VAT and SAT, participant was positioned in a lying position on the scanning table, transverse axial images (axial in-phase/out-phase with a repetition time of 140 ms and echo time of 4.2 and 2 ms for the in-phase and the out-phase, respectively; a 42 cm field of view; matrix size of 256 × 256; 1 number of excitation; acquisition time of 40 s and slice thickness was 0.8 cm and interslice space was 0.4 cm) were obtained from the xiphoid process to L4-L5 and from L4-L5 to the femoral heads[3,14,16].

DXA scans were performed using a Lunar DXA (GE Healthcare, Chicago, IL) bone densitometer at the Richmond Virginia Medical Center at pre-trial phase, BL and PI. The clinical DXA procedures and estimates of precision were previously published[18]. Total body DXA scans were captured to assess total body weight, lean mass, and fat mass. Scans were performed for 5-10 min and analyzed by a DXA trained researcher using Lunar enCORE software Version 10 (GE Healthcare, Chicago, IL).

After an overnight fast of 10-12 h, participants were kept in a dark room for 20-30 min to attain a resting state during which BMR was measured using a canopy that was attached to a vacuum to draw expired gases to the flowmeter of the metabolic unit (COSMED KB42, manufacturer) as previously described[7,19].

RESULTS

The current case report is a retrospective analysis to a participant that was enrolled in our concluded clinical trial in the TRT only group[16]. For the entire 16 wk, the participant was administered 4 mg/d of TRT. His baseline testosterone level was 440 ng/dL, and increased in weeks 4, 8 and 12 to 625 ng/dL, 753 ng/dL and 613 ng/dL, respectively. At post-intervention measurement, testosterone level without using the patches dropped to 124 ng/dL.

The trends for total caloric intake, percentages carbohydrate, fat, protein, and soluble fiber intake are presented in Figure 2 and Figure 3. Table 2 presents data for each dietary variable and percentages difference between the participant and the study cohort. The case report reduced total caloric intake by 25% (445 kcal/d) and consumed 12% fewer calories than his cohort during phase II (Table 2, Figure 2).

The participant and cohort both consumed 41% of their calories as carbohydrates (Table 2). The percentage carbohydrates consumed by the case report or the cohort did not change over the course of 16 wk. The case report reduced his fat intake by 7% over the course of intervention, with almost no change in fat intake (< 1%) observed by the cohort (Table 2, Figure 3). During phase I, the participant consumed roughly the same proportion of calories from fat as his cohort (case: 37%; cohort: 36%); however, during phase II, the participant consumed 6% less calories from fat.

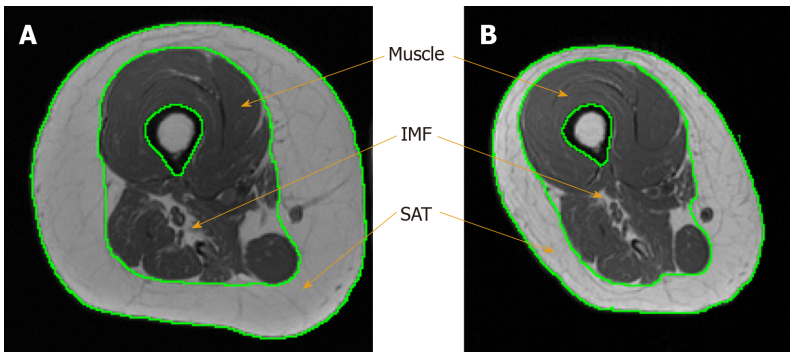

Figure 1 Robust changes in subcutaneous adipose tissue, intramuscular fat and muscle size between baseline and post-intervention measurements. A: Baseline magnetic resonance imaging (MRI) of the right thigh showing large subcutaneous adipose tissue (SAT) and intramuscular fat (IMF) depots prior to dietary intervention; B: Post-intervention matched MRI of right thigh after 16 wk of intervention showing reduced SAT and IMF depots and increased muscle cross-sectional area.

For the case report, percentage calories from protein increased by 7.6% in phase II compared to phase I of the trial (Table 2, Figure 3). Compared to the study cohort, the case report consumed 8% more calories from protein during phase II of the trial.

Finally, soluble fiber intake remained relatively consistent in both case report and the study cohort; however, the case report consumed more than twice the amount of soluble fiber throughout the 16 wk trial (Table 2). During the first and second phases of the trial, the participant consumed roughly 60% and 70% more soluble fiber than the study cohort, respectively. Moreover, the case report increased his soluble fiber intake by 2% during phase II, while the cohort consumed 7% less soluble fiber compared to the initial phase of the trial.

Body composition assessments for the case report acquired at baseline and post-intervention are presented in Table 3. The participant reduced his total body weight by 6.4 kg (8%). Additionally, he lost 8.8 kg (29%) of body fat and gained 3.1 kg (7%) of lean mass. Moreover, the participant's thigh SAT and absolute IMF CSAs decreased by 31 and 39%, respectively. Conversely, the participant's whole muscle and absolute muscle CSAs increased by 4% and 9%, respectively. Figure 1 illustrates the robust changes in SAT, IMF and muscle size between baseline and post-intervention measurements. Trunk VAT and SAT CSA decreased by 12% and 22% following 16 wk.

Lipid panel demonstrated increase in low-density lipoprotein cholesterol from 121 to 130 $mgdL^{-1}$ (7.4%) with concomitant decrease in triglycerides from 121 to 83 $mgdL^{-1}$ (31.4%) and increase in HbA1c from 5.1% to 5.5%. No detectable changes were noted HDL-C, total cholesterol and ratio of total cholesterol: HDL-C. Baseline BMR of the case report was 1388.4 kcal/d and remained unchanged (1365.6 kcal/d) following 16 wk of administering TRT.

DISCUSSION

The current case report was analyzed in a retrospective fashion. The findings demonstrated that lowering caloric intake and percentage macronutrients of fat and protein may have contributed to positive changes in total and regional body composition in a male with chronic SCI. The addition of TRT may primarily helped to maintain lean mass and BMR; which is commonly impacted negatively during a weight loss regimen. The participant lost 8% (6.4 kg) of his total body weight, which is consistent with a previous report that noted a total body weight loss of 7% following Mediterranean-style diet in three men with SCI[10]. Whole body lean mass increased by 7% over 16 wk. Participant's absolute thigh muscle CSA increased by 9% as accompanied with l2% and 22% decrease in trunk VAT and SAT, respectively. Clinically, these changes are highly significant because of the recognized associations between lean mass, BMR, and several cardio-metabolic disorders after SCI[2-5]. The current case report also suggests that high protein intake with TRT may have played a role in preservation of lean mass, especially with reduction in caloric intake.

A reduction in total caloric intake by 440 kcal/d may explain some of the observed changes in body composition. Despite the 25% reduction in caloric intake, we could not refer to it as a caloric restriction study because the intervention was only limited to 8 wk period. Caloric restriction studies reported period close to 6 mo up to a year[32].

Table 2 Data for case participant and cohort dietary consumption during, pre-trial over 4 wk (only for the case report), phases I (weeks 1-8) and II (weeks 9-16) of the intervention. Percentage difference between phases I and II, as well as between the case report and the cohort

Energy (kcal)			
	Case	Cohort	%difference
Pre-trial	1935		
Phase I	1801.8	1528.9 ± 538	18%
Phase II	1357.2	1543.2 ± 544	- 12%
%difference	- 25%	1%	
Calories from protein (%)			
	Case	Cohort	%difference
Pre-trial	19.0		
Phase I	20.6	20.80 ± 5.9	- 0.22%
Phase II	28.2	20.25 ± 5.9	7.98%
%difference	7.66	- 0.54	
Calories from carbohydrate (%)			
	Case	Cohort	%difference
Pre-trial	39.0		
Phase I	41.1	41.4 ± 7.6	- 0.30%
Phase II	39.9	41.6 ± 10	- 1.70%
%difference	- 1.17	0.23	
Calories from fat (%)			
	Case	Cohort	%difference
Pre-trial	40.8		
Phase I	36.8	36.0 ± 6.7	0.75%
Phase II	30.3	36.7 ± 5.7	- 6.45%
%difference	- 6.50	0.71	
Soluble dietary fiber (g)			
	Case	Cohort	%difference
Pre-trial	6.56		
Phase I	6.55	4.19 ± 1.6	56%
Phase II	6.67	3.89 ± 2.1	71.5%
%difference	2%	- 7%	

Differences for percentage protein, percentage carbohydrate, and percentage fat were calculated as the absolute difference between phase I and phase II or differences between the case report and the studied cohort.

Based on the current findings, it is possible to speculate that combining exercise with a similar dietary manipulation may be an effective strategy to reduce cardio-metabolic risk factors after SCI. We have previously shown that neuromuscular electrical stimulation (NMES)-resistance training for 12-16 wk accompanied with a standard dietary program (45% carbohydrate, 30% fat and 25% protein) was an effective strategy in reducing VAT in persons with SCI[16,20]. Although the case report did not receive resistance training[16], daily administration of TRT may have contributed to preservation of lean mass and loss of both VAT and SAT. This is really important because a recent report demonstrated the negative association between serum testosterone level and VAT. Persons with lower testosterone level have 72% greater VAT than those with normal testosterone level[14].

BMR accounted for 65% of the total energy expenditure and may play a major role in maintaining optimal energy balance[21]. During the first 8 wk, the participant consumed an average of 1802 kcal/d, which exceeded his measured BMR (1388.4 kcal/d). During phase II, the average caloric intake was 1357.2 kcal/d or 440 kcal lower than what has been consumed in the first 8 wk. Despite the reduction in caloric intake following Phase II, BMR remained unchanged at the end of the 16 wk. Administering TRT may have had a protective effect in maintenance of BMR by preserving lean mass, because reduction in BMR could potentially lead to further gain in body weight.

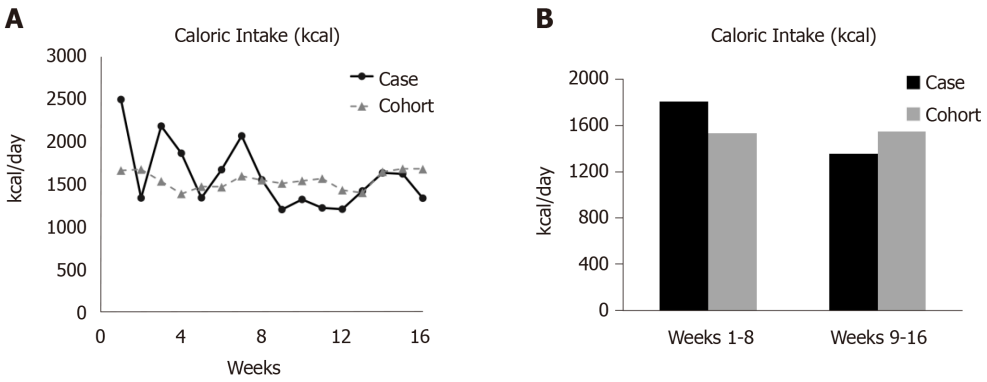

Figure 2 The trend in caloric consumption (kcal) of the participant and cohort during the course of the study (A) and the average caloric consumption of the case and cohort during the first and second phases of intervention (B).

A previous trial using weekly dietary recalls suggested that persons with SCI consumed a high fat diet (32%-50% fat)[7]. The case report reduced his caloric fat intake by 6.5% between phases I and II and maintained a recommended daily allowances (RDA) of 30%. However, it remains unclear whether the improvements in body composition are primarily driven by overall caloric reduction or decreasing percentage fat intake. Additionally, percentage carbohydrate was maintained in the range between 39.9%–41.6% across the 16 wk for both the case report and cohort. The average carbohydrate consumption for the case report and the study cohort was consistently less than the recommended RDA of 45%, likely due to higher fat consumption by the study cohort throughout the 16 wk and the case report in Phase I.

Increased protein intake during phase II may have contributed to the observed gains in lean mass and decreased total-body and regional adiposity. Dietary analysis revealed that the participant increased his protein intake by 8% compared to phase I. He also consumed 8% more calories from protein than the study cohort during phase II of the trial. Increased protein consumption likely contributed to a positive nitrogen balance, creating an ideal environment for protein synthesis, especially when accompanied by TRT[9,22]. The Food and Nutrition Board of the National Academy of Sciences recommends a modest 0.8 g of protein per kg of body weight or roughly 10%-30% of daily caloric intake[23]. The current SCI guidelines recommend that persons with SCI consume 0.8-1.0 g/kg of body weight, with additional protein added in the presence of pressure ulceration[23]. We have previously shown that persons with SCI consumed close to 1.1 g/kg body weigh during 12 wk of resistance training[20]. Because the case report and the study cohort received a similar dose of TRT, it is fair to speculate that the combining effects of higher protein intake and TRT may result in increase in whole body lean mass and thigh muscle CSA in the case report. However, a recent study noted that high protein intake for 8 wk did not result in increase in muscle size after SCI[24]. The authors recommended that loading the muscle using surface NMES with resistance training is considered a favorable rehabilitation approach to ameliorate muscle atrophy after SCI[24].

Moreover, because protein requires substantial energy (20 of BMR) to catabolize after ingestion, protein may have shifted substrate utilization from reliance on carbohydrates to fats as source of energy[25]. This shift may have contributed to the reductions observed in SAT, IMF, and total body fat. However, as noted earlier, percentage carbohydrates di were not different between phase I and phase II of the trail; suggesting that the case report consumed enough carbohydrates and utilized both carbohydrates and fats as source for energy.

The 2015-2020 Dietary Guidelines for Americans recommends 6-8 g of soluble fiber daily[26].Throughout the 16 wk trial, the participant consumed 7 g of soluble fiber per day. Consistently, the case report consumed an average of 3.8 and 4.1 more grams of soluble fiber than the cohort during phase I and II, respectively. Because fiber intake showed no changes over 16 wk, this may have played an indirect role in the changes observed in body weight and body composition. Fiber intake was shown to be associated with weight loss due to increased appetite control and slower digestion in abled-bodied individuals[27,28]. Additionally, a meta-analysis concluded that the risk of type II diabetes decreased by 6% per 2 g per day increment in fiber intake for men and women.

The current case report is purely a retrospective observational study, because we did not intentionally plan to manipulate participant's dietary habits compared to the

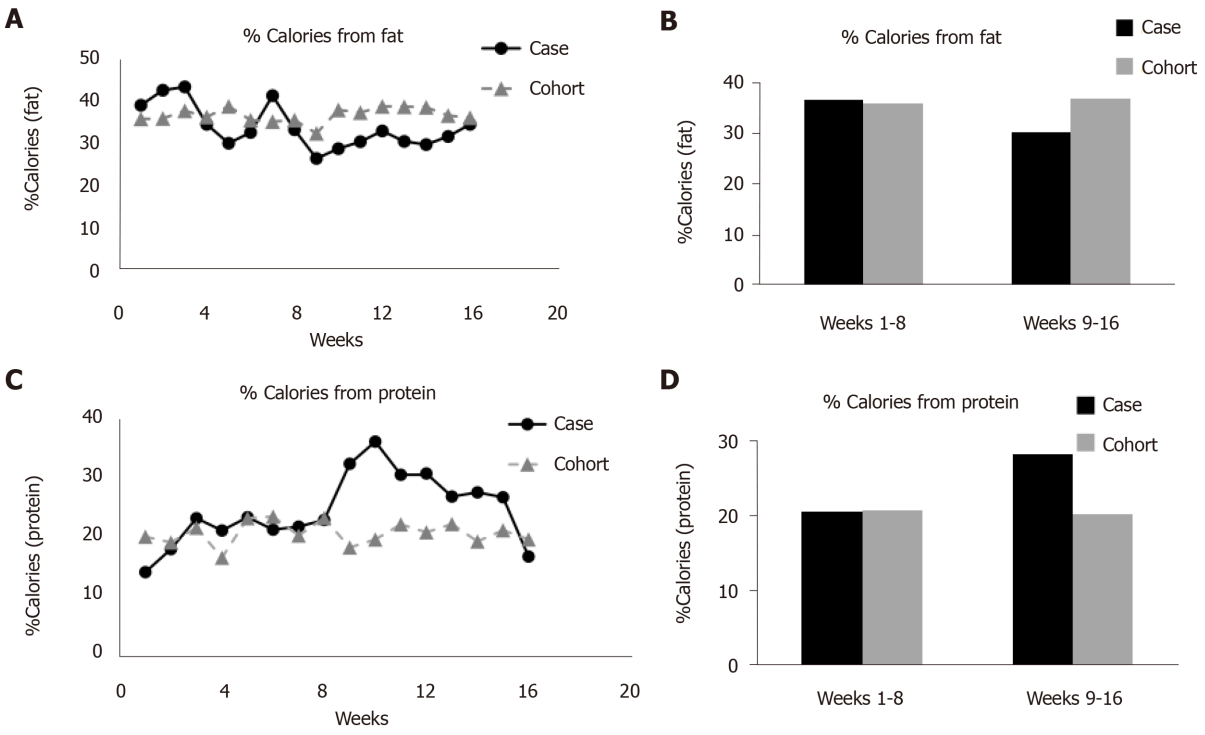

Figure 3 Percentage calories from fat. A: Percentage fat intake of the participant and cohort during the course of the study; B: The average percentage fat consumption during the first and second phases of intervention; C: Percentage protein consumption of the participant and cohort during the course of the study; D: The average percentage protein intake during the first and second phases of intervention.

study cohort. We have also shown a snap-shot of body composition before and after intervention; body composition should have been measured at the end of phase I and before starting phase II. Direct comparisons in body composition parameters were also not performed between the case report and the study cohort. It is difficult based on the current observation to indicate that the changes in body composition are solely due to manipulation in dietary habits; Therefore, causality cannot be directly determined; the assertions made are purely speculative and further studies are warranted. We also did not measure levels of physical activity among our study cohort. During the course of the trial, increasing level of physical activity may have contributed to significant changes in body composition. However, we studied persons with motor complete SCI who are the lowest on the spectrum of physical activity. Despite the fact that clear instruction was given of not to engage in any routine exercise program, physical activity logs should have been collected to monitor free living activity during the course of the trial.

In conclusion, dietary manipulation of caloric intake and macronutrients (percentage fat and percentage protein) resulted in remarkable changes in body composition in a person with motor complete SCI. Reduction in caloric intake and TRT may positively serve to decrease both fat mass and VAT in the case report. The 8 wk dietary manipulation program was associated with remarkable weigh loss without losing the metabolically active lean tissue. Supplementation of TRT combined with high protein intake may have served as a protective factor to preserve both lean mass and BMR in the participant with SCI. Considering the retrospective nature of the case report, there are number of confounding factors that may have contributed to the findings and further interventional studies are warranted to confirm the current observation.

Table 3 Body composition data of the case participant following 16 wk of dietary manipulation and testosterone replacement therapy

Body Composition	Pre-trial	BL	P1	% Change
DXA-Fat (kg)	30.6	30.20	21.41	-29
DXA-Lean (kg)	44.4	43.27	46.39	7.2
DXA-Body Weight (kg)	77.9	76.70	70.30	-8.3
MRI-SAT (cm^2)	-	92.25	64.12	-31
MRI-W.M. (cm^2)	-	69.73	72.13	3.5
MRI-ABS.M (cm^2)	-	61.62	67.17	9.0
MRI-ABS.IMF (cm^2)	-	8.10	4.96	-39
MRI-%IMF (%)	-	11.80	7.05	-4.8[1]
MRI-VAT (cm^2)	-	46	40.5	-12%
MRI-trunk SAT (cm^2)	-	182	142	-22%

DXA: Dual energy x-ray absorptiometry; MRI: Magnetic resonance imaging; MRI-W.M.: Whole thigh muscle CSA; MRI-ABS.M: Absolute thigh muscle CSA; MRI-ABS.IMF: Absolute intramuscular fat CSA; VAT: Visceral adipose tissue; SAT: Subcutaneous adipose tissue; BL: Baseline; PI: Post-intervention. The pre-trial phase was conducted 4 wk prior to baseline measurements. Body composition was only measured by DXA in the pre-trial phase. % change was calculated as [(P1 - BL) / BL] × 100%.
[1]: Change in % IMF is presented as the difference between P1-BL.

ARTICLE HIGHLIGHTS

Research background
Reduced level of physical activity, high-fat diet and skeletal muscle atrophy are key factors that are likely to contribute to deleterious changes in body composition and metabolic following spinal cord injury (SCI). Reduced caloric intake with lowering percentage macronutrients of fat and increasing protein intake may likely to improve body composition parameters and decrease ectopic adiposity after SCI.

Research motivation
Currently, there is no standard of care of established evidence on how to improve body composition parameters and to reduce ectopic adiposity after SCI.

Research objectives
To highlight the necessary dietary adjustments as far as caloric and macronutrient intakes responsible for improving body composition and metabolic profile following participation in a 16 wk clinical trial of administering low-dose testosterone replacement therapy in a male with SCI.

Research methods
We, retrospectively, tracked the dietary habits and body composition parameters in a 31-year-old male with motor-complete T5 SCI after administering low-dose testosterone replacement therapy (TRT) for 16 wk. Detailed body composition was evaluated *via* dual energy x-ray absorptiometry and magnetic resonance imaging. Participant was asked to turn in weekly 5 d dietary recalls to measure total energy intake, percentage carbohydrate, percentage fat, percentage protein, and total soluble fiber intake.

Research results
Lowering caloric intake by 25% and fat intake by 6.5% resulted in decreased body weight, total and regional body fat mass and ectopic adiposity. Both lean mass and BMR remained physiologically unchanged following the 16 wk intervention.

Research conclusions
The current case report highlighted the significance of reducing caloric intake and manipulating macronutrients with TRT on the changes in total and regional body composition in a male with SCI.

Research perspectives
The current case report may serve as supporting evidence for future clinical trial that may target manipulation of dietary intake with and without ergogenic aids similar to exercise and TRT to improve cardio-metabolic profile in persons with SCI.

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ORIGINAL ARTICLE

Retrospective Study

Risk factors, clinical features, and short-term prognosis of spontaneous fungal peritonitis in cirrhosis: A matched case-control study

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Author contributions: Huang CH and Pang LT wrote the paper; Pang LT, Ge TT, Xu QM, and Xu LC performed data collection; Xu LC and Huang CH participated in the design of the study and analysed the data; Chen Z conceived the study, participated in study design and coordination, and helped draft the manuscript; Ge TT prepared the figures; all the authors read and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the institutional review board of The First Affiliated Hospital, Zhejiang University School of Medicine (No. 17-615).

Informed consent statement: Informed consent for this study was not required because the analysis used anonymous clinical data that were obtained after each patient agreed to be treated by written consent.

Conflict-of-interest statement: The authors declare that no competing interest exists.

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Abstract

BACKGROUND

Spontaneous peritonitis is one of the most common infectious complications in cirrhotic patients with ascites. Spontaneous fungal peritonitis (SFP) is a type of spontaneous peritonitis that is a less recognized but devastating complication in end-stage cirrhosis. Although high mortality was previously noted, scant data are available to fully define the factors responsible for the occurrence of SFP and its mortality.

AIM

To illustrate the differences between SFP and spontaneous bacterial peritonitis (SBP) and discuss the risk factors for the occurrence of SFP and its short-term mortality.

METHODS

We performed a matched case-control study between January 1, 2007 and December 30, 2018. Patients with SFP were included in a case group. Sex-, age-, and time-matched patients with SBP were included in a control group and were further divided into control-1 group (positive bacterial culture) and control-2 group (negative bacterial culture). The clinical features and laboratory parameters, severity models, and prognosis were compared between the case and control groups. Logistic regression analysis was used to determine the risk factors for occurrence, and the Cox regression model was used to identify the predictive factors for short-term mortality of SFP.

RESULTS

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Patients with SFP exhibited more severe systemic inflammation, higher ascites albumin and polymorphonuclear neutrophils, and a worsened 15-d mortality than patients in the control groups. Antibiotic administration (case *vs* control-1: OR = 1.063, 95%CI: 1.012-1.115, *P* = 0.014; case *vs* control-2: OR = 1.054, 95%CI: 1.014-1.095, *P* = 0.008) remarkably increased the occurrence of SFP or fungiascites. Hepatorenal syndrome (HR = 5.328, 95%CI: 1.050-18.900) and total bilirubin (μmol/L; HR = 1.005, 95%CI: 1.002-1.008) represented independent predictors of SFP-related early mortality.

CONCLUSION
Long-term antibiotic administration increases the incidence of SFP, and hepatorenal syndrome and total bilirubin are closely related to short-term mortality.

Key words: Spontaneous fungal peritonitis; Risk factor; Cirrhosis

Core tip: Spontaneous fungal peritonitis (SFP) is a less recognized but severe complication in cirrhotic patients. In this retrospective study, we found that patients with SFP exhibited more severe systemic inflammation, higher ascites albumin and polymorphonuclear neutrophils, and a worsened 15-d mortality than patients with spontaneous bacterial peritonitis. Long-term antibiotic administration increases the incidence of SFP, while hepatorenal syndrome and total bilirubin are valuable in predicting short-term mortality.

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INTRODUCTION

Spontaneous peritonitis is one of the most common infectious complications, with a prevalence ranging from 7% to 27% and mortality from 10% to 46% at 1 year in cirrhotic patients with ascites[1-3]. In advanced cirrhosis, damage to the reticulo-endothelial system and gut barrier compromises the immune surveillance function of the organ and hinders the bactericidal ability of phagocytic cells, increasing the opportunity for bacteria to translocate from the gut to the abdominal cavity[4]. Additionally, ascites is transudative and contains agents with a low immune activity, providing a good environment for pathogen growth. The risk factors for the incidence and mortality of patients with spontaneous bacterial peritonitis (SBP) have been comprehensively described. A high bilirubin level, a low ascitic fluid protein concentration, and an episode of variceal haemorrhage are strongly associated with SBP occurrence[5]. Renal injury is a reliable predicting factor for mortality and develops in 30%-40% of patients with SBP[6].

Spontaneous fungal peritonitis (SFP) is a type of spontaneous peritonitis, and it is a less recognized but devastating complication in end-stage cirrhosis. Previous studies have shown that fungi can be responsible for 3.6% of spontaneous peritonitis cases in cirrhotic patients, while the 28-d mortality can be as high as 56%-73.3%[7-10]. Although high mortality was previously noted, scant data are available to fully define the factors responsible for the occurrence of SFP and its mortality.

To improve the survival rate, it is crucial to fully recognize the risk factors responsible for the occurrence and mortality of SFP and further optimize stratification. Additionally, recognizing the clinical features is critical for the early diagnosis of SFP. The aims of the present case-control study were to: (1) Compare the difference in the clinical manifestations of SFP and SBP; (2) Examine the risk factors for the occurrence and short-term mortality of SFP; and (3) Evaluate the predictive ability of different prognostic scoring systems.

MATERIALS AND METHODS

Patients and settings

Patients were initially identified from the hospital's microbiology database. In total, 3119 patients with culture-positive ascites fluid were screened between January 1, 2007 and December 31, 2018 at the First Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China). Cirrhosis was diagnosed by (1) Liver biopsy; (2) Radiological evidence of liver nodularity in patients with chronic liver diseases; and (3) Clinical evidence of the signs of portal hypertension or hepatic decompensation. The following diagnostic criteria were determined for spontaneous peritonitis: (1) Ascitic fluid polymorphonuclear neutrophil (PMN) count (≥250 cells/mm^3; and (2) Exclusion of abdominal surgical procedures or endoscopic biliary intervention during the past 4 wk. Patients with spontaneous peritonitis with fungal growth from ascites culture were identified as SFP and were included in a case group. Patients with fungiascites were identified as those with an ascitic PMN count lower than 250 cells/mm^3 but showed fungal growth from ascites culture. Control subjects were matched for age, sex, and time and were randomly selected from the same database. Forty-four patients (1:2) with bacterial culture-positive spontaneous peritonitis were divided into control-1 group, and 72 patients (1:3) with culture-negative spontaneous peritonitis were divided into control-2 group.

Data collection

The data of each patient were collected retrospectively from inpatient records and included sex, age, alcohol abuse, smoking status, antibiotic treatment, aetiology of cirrhosis, clinical presentation, cirrhotic complications, co-morbidity, laboratory examination, microbiological data, intensive care unit (ICU) admission, and prognosis. All the data were collected at the diagnosis of spontaneous peritonitis. Nosocomial infections were infections confirmed after 48 h of admission. Cirrhotic complications were identified as previously described[11]. A systemic inflammatory response (SIRS) was confirmed when at least two of the following symptoms appeared: a heart rate higher than 90 per minute; a temperature > 38 °C or < 36 °C; a respiratory rate > 20/min; and a white blood cell (WBC) count > 12000/mm^3 or < 4000/mm^3[12]. Prognostic models, including the Child-Turcotte-Pugh (CTP), sequential organ failure assessment (SOFA), model for end-stage liver disease (MELD), integrated MELD (iMELD), MELD-Na, chronic liver failure-SOFA (CLIF-SOFA), and acute physiology and chronic health evaluation (APACHE) II score, were used to predict the 15-d mortality. CTP, MELD, iMELD, and MELD-Na were applied to assess disease severity and prognosis. The calculation of MELD is as follows: 3.8 × loge (total bilirubin, mg/dL) + 9.6 × loge (creatinine, mg/dL) + 11.2 × loge (international normalized rate) + 6.4 × (aetiology of 0 for alcoholic or cholestatic cirrhosis; 1 for others). MELD-Na is 1.59 × (135 - Na) + MELD. The ACLF-SOFA score was proposed to assess organ failure in patients with acute-on-chronic liver failure by evaluating functional failures of the liver, kidney, brain, coagulation, circulation, and respiration[13]. The APACHE II score was mainly evaluated in the first 24 h in ICU but was calculated at the time of the diagnosis of spontaneous peritonitis in this study.

Statistical analysis

The data were statistically analysed using SPSS software version 20 (IBM Inc., Chicago, IL, United States). We defined statistical significance when $P < 0.05$. The data are expressed as the mean ± standard deviation (SD) if they were normally distributed or as the median ± interquartile range (IQR) if they were not. Student's *t*-test or the Wilcoxon test was used to analyse the difference between continuous variables depending on whether the data were in normality, and the χ^2-test or Fisher's exact probability test was used for categorical variables. Univariate logistic regression analysis was used to recognize risk factors for SFP occurrence. The Cox regression model was used to examine the relationship between independent variables and the 15-d mortality in patients with SFP or fungiascites. The cumulative incidence of death was described by Kaplan-Meier analysis and was compared in each group by the log-rank test. The predictive ability of the different prognostic scoring systems was compared using the receiver operating characteristic (ROC) curve. The value of different prognostic models was compared using DeLong's test.

RESULTS

Comparing the clinical manifestations between SFP and SBP

In this study, we screened 410 (13.1%) patients with fungal positivity in ascitic fluid

culture from 3119 patients with positive ascites culture from January 1, 2007 to December 30, 2018. Twenty-two (0.71%) cirrhotic patients were consistent with the diagnosis of SFP, and 13 (0.42%) were consistent with the diagnosis of fungiascites.

The clinical characteristics and outcomes of the case cohort and control cohort are depicted in Table 1. The control group was further divided into the SBP with positive bacterial culture group (control-1, n = 44) and SBP with negative bacterial culture group (control-2, n = 72). Of the 22 patients with SFP, the mean age was 60 ± 11.6 years and 17 (77.3%) were male. The case and control cohorts did not show differences in baseline characteristics, including current smoking, alcohol abuse, and cause of cirrhosis. Regarding the complications of cirrhosis, SFP patients showed a higher frequency of variceal bleeding (SFP *vs* control-1 P = 0.050) and hepatorenal syndrome (SFP *vs* control-2 P = 0.023). However, the Charlson comorbidity index showed no difference between the cohorts. Patients with SFP showed a more serious inflammatory response. The C-reaction protein (CRP) levels (SFP *vs* control-1: P < 0.001; SFP *vs* control-2 P < 0.001), WBC (SFP *vs* control-1: P = 0.001; SFP *vs* control-2: P < 0.001), ascitic PMNs (SFP *vs* control-2: P = 0.004), SIRS (SFP *vs* control-2: P < 0.001), and fever (SFP *vs* control-2: P = 0.02) were higher in the SFP cohort. Additionally, a significant difference was also observed in the length of antibiotic treatment before peritonitis (SFP *vs* control-1: P < 0.001; SFP *vs* control-2: P < 0.001). Notably, co-infection with bacteria was much common in SFP (SFP *vs* control-2: P < 0.001) with a higher frequency of pneumonia and blood infection.

SFP and fungiascites were also compared in our study and are shown in Table 2. *Candida spp*. was the most commonly isolated fungus in SFP or fungiascites. Comparing the baseline characteristics of SFP with fungiascites, the length of antibiotic treatment before peritonitis and antifungal therapy were similar, but WBC (P = 0.046) and CRP (P = 0.010) were higher in the SPF group.

Risk factors for the occurrence of SFP

The risk factors analysed for patients with SFP and the matched control group are shown in Table 3. The factors that may be related to SFP were compared between the case and control groups by univariate logistic regression analysis. The length of antibiotic administration was closely related to SFP compared with the control-1 group (OR = 1.063, 95%CI: 1.012-1.115, P = 0.014) or control-2 group (OR = 1.054, 95%CI: 1.014-1.095, P = 0.008). The median length of antibiotic administration before the occurrence of SFP or fungiascites was 12 d in our study (Figure 1). Additionally, variceal bleeding (SFP *vs* control-1: OR = 3.619, 95%CI: 1.065-12.296, P = 0.039) and hepatorenal syndrome (SFP *vs* control-2: OR = 4.000, 95%CI: 1.312-12.194, P = 0.015) were also significantly associated with SFP. However, in univariate analysis, high CTP and MELD scores were not shown to be risk factors for SFP.

Risk factors associated with early mortality

SFP is a devastating complication of cirrhosis and has the most undesirable consequence in the short term. The 15-d survival or death events were recorded in all patients. As shown in Table 1, the case group (10/22) exhibited a significantly higher mortality than the control-1 group (9/44 P = 0.046) and control-2 group (5/72 P < 0.001). However, the mortality between SFP and fungiascites (3/13 P = 0.28) did not show a statistically significant difference (Table 2, Figure 2A). Furthermore, the risk factors that may be related to the 15-d mortality in patients with SFP or fungiascites were analysed using the univariate Cox regression model (Table 4). The parameters hepatorenal syndrome, WBC, total bilirubin, creatinine, serum sodium, and severity scores (MELD, SOFA, CTP, and APACHE II) were identified as significant risk factors for SFP and fungiascites mortality within 15 d. The significant risk factors were applied to the multivariate Cox regression model. Hepatorenal syndrome (HR = 5.328, 95%CI: 1.050-18.900, P = 0.010) and total bilirubin (HR = 1.005, 95%CI: 1.002-1.008, P = 0.002) emerged as independent risk factors for 15-d mortality in SFP and fungiascites.

Based on the identified risk factors for 15-d mortality, the optimal cut-offs were used to stratify patients, and their survival was compared by the Kaplan–Meier curve (Figure 2). Patients with SOFA ≥ 8 (AUROC: 0.850, 95%CI: 0.707-0.993), MELD ≥ 19 (AUROC: 0.724, 95%CI: 0.514-0.934), WBC ≥ 10 × 10^9/L (AUROC: 0.733, 95%CI: 0.560-0.905), total bilirubin ≥ 150 mg/dL (AUROC: 0.860, 95%CI: 0.708-1.000), and creatinine ≥ 101 μmol/L (AUROC: 0.753, 95%CI: 0.575-0.932) at the time of SFP and fungiascites diagnosis presented higher risks for short-term mortality. Additionally, patients who were complicated with hepatorenal syndrome further increased the mortality and presented a poor prognosis (Figure 2D).

Value of prognostic models in predicting the outcome of SFP and fungiascites

Six models were tested to predict the 15-d mortality in patients with SFP or fungiascites (Table 5). Among the models, SOFA exhibited a higher AUROC (0.85,

Table 1 Comparison of clinical manifestations between spontaneous fungal peritonitis (case) and spontaneous bacteria peritonitis with a positive (control-1) or negative bacterial culture (control-2)

Variable	Case (*n* = 22)	Control-1 (*n* = 44)	*P*-value	Control-2 (*n* = 72)	*P*-value
Demographics data					
Age (yr), M ± SD	60.0 ± 11.6	58.0 ± 12.5	0.55	56.9 ± 10.5	0.32
Sex (% male)	17 (77.3%)	37 (82.2%)	0.51	55 (74.3%)	1
Current smoking *n* (%)	7 (31.8%)	20 (45.5%)	0.43	32 (44.4%)	0.33
Alcohol abuse *n* (%)	7 (31.8%)	16 (36.4%)	0.79	30 (41.3%)	0.46
Aetiology of cirrhosis					
Viral *n* (%)	14 (63.6%)	27 (61.4%)		44 (61.1%)	
Alcohol *n* (%)	2 (9.1%)	8 (18.2%)	0.66	18 (25.0%)	0.334
Others *n* (%)	6 (27.3%)	9 (20.5%)		13 (18.1%)	
Complication					
Variceal bleeding *n* (%)	8 (36.4%)	6 (13.6%)	0.05	18 (25.0%)	0.41
Hepatorenal syndrome *n* (%)	8 (36.4%)	10 (22.7%)	0.26	9 (12.5%)	0.023
HE *n* (%)	8 (36.4%)	12 (27.3%)	0.57	14 (19.4%)	0.15
Charlson index (IQR)	4 (3.7-5.0)	4 (3.0-5.0)	0.46	3 (3-5)	0.007
Laboratory examination					
WBC, 10^9 cells/L (IQR)	11.7 (8.2-19.1)	5.6 (2.9-11.2)	0.001	6.2 (4.0-9.5)	<0.001
C-reactive protein, mg/L (IQR)	77.4 (55.9-138.2)	31.4 (14.7-50.6)	<0.001	22.7 (8.9-42.1)	<0.001
Creatinine, μmol/L (IQR)	98.0 (69.5-147.8)	86.0 (60.5-165.0)	0.75	81 (67.0-105.0)	0.228
Albumin, g/dL (M ± SD)	28.1 ± 4.1	26.6±7.5	0.41	29.8 ± 4.9	0.09
Total bilirubin, μmol/L(IQR)	103.5 (27.5-271.5)	85 (34.2-196.5)	0.96	59.5 (30.0-129.0)	0.51
INR (IQR)	1.40 (1.2-2.0)	1.6 (1.3-2.1)	0.37	1.5 (1.3-1.7)	0.56
Ascites PMN (IQR)	2550 (338-4700)	1800 (650-4500)	0.56	550 (302-1375)	0.004
Ascites albumin g/dL (M ± SD)	18.0±8.2	11.4 ± 7.3	0.002	13.1 ± 9.5	0.009
Clinical presentation					
Abdominal pain	7 (31.8%)	17 (38.6%)	0.79	17 (23.6%)	0.578
Fever (T ≥ 38°C)	12 (54.5%)	22 (50.0%)	0.79	19 (26.4%)	0.02
Antibiotic treatment before peritonitis (d)	15.4 (3.8-24.8)	2 (0.3-10.0)	0.001	2 (0-8.0)	<0.001
PPI administration	8 (36.4%)	27 (61.4%)	0.07	43(59.7%)	0.086
Nosocomial infection	13 (59.1%)	30 (68.2%)	0.59	44 (61.1%)	1
ICU admission	1 (4.5%)	2 (4.5%)	1	1 (1.4%)	0.42
Septic shock *n* (%)	7 (31.8%)	8 (18.2%)	0.23	3 (4.2%)	0.001
SIRS *n* (%)	14 (63.6%)	20 (45.5%)	0.2	14 (19.4%)	<0.001
Concomitant bacterial infection	12 (54.5%)	13 (29.5%)	0.12	3 (4.2%)	<0.001
Blood infection	6 (27.2%)	9 (20.5%)	1	1 (1.4%)	<0.001
Pneumonia	3 (13.6%)	3 (6.8%)	0.39	2 (2.8%)	0.048
Bacterial peritonitis	9 (40.9%)	-	-	-	-
Other sites	1 (4.5%)	1 (2.3%)	-	1 (1.4%)	-
Severity score					
SOFA (M ± SD)	7.1 ± 3.8	7.6 ± 4.7	0.65	5.2 ± 2.6	0.035
CLIF-SOFA	7.1 ± 3.4	8.1 ± 4.4	0.33	5.6 ± 3.0	0.048
APACHE II	7.6 ± 6.1	6.7 ± 5.4	0.58	3.0 ± 3.1	<0.001
MELD (IQR)	15.9 (7.5-25.2)	18.3 (9.3-25.9)	0.76	14.6 (9.7-20.3)	0.57
MELD-Na (IQR)	23.0 (10.4-35.1)	20.4 (9.7-31.1)	0.88	15.5 (10.1-25.0)	0.17
CTP (IQR)	11.0 (8-12.3)	11.5 (10.0-12.0)	0.39	10 (9.0-12.0)	0.48
15-d mortality	10 (45.1%)	9 (20.4%)	0.046	5 (6.9%)	<0.001

M: Mean; SD: Standard deviation; IQR: Interquartile range; HE: Hepatic encephalopathy; INR: International normalized rate; PMN: Polymorphonuclear neutrophil; ICU: Intensive care unit; PPI: Proton pump inhibitor; SIRS: Systemic inflammatory response; SOFA: Sequential organ failure assessment; CLIF-SOFA: Chronic liver failure-sequential organ failure assessment; APACHE II: Chronic liver failure-sequential organ failure assessment; MELD: Model for end-stage liver disease; CTP: Child-Turcotte-Pugh.

95%CI: 0.707-0.993) in predicting 15-d mortality. The Delong test was used to compare

Table 2 Comparison of clinical manifestations between spontaneous fungal peritonitis and fungiascites

Variable	Total (*n* = 35)	SFP (*n* = 22)	Fungiascites (*n* = 13)	*P*-value
Antibiotic treatment before peritonitis (d)	12 (5.0-23.0)	15.4 (3.8-24.8)	12.0 (6.0-22.0)	0.8
Anti-fungal therapy	15 (42.9%)	8 (36.4%)	7 (53.8%)	0.48
Septic shock *n* (%)	8 (22.9%)	7 (31.8%)	1 (4.2%)	0.21
WBC, 10^9 cells/L (IQR)	9.4 (5.6-18.1)	11.7 (8.2-19.1)	6.8 (3.6-12.0)	0.046
C-reactive protein, mg/L (IQR)	69.0 (33.3-110.5)	77.4 (55.9-138.2)	36.6 (13.4-72.1)	0.01
SIRS *n* (%)	19 (54.3%)	14 (63.6%)	5 (38.5%)	0.18
Fungus				
Candida spp.	26 (74.2%)	18 (81.8%)	8 (61.5%)	-
Trichosporon	2 (5.7%)	1 (4.5%)	1 (7.6%)	-
Aspergillus	5 (14.3%)	3 (13.6%)	2 (15.3%)	-
Cryptococcus laurentii	2 (5.7%)	0 (0%)	2 (15.3%)	-
Severity score				
SOFA (M ± SD)	6.8 ± 3.5	7.1 ± 3.8	5.2 ± 2.6	0.77
MELD (IQR)	14.7 (8.0-24.3)	15.9 (7.5-25.2)	14.2 (8.8-24.8)	0.92
CTP (IQR)	11.0 (9.0-12.0)	11.0 (8.0-12.3)	11.0 (9.0-11.5)	0.7
15-d mortality	13 (37.1%)	10 (45.1%)	3 (23.7%)	0.28

M: Mean; SD: Standard deviation; IQR: Interquartile range; SOFA: Sequential organ failure assessment; MELD: Model for end-stage liver disease; CTP: Child-Turcotte-Pugh.

the value between SOFA and five other predicting models. The remaining five models did not show a statistical difference compared with SOFA.

DISCUSSION

SFP is a rare but devastating complication in end-stage cirrhosis, and its clinical characteristics as well as the risk factors for its occurrence and prognosis were less depicted previously. In the current case-control study, we compared the clinical features and susceptible factors between SFP patients and SBP patients with bacterial culture-positive (Control-1) or bacterial culture-negative (Control-2) results. To the best of our knowledge, this is the largest retrospective study of patients with SFP and fungiascites. We found the following: (1) SFP patients exhibited more severe systemic inflammation, including elevated WBC and CRP levels, higher frequency of SIRS, and higher short-term mortality; (2) Long-term antibiotic administration remarkably increased the occurrence of SFP or fungiascites, and the median length of antibiotic administration before the SFP diagnosis was 12 d in our study; (3) Patients with SFP displayed a worse prognosis than patients with SBP but showed no significant difference with fungiascites; and (4) Hepatorenal syndrome, total bilirubin (≥150 mg/dL), and creatinine (≥101 μmol/L) represented independent predictors of SFP-related early mortality.

Spontaneous peritonitis is one of the most common infectious complications of end-stage cirrhosis and often leads to the rapid deterioration of liver function[14]. SFP is a subtype of spontaneous peritonitis. Because fungi are much larger in size than bacteria, their translocation across the gut mucosa seems more difficult than bacterial translocation. Thus, the incidence rate of SFP is much lower than that of SBP. As reported previously, SFP accounted for 15% of invasive fungal infections in acute-on-chronic liver failure and 3.6% of patients with liver cirrhosis and spontaneous peritonitis[15]. We found that SFP was much stronger in inducing an inflammatory response than SBP or fungiascites. Systemic inflammation is closely associated with a worse outcome[16]. High levels of pro-inflammatory cytokines disrupt hemodynamic stability and facilitate portal hypertension-related complications[17]. Systemic inflammation has been shown to favour serious complications such as variceal bleeding, encephalopathy, and acute renal failure[11,18,19]. An intense inflammatory response in patients with SFP may be a key factor in initiating fast deterioration of cirrhosis and resulting in undesirable prognosis.

Clarifying risk factors is useful to identify candidates for early treatment. Previous studies have indicated that high CTP or MELD scores, invasive procedures, and length of hospital stay increased the risk of SFP in cirrhosis[20]. A recent meta-analysis

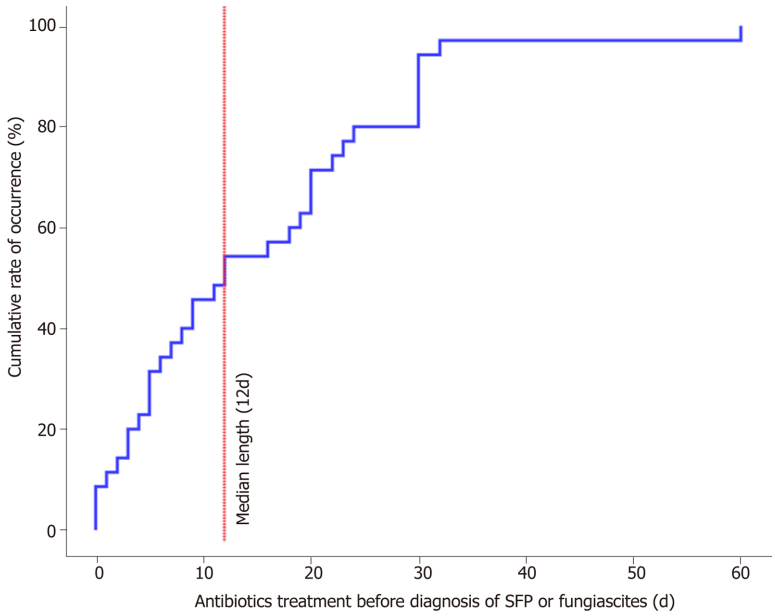

Figure 1 Length of antibiotic administration before occurrence of SFP.

indicated that hospitalization is related to a significant increase in SFP risk[21]. However, we found no significant difference between SFP and SBP in the length of hospital stay. We found that long-term antibiotic administration could increase the occurrence of SFP. This result is in agreement with the data of previous reports related to fungal infection in patients with end-stage liver disease[15,22]. Additionally, a case reported by Mark D Berzsenyi cued the link between the long-term administration of antibiotics and SFP[23]. Antibiotic administration disturbs the balance between bacteria and fungi and leads to excessive growth of fungi, making the opportunity for increased fungal translocation[9]. Compared with the control groups, variceal bleeding and hepatorenal syndrome were also associated with the occurrence of SFP. The complications of cirrhosis that refer to hemodynamic instability may further impair intestinal barrier function and promote fungal translocation. In contrast to previous reports, the severity of disease (MELD or CTP scores) showed no difference between the SFP and control groups[9].

Considering the fast course of SFP, death mainly occurred within 2 wk after diagnosis. The risk factors for 15-d mortality were also discussed. Consistent with previous reports[7], we found that the 15-d mortality of SFP showed no significant difference compared with that of fungiascites but was higher than that of SBP. Notably, mortality was not influenced by antifungal therapy in our study. Because traditional empirical antibiotic therapy was used to identify fungi and a long period was applied for the remaining culture, many patients died prior to obtaining the culture result. Only 36.4% of patients with SFP received antifungal therapy in our study. However, it was reported that adequate antifungal treatment improved survival of cirrhotic patients with candidemia and intra-abdominal candidiasis[24]. Therefore, timely and adequate antifungal treatment may be important to improve prognosis. Because of the low incidence of SFP, the risk factors for mortality were only discussed in a small-sized cohort. The multivariate Cox regression analysis performed in our study indicated that hepatorenal syndrome, total bilirubin, and creatinine were three independent risk factors for short-term mortality. Bremmer *et al*. showed that the APACHE II score was a predictor of 28-d mortality[7]. Renal dysfunction was a main prognostic factor for 15-d mortality of SFP in the current study. Creatinine ≥ 101 μmol/L was an optimal cut-off point to predict a poor prognosis. These findings agree with previous findings for SBP. Tandon *et al*[25] reported that renal dysfunction was the most important independent predictor of mortality in cirrhotic patients with SBP. Additionally, liver function was another important prognostic factor. Total bilirubin ≥ 150 mg/dL and MELD ≥ 19 acted as good discriminators of subsequent SFP 15-d mortality. Notably, the cut-off point of MELD to predict SFP 15-d mortality was slightly lower than that in a previous report on SBP-related 30-d mortality (MELD ≥ 22)[26,27]. The predictive value of the six prognostic models was compared. SOFA exhibited the highest AUROC among the selected models, while DeLong's test indicated no significant difference between SOFA and the remaining five models. However, low sample size may conceal the difference. The value of prognosis should

Table 3 Risk factors for spontaneous fungal peritonitis as determined by univariate logistic regression analysis

Variable	Control-1 group (*n* = 44) *vs* Case group (*n* = 22)		Control-2 (*n* = 72) *vs* Case group (*n* = 22)	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Variceal bleeding	3.619 (1.065-12.296)	0.039	1.71 (0.619-4.751)	0.3
Hepatorenal syndrome	1.943 (0.635-5.947)	0.245	4.00 (1.312-12.194)	0.015
HE	1.524 (0.511-4.546)	0.45	2.367 (0.831-6.742)	0.107
Charlson index	0.936 (0.682-1.284)	0.681	1.266 (0.911-1.759)	0.16
chemoradiotherapy	2.048 (0.122-34.370)	0.618	3.381 (0.203-56.396)	0.396
Alcohol abuse	0.817 (0.275-2.422)	0.715	0.657 (0.237-1.798)	0.41
Length of hospital stay (d)	0.974 (0.944-1.004)	0.092	0.997 (0.969-1.035)	0.874
Antibiotic treatment before diagnosis (d)	1.063 (1.012-1.115)	0.014	1.054 (1.014-1.096)	0.008
PPI administration	0.436 (0.153-1.239)	0.119	0.467 (0.177-1.234)	0.124
Child C grade	0.551 (0.173-1.755)	0.313	1.211 (0.438-3.352)	0.712
MELD score	0.988 (0.942-1.035)	0.603	1.025 (0.970-1.083)	0.38

HE: Hepatic encephalopathy; PPI: Proton pump inhibitor; MELD: Model for end-stage liver disease; OR: Odds ratio; CI: Confidence interval.

be tested in a large cohort.

Our study had some limitations. Considering the low sample size of the current study, more samples are required to fully determine the risk factors for occurrence and mortality. As a one-centre and retrospective study, a potential bias in data collection may result in a statistical bias. Additionally, it was difficult to distinguish between SFP and SBP using fungal colonization, which may lead to inaccurate results.

Nevertheless, our investigation provides a comprehensive study that characterizes the clinical features of SFP. We found that long-term antibiotic administration increases the risk of SFP occurrence. Hepatorenal syndrome and total bilirubin are closely related to short-term mortality.

Table 4 Cox regression analyses of risk factors associated with 15-d mortality (dead: *n* = 13; alive: *n* = 22) in patients with spontaneous fungal peritonitis or fungiascites

	Univariate		Multivariate	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age	0.959 (0.918-1.003)	0.066		
Variceal bleeding	0.872 (0.285-2.666)	0.81		
Hepatorenal syndrome	7.3 (2.216-24.435)	0.001	5.328 (1.050-18.900)	0.01
HE	2.654 (0.889-7.925)	0.08		
Charlson index	1.155 (0.742-1.796)	0.523		
WBC, 10^9 cells/L	1.064 (1.009-1.122)	0.023	1.062 (0.933-1.137)	0.081
C-reactive protein, mg/L	1.003 (0.992-1.015)	0.564		
INR	1.201 (0.520-2.776)	0.668		
Total bilirubin, μmol/L	1.005 (1.003-1.008)	<0.001	1.005 (1.002-1.008)	0.002
Creatinine, μmol/L	1.010 (1.003-1.017)	0.005		
Serum sodium, mmol/L	0.883 (0.814-0.958)	0.003	0.949 (0.867-1.039)	0.256
Concurrent bacterial infection	0.715 (0.240-2.129)	0.546		
Anti-fungal therapy	0.758 (0.248-2.319)	0.627		
SIRS	3.458 (0.948-12.611)	0.06		
SOFA	1.305 (1.132-1.505)	<0.001		
MELD	1.080 (1.021-1142)	0.008		
CTP	1.727 (1.214-2.483)	0.002		
APACHE II	1.113 (1.025-1.207)	0.01		

HE: Hepatic encephalopathy; INR: International normalized rate; SIRS: Systemic inflammatory response; SOFA: Sequential organ failure assessment; APACHE II: Chronic liver failure-sequential organ failure assessment; MELD: Model for end-stage liver disease; CTP: Child-Turcotte-Pugh; OR: Odds ratio; CI: Confidence interval; HR: Hazard ratio.

Table 5 Performance of six prognostic scoring systems in predicting mortality in patients with spontaneous fungal peritonitis / fungiascites

Prognostic model	Auroc (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	*Z* score	*P*-value
SOFA	0.850 (0.707-0.993)	61.5 (31.8-86.1)	90.9 (70.8-98.9)		
CLIF-SOFA	0.825 (0.686-0.964)	84.6 (54.6-98.1)	77.3 (54.6-92.2)	0.498	0.619
CTP	0.825 (0.675-0.975)	69.2 (38.6-90.9)	86.4 (65.1-97.1)	0.42	0.674
APPACHE II	0.722 (0.521-0.923)	61.5 (31.6-90.9)	86.4 (65.1-97.1)	1.335	0.182
MELD-Na	0.759 (0.556-0.962)	76.9 (46.2-95.0)	77.3 (54.6-92.2)	0.723	0.469
MELD	0.724 (0.514-0.934)	69.2 (38.6-90.9)	86.4 (65.1-97.1)	1.035	0.301
SIRS	0.680 (0.496-0.864)	76.9 (46.2-95.0)	59.1 (36.4-79.3)	1.429	0.153

SIRS: Systemic inflammatory response; SOFA: Sequential organ failure assessment; CLIF-SOFA: Chronic liver failure-sequential organ failure assessment; APACHE II: Chronic liver failure-sequential organ failure assessment; MELD: Model for end-stage liver disease; CTP: Child-Turcotte-Pugh.

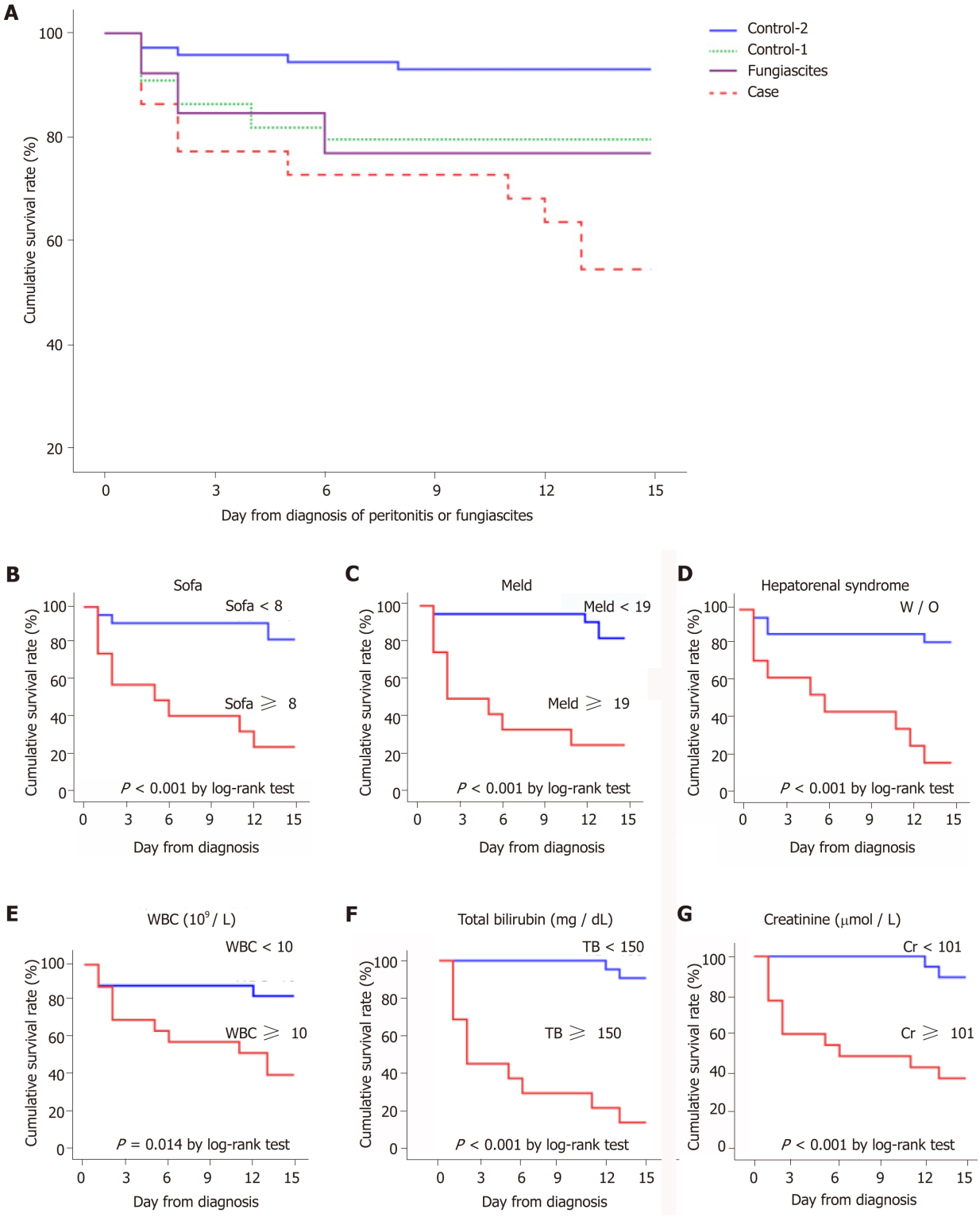

Figure 2 Kaplan-Meier diagrams. A: Kaplan-Meier diagram depicting 15-d mortality among patients in different groups (log-rank test, case *vs* fungiasictes, P = 0.228, case *vs* control-1 P = 0.046, case *vs* control-2 P < 0.001); B-G: Optimal cut-offs were used to stratify patients and compare their respective survival.

ARTICLE HIGHLIGHTS

Research background

Spontaneous peritonitis is one of the most common infectious complications in cirrhotic patients with ascites. However, spontaneous fungal peritonitis is a less recognized but devastating complication in end-stage cirrhosis.

Research motivation

To improve the survival rate, it is crucial to identify the risk factors for occurrence and mortality

and to optimize stratification. Additionally, recognizing the clinical features is critical for the early diagnosis of spontaneous fungal peritonitis (SFP).

Research objectives
We aimed to illustrate the differences between SFP and spontaneous bacterial peritonitis (SBP) and discuss the risk factors for occurrence and short-term mortality of SFP.

Research methods
In this case-control study, 138 cirrhotic patients with spontaneous peritonitis were recruited. Patients with SFP were included in a case group. Sex-, age-, and time-matched SBP patients were included in a control group. Furthermore, the control group was divided into control-1 group (positive bacterial culture) and control-2 group (negative bacterial culture), according to the bacterial culture result. Differences in the clinical features, laboratory examinations, severity models, and prognosis were compared between the case and control groups. The risk factors for the occurrence of SFP were identified by the logistic regression model. The short-term mortality of SFP was determined by the Cox regression model. Additionally, the predictive ability of different prognostic scoring systems was evaluated.

Research results
Patients with SFP had severe systemic inflammation, including higher white blood cell counts and C-reaction protein levels, and exhibited poor short-term mortality. However, no significant difference was found regarding the short-term mortality between patients with SFP and fungiascites. Long-term antibiotic administration dramatically increased the occurrence of SFP or fungiascites. The median length of antibiotic administration before the occurrence of SFP or fungiascites was 12 d in our study. Hepatorenal syndrome (HR = 5.328, 95%CI: 1.050-18.900) and total bilirubin (μmol/L, HR = 1.005, 95%CI: 1.002-1.008) represented independent predictors of SFP-related early mortality.

Research conclusion
The present study found that long-term antibiotic administration increases the incidence of SFP and that hepatorenal syndrome and total bilirubin are closely related to short-term mortality.

Research prospective
Although a large sample size is required for further evaluation, our investigation provides a comprehensive study on characterizing the clinical features of SFP.

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ORIGINAL ARTICLE

Retrospective Study

Incidence of portal vein thrombosis after splenectomy and its influence on transjugular intrahepatic portosystemic shunt stent patency

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Author contributions: Dong F designed the research; Luo SH wrote the manuscript; Huang H carried out the experiment; Zheng LJ prepared the figures and tables; Zhang XQ performed data analysis; Chu JG was responsible for the experiment; and Yao KC supervised the study.

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Abstract

BACKGROUND

Transjugular intrahepatic portosystemic shunt (TIPS) is widely accepted as an alternative to surgery for management of complications of portal hypertension. TIPS has been used to treat portal vein thrombosis (PVT) in many centers since the 1990s. Although TIPS has good therapeutic effects on the formation of PVT, the effect of PVT on TIPS stenting has rarely been reported. Patients with splenectomy and pericardial devascu-larization have a high incidence of PVT, which can markedly affect TIPS stent patency and increase the risk of recurrent symptoms associated with shunt stenosis or occlusion.

AIM

To investigate the incidence of PVT after splenectomy and its influence on the patency rate of TIPS in patients with cirrhosis and portal hypertension.

METHODS

Four hundred and eighty-six patients with portal hypertension for refractory

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ascites and/or variceal bleeding who required TIPS placement between January 2010 and January 2016 were included in this retrospective analysis. Patients without prior splenectomy were defined as group A (n = 289) and those with prior splenectomy as group B (n = 197). The incidence of PVT before TIPS was compared between the two groups. After TIPS placement, primary patency rate was compared using Kaplan–Meier analysis at 3, 6, 9 and 12 mo, and 2 and 3 years. The clinical outcomes were analyzed.

RESULTS

Before TIPS procedure, the incidence of PVT in group A was lower than in group B (P = 0.003), and TIPS technical success rate in group A was higher than in group B (P = 0.016). The primary patency rate in group A tended to be higher than in group B at 3, 6, 9 and 12 mo, 2 years and 3 years (P = 0.006, P = 0.011, P = 0.023, P = 0.032, P = 0.037 and P = 0.028, respectively). Recurrence of bleeding and ascites rate in group A was lower than in group B at 3 mo ($P \leq 0.001$ and P = 0.001), 6 mo (P = 0.003 and P = 0.005), 9 mo (P = 0.005 and P = 0.012), 12 mo (P = 0.008 and P = 0.024), 2 years (P = 0.011 and P = 0.018) and 3 years (P = 0.016 and P = 0.017), respectively. During 3-years follow-up, the 1-, 2- and 3-year survival rate in group A were higher than in group B (P = 0.008, P = 0.021, P = 0.018, respectively), but there was no difference of the incidence of hepatic encephalopathy (P = 0.527).

CONCLUSION

Patients with prior splenectomy have a high incidence of PVT, which potentially increases the risk of recurrent symptoms associated with shunt stenosis or occlusion.

Key words: Portal hypertension; Transjugular intrahepatic portosystemic shunt; Splenectomy; Portal vein thrombosis

Core tip: There are several approaches for treatment of portal hypertension related varices and variceal hemorrhage, including drugs, endoscopic variceal ligation, transjugular intrahepatic portosystemic shunt, splenectomy with pericardial devascularization and liver transplantation. Transjugular intrahepatic portosystemic shunt is widely accepted as an alternative to surgery for management of complications of portal hypertension such as variceal bleeding, refractory ascites, Budd–Chiari syndrome, hepatorenal syndrome, hepatic hydrothorax and even hepatopulmonary syndrome. Patients with splenectomy with pericardial devascularization had a high incidence of portal vein thrombosis, which can markedly affect transjugular intrahepatic portosystemic shunt stent patency and potentially increase the risk of recurrent symptoms associated with shunt stenosis or occlusion.

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INTRODUCTION

Portal hypertension secondary to liver cirrhosis is mainly due to chronic hepatitis and alcoholic liver disease[1]. Esophagogastric varices and ascites secondary to portal hypertension are common major complications of liver cirrhosis[2]. Esophagogastric varices are a serious, life-threatening complication and hypersplenism is often associated with portal hypertension in cirrhotic patients[3].

There are several approaches for treatment of portal hypertension related varices and variceal hemorrhage, including drugs, endoscopic variceal ligation, transjugular intrahepatic portosystemic shunt (TIPS), splenectomy with pericardial

devascularization (SPD) and liver transplantation[4]. SPD without liver transplantation has been widely accepted as a surgical treatment for cirrhosis in patients with variceal bleeding and secondary hypersplenism in China for many years[5]. However, when compared with other treatments, simple splenectomy and SPD are associated with an increased incidence of postoperative complications, such as portal vein thrombosis (PVT)[6].

TIPS is widely accepted as an alternative to surgery for management of complications of portal hypertension such as variceal bleeding, refractory ascites, Budd–Chiari syndrome, hepatorenal syndrome, hepatic hydrothorax and even hepatopulmonary syndrome[7]. TIPS has been used to effectively treat PVT in many centers since the 1990s[8]. PVT is still considered a contraindication to the creation of a TIPS, however the advantages of TIPS for PVT in patients with cirrhosis are evident[9] as it addresses portal hypertension and reconstructs portal vein (PV) flow.

Despite its efficacy in treatment of complications of portal hypertension, TIPS is prone to shunt stenosis or occlusion leading to shunt failure, and approximately half of all patients with TIPS require shunt revision during follow-up[10], which makes close surveillance and frequent costly revisions mandatory[11] especially in patients with PVT despite the use of stent grafts covered with polytetrafluoroethylene. Even with these new stents, post-TIPS shunt obstruction and a high rate of clinical symptom recurrence remain problematic.

Although TIPS has good therapeutic effects on the formation of PVT, the effect of PVT on TIPS stenting has rarely been reported. The purpose of this study was to evaluate the incidence of PVT after splenectomy and its influence on the patency rate of TIPS in patients with cirrhosis of portal hypertension.

MATERIALS AND METHODS

Patients

A total of 486 patients who underwent a TIPS procedure between January 2010 and January 2016 were enrolled retrospectively. The study protocol was approved by the Institutional Review Board and Ethics Committee, and all the patients provided a written consent at the time of operation in the hospital. All procedures were conducted according to the guidelines approved by the ethics committee. We reviewed the patients' medical records and medical images to gather information regarding the underlying etiologies, clinical presentations, age, sex and severity of cirrhosis.

Study design

This was a multi-center, retrospective study. Patients with cirrhosis without prior splenectomy served as group A (n = 289), and those with cirrhosis and prior splenectomy served as group B (n = 197). Three hundred and sixty-five patients with portal-hypertension-related complications of recurrent variceal bleeding after band ligation and/or glue injection, 121 patients with refractory ascites and 86 with both who underwent TIPS were included. The incidence of PVT before TIPS was compared between the two groups. After TIPS placement, primary patency rate was compared at 3, 6, 9 and 12 mo, and 2 and 3 years. The clinical outcomes were analyzed.

Patients with acute PVT, variceal bleeding as an emergency indication, hepatic encephalopathy (HE), severe right-sided heart failure, severe liver failure, polycystic liver disease, dilated biliary ducts, age > 75 years, Child–Pugh score > 11, Model for End-stage Liver Disease score > 18, hepatic carcinoma, sepsis or spontaneous bacterial peritonitis and patients who underwent liver transplantation were excluded.

Diagnosis and definitions

Color Doppler ultrasound was performed initially for the diagnosis of PVT. It revealed that the main PV was obstructed along with a reduction or absence of portal flow or disappearance of the native PV and formation of extensive collaterals. Contrast-enhanced computed tomography and/or magnetic resonance imaging showed stenosis, filling defects or complete occlusion of the PV with or without collaterals.

Acute PVT was defined by the absence of collateral vessels and any one of the following: (1) Aapid onset of abdominal pain due to PVT within 14 d and intestinal ischemia or infarction without chronic thrombosis; or (2) A high intraluminal density within the PV on non-contrast-enhanced computed tomography. Chronic PVT was defined by at least one of the following: (1) A low intraluminal density on contrast-enhanced computed tomography; (2) Replacement of the original main PV (MPV) with a fibrotic cord or no identifiable MPV; or (3) Presence of portal cavernoma.

Thrombosis in the MPV was further classified as partial occlusion, complete occlusion and fibrotic cord in place of the original MPV.

TIPS procedure

Using standard local anesthesia, TIPS was performed through a transjugular approach, and the technique has been described previously[12]. For PVT patients with cirrhosis, the TIPS procedure was performed as described previously[13]. The entire length of the intrahepatic tract was covered by the 8-mm stent graft (Fluency; BARD, Voisins le Bretonneux, France or Viatorr; W.L. Gore and Associates, Flagstaff, AZ, United States). The shunts were dilated to full nominal diameter to reach a target portosystemic gradient of < 12 mmHg, and prominent gastroesophageal collateral vessels observed during the TIPS procedure were embolized with coils (Cook Inc., Bloomington, IL, United States).

Direct portography was then performed to confirm if the PV system was entirely patent. After the TIPS procedure, patients were treated with intravenous heparin (4000 U/d; Chase Sun Pharma Co. Ltd, Tianjing, China) and oral warfarin (2.5 mg/d; Orion Pharma Co. Ltd, Orionintie, Finland).

Follow-up

Patients underwent baseline duplex sonography on the day after TIPS. The results were compared with subsequent shunt velocities. After TIPS, patients were followed up using the same protocol for each group *via* outpatient visit 1 mo after the procedure and then every 3 mo or whenever needed. Clinical examination, blood chemistry test and assessment of HE were carried out during the follow-up period. Ultrasonography was also performed after TIPS or in case of recurrent bleeding or ascites.

Shunt dysfunction or significant recurrent symptoms were used as endpoints for the loss of primary unassisted patency. TIPS angiography was performed in these patients and TIPS revision was made when hemodynamically significant shunt stenosis was > 50% with recurrent variceal bleeding and ascites, and portosystemic pressure gradient was ≥ 15 mmHg without grade III/IV HE (West Haven Criteria)

Statistical analysis

Results are expressed as mean ± SD. Patency time was calculated by the Kaplan–Meier method, and the median time was compared by the log-rank test. Variables were subjected to logistic regression analysis. Differences between the groups were compared using one-way analysis of variance and least significant difference *t* test. $P < 0.05$ was considered statistically significant. SPSS version 20.0 (SPSS, Chicago, IL, United States) was used for the statistical analysis.

RESULTS

Between January 2010 and January 2016, there were 289 patients with cirrhosis with no prior splenectomy in group A, and 197 patients with cirrhosis who underwent splenectomy in group B. The etiology, clinical presentations, age, sex and severity of cirrhosis did not differ significantly (Table 1). In group A, the incidence of PVT was 11.0% (65/289). In group B, the incidence of PVT was 44.2% (87/197). The distribution of patients is shown in Figure 1. The incidence of PVT in group B was higher than in group A, and the difference was significant between the two groups ($P = 0.003$).

Of the 289 patients in group A, 255 (88.2%) cases had technically successful TIPS compared with 144 (73.1%) cases in group B. TIPS technical success rate in group A was higher than in group B ($P = 0.016$). No patient died of severe procedure-related complications within 30 d after TIPS (Figure 2). After TIPS, the mean portosystemic pressure gradient decreased from 32.43 ± 6.64 to 11.15 ± 1.20 mmHg in group A ($P = 0.027$), and 31.90 ± 4.63 to 10.79 ± 1.18 mmHg in group B ($P = 0.025$). There were significant differences before and after TIPS ($P < 0.05$), but there was no difference before and after TIPS between the two groups ($P = 0.447$, $P = 0.605$, respectively) (Table 2).

The primary patency rate for group A was 97.6% at 3 mo, 88.6% at 6 mo, 84.3% at 9 mo, 69.4% at 12 mo, 51.0% at 2 years and 30.6% at 3 years. In group B, the patency rate was 88.1% at 3 mo, 78.7% at 6 mo, 68.1% at 9 mo, 45.1% at 12 mo, 26.4% at 2 years and 12.5% at 3 years. Compared with the two groups, there were significant statistical differences at the time 3 mo, 6 mo, 9 mo, 12 mo, 2 year and 3 year ($P = 0.006$, $P = 0.011$, $P = 0.023$, $P = 0.032$, $P = 0.037$, $P = 0.028$, respectively). The median patency time of the total 3 years was 12 mo in group A (95% confidence interval (CI): 10-14) and 4 mo in group B (95%CI: 3-6), and a significant difference was observed in stent dysfunction times between groups A and B ($P = 0.009$, log-rank test) (Table 3).

Table 1 Demographic characteristics of the patients

Characteristics		Groups		*P* value
		A	B	
n	486	289	197	0.614
Gender	Male	148	108	0.715
	Female	141	89	
Age in yr		36.25 ± 15.43	35.20 ± 14.14	0.710
Etiology	Hepatitis B	184	131	0.743
	Hepatitis C	51	32	
	Ethanol consumption	34	26	
	Cryptogenic hepatitis	10	8	
Child-Pugh score	A	37	21	0.584
	B	213	153	
	C	35	27	
Model for end-stage liver disease score		9.49 ± 2.05	9.35 ± 1.99	0.508
Variceal bleeding	365	215	150	0.329
Refractory ascites	121	76	45	0.672
Both variceal bleeding and refractory ascites	86	52	34	0.481
Laboratory tests				
Alanine transaminase as U/L		59.34 ± 11.41	63.05 ± 10.17	0.742
Aspartate transaminase as U/L		72.36 ± 12.09	68.45 ± 13.23	0.689
Alkaline phosphatase as U/L		193.43 ± 24.62	208.49 ± 32.54	0.893
Total bilirubin as μmol/L		14.03 ± 5.15	16.21 ± 4.28	0.754
Albumin as g/L		31.29 ± 1.46	29.19 ± 1.48	0.431
Prothrombin time in s		14.72 ± 3.28	15.43 ± 3.17	0.638
Platelet count as × 10^9/L		45.27 ± 12.38	38.39 ± 13.47	0.374
Clinical presentation				
Abdominal distention		146	85	0.243
Abdominal pain		78	49	0.217
Weakness		46	37	0.158
Poor appetite		163	117	0.362
Jaundice		42	29	0.293
Lower limbs edema		32	24	0.675
Endoscopic therapy		538	372	0.427
Ascites paracentesis		227	147	0.489

Total shunt malfunction occurred 378 times of 289 patients in group A and 419 times of 197 patients in group B. There was a significant difference in stent dysfunction times between groups A and B (P = 0.006, log-rank test). The patients with stent dysfunction underwent balloon dilation. After stent revision, their symptoms disappeared.

Incidence of recurrent bleeding (Table 4) and ascites (Table 5) in group B was higher than in group A at 3 mo (14.6% *vs* 5.1%, $P \leq 0.001$; 16.7% *vs* 5.9%, P = 0.001), 6 mo (25.7% *vs* 9.8%, P = 0.003; 24.3% *vs* 10.2%, P = 0.005), 9 mo (29.8% *vs* 15.3%, P = 0.005; 35.4% *vs* 20.0%, P = 0.012), 12 mo (39.6% *vs* 20.0%, P = 0.008; 43.8% *vs* 34.1%, P = 0.024), 2 years (45.1% *vs* 29.0%, P = 0.011; 39.6% *vs* 27.8%, P = 0.018) and 3 years (59.7% *vs* 40.0%, P = 0.016; 56.3% *vs* 40.8%, P = 0.017).

The median time to recurrent bleeding was 10 mo in group A (95%CI: 8-12) and 5 mo in group B (95%CI: 4-7). The median time to recurrence of ascites was 11 mo in group A (95%CI: 6-16) and 16 mo in group B (95%CI: 12-19). There were significant differences in median time to recurrent bleeding and ascites between the two groups (P = 0.009, $P \leq 0.001$, log-rank test).

During the 3-year follow-up, the 1-year survival rate was 92.9% *versus* 85.4%, 2-year survival rate was 83.9% *versus* 68.1%, and 3-year survival rate was 69.4% *versus* 56.3% in group A and group B. Compared with group B, the 1-, 2-, and 3–year survival rates

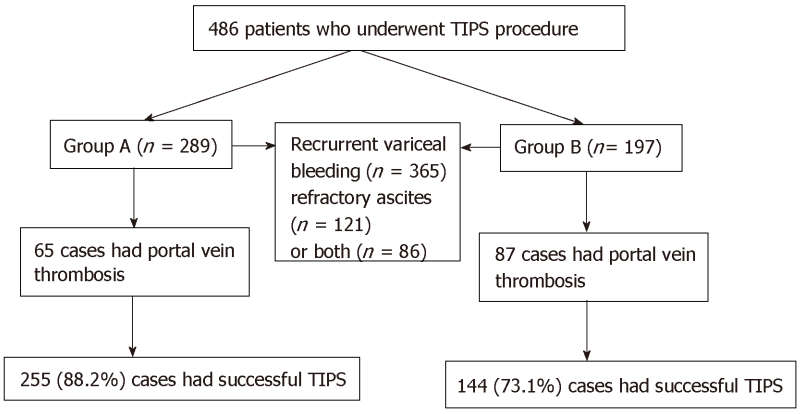

Figure 1 Distribution of patients. There were 289 patients with no prior splenectomy in group A and 197 patients with cirrhosis who underwent splenectomy in group B. In group A, 65 cases had portal vein thrombosis. In group B, portal vein thrombosis was seen in 87 cases. TIPS: Transjugular intrahepatic portosystemic shunt.

in group A were longer (P = 0.008, P = 0.021 and P = 0.011, respectively) (Table 6) (Figure 3).

HE occurred in 70 patients in group A and in 35 patients in group B during follow-up with an incidence of 27.5% and 24.3%, respectively. There were no significant differences between the groups (P = 0.527). After drug treatment, the symptoms disappeared in patients with grade overt and grade II of HE. In patients with grade III and grade IV of HE, the symptoms disappeared after 18 stents were implanted for shunt reduction.

DISCUSSION

Portal hypertension is a consequence of liver cirrhosis; the mechanisms by which it develops are complicated and associated with changes in the vascular architecture of the liver due to fibrosis and regenerative nodules[14]. Surgical treatments have been designed to prevent many complications. Currently, SPD is the most commonly used method in China[15]. SPD is one of the common treatment methods for patients with cirrhosis with portal-hypertension-related complications and hypersplenism[16] and can correct hypersplenism and reduce PV blood flow and pressure within a short period of time[17].

However, the availability of many treatment methods suggests that no one in particular yields entirely satisfactory outcomes for all patients or in all clinical situations[18]. Splenectomy in patients with portal hypertension does not resolve the risk of PVT, and it can further aggravate portal hypertension, cause PVT, increase the probability of rebleeding and ultimately affects quality of life[19,20]. In the study of resection of spleen, reduction of portal venous pressure depends on the splenic venous blood reflux and portal venous shunt. Resection of the communicating branches from the splenic hilus will cause increased portal venous pressure and portal venous thrombosis.

The incidence of PVT is mostly 12%-72% after splenectomy or SPD, and the risk factors for PVT after splenectomy have been studied[21,22]. Patients with portal hypertension were seeking TIPS treatment in our center. However, it has been found that the probability of PVT is significantly increased after splenectomy. This highlights the difficulties in the TIPS procedure, and it also affects the patient prognosis and the effect of liver transplantation. We found that the total incidence of PVT after splenectomy was 44.2%, which was higher in the splenectomy group than that in the group without splenectomy.

TIPS creation has been widely used in the treatment of patients with esophageal and gastric variceal bleeding secondary to portal hypertension and has achieved good results[23,24]. With the improvement of procedure methods and instruments, the incidence of complications after TIPS has greatly decreased. Although being effective in preventing such syndromes, TIPS may cause shunt stenosis or occlusion leading to shunt failure. Stent stenosis and occlusion are the main complications of TIPS placement and cause recurrent bleeding and ascites[25].

There are multiple causes of thrombosis after splenectomy. It is believed that splenectomy reduces synthesis of coagulation factors in patients with liver cirrhosis,

Table 2 Clinical characteristics of the patients

Characteristics	Group	*n*	Portal vein thrombosis		Portal vein thrombo-sis rate	χ^2	*P* va-lue
			Yes	No			
Portal vein thrombosis	A	289	65	224	11.0	25.60	0.003
	B	197	87	110	44.2		
			TIPS success		TIPS success rate (%)		
			Yes	Not			
TIPS	A	289	255	34	88.2	19.28	0.016
	B	197	144	53	73.1		
Portosystemic gradient (mmHg) Pre-TIPS	A	255	32.43 ± 6.64				0.447
	B	144	31.90 ± 4.63				
Portosystemic gradient (mmHg) Post-TIPS	A	255	11.15 ± 1.20			0.027	0.60
						0.025	

TIPS: Transjugular intrahepatic portosystemic shunt.

and the scavenging activity of tissue plasminogen activator is decreased resulting in a high blood coagulation state[26]. In addition, the risk of PVT after splenectomy can be caused by lack of microcirculation, increased blood viscosity, blood stasis induced by splenic vein stump, decreased blind pouch postoperative PV pressure, slower blood flow and platelet count[27,28]. The presence of these factors can lead to the formation of PVT and have a continuous impact on the PV system despite treatment with TIPS. It is also easy to cause thrombosis in the TIPS shunt and PV system and to cause stenosis or occlusion of the TIPS shunt, and these factors promote each other.

PVT can develop in the trunk of the PV, including its right and left intrahepatic branches, or it can originate everywhere in the portal system and may even extend to the splenic or superior mesenteric veins or towards the liver involving the intrahepatic PV branches[29]. PVT leads to portal hypertension and cavernous transformation of the PV, which causes difficulty with TIPS creation[30]. Although TIPS has good therapeutic effects on the formation of PVT, the effect of PVT on TIPS stenting is rarely reported.

In our study, the incidence of PVT in group A was lower than in group B, and the success rate of TIPS placement was also higher in group A. Our results indicated that PVT easily forms after splenectomy as described previously, and it creates difficulty for treatment with TIPS and other methods. The patency rate after TIPS in group A was higher than in group B, the median unassisted patency time in group A was longer than in group B, and recurrent bleeding and ascites in group A were less than in group B. Our results confirmed that prior splenectomy is an important determinant of shunt patency.

It is reported[31] that after TIPS treatment, hypersplenism is relieved due to decreased PV pressure and splenic blood flow, which can improve quality of life. However, there are still some patients with hypersplenism with no satisfactory outcome of treatments, including partial splenic arterial embolization, which can improve the symptoms of hypersplenism[32,33]. In patients with cirrhosis who are prone to PVT, which can lead to difficulty with TIPS creation and stent stenosis or occlusion, we suggest that splenectomy should be considered carefully.

The present study has some limitations. TIPS was established by the left branch of the intrahepatic PV, which may affect the results of patency rate. This is only a retrospective study. Randomized controlled trials are needed to verify our results.

In conclusion, patients with portal hypertension with prior splenectomy had a high incidence of PVT, which is an important determinant of TIPS stent patency and potentially increases the risk of recurrent symptoms associated with shunt stenosis or occlusion. Patients with portal hypertension have the opportunity to avoid splenectomy if they are undergoing TIPS treatment.

Table 3 Clinical characteristics of the patients in stent primary patency rate

Time	Group	Patency		Patency rate, %	χ^2	*P* value
		Yes	Not			
3 mo	A	249	6	97.6	15.18	0.006
	B	127	17	88.1		
6 mo	A	226	29	88.6	10.34	0.011
	B	109	35	75.7		
9 mo	A	215	40	84.3	14.24	0.023
	B	98	46	68.1		
12 mo	A	177	78	69.4	25.93	0.032
	B	65	79	45.1		
2 yr	A	130	125	51.0	22.75	0.037
	B	38	106	26.4		
3 yr	A	78	177	30.6	21.39	0.028
	B	18	126	12.5		
		Median stent patency in mo	Four quantile spacing in mo			
Total	A	12	(10, 14)			0.001

Table 4 Clinical characteristics of the patients in recurrent bleeding rate

Time	Group	Bleeding		Recurrence of bleeding, %	χ^2	*P* value
		Yes	No			
3 mo	A	13	242	5.1	12.13	≤ 0.001
	B	21	123	14.6		
6 mo	A	25	230	9.8	19.53	0.003
	B	37	107	25.7		
9 mo	A	39	216	15.3	13.18	0.005
	B	43	101	29.8		
12 mo	A	51	204	20.0	20.90	0.008
	B	57	87	39.6		
2 yr	A	74	181	29.0	12.10	0.011
	B	65	79	45.1		
3 yr	A	102	153	40.0	16.20	0.016
	B	86	58	59.7		
		Median recurrent bleeding in mo	Four quantile spacing in mo			
Total	A	10	(8, 12)			
	B	5	(4, 7)			≤ 0.001

Table 5 Clinical characteristics of the patients in recurrence of ascites

Time	Group	Ascites		Recurrence of ascites, %	χ^2	*P* value
		Yes	No			
3 mo	A	15	240	5.9	9.82	0.001
	B	24	120	16.7		
6 mo	A	26	229	10.2	16.15	0.005
	B	35	109	24.3		
9 mo	A	51	204	20.0	12.16	0.012

	B	51	93	35.4			
12 mo	A	87	168	34.1	4.50	0.024	
	B	63	81	43.8			
2 yr	A	71	184	27.8	6.56	0.018	
	B	57	87	39.6			
3 yr	A	104	151	40.8	10.02	0.017	
	B	81	63	56.3			
		Median recurrent of ascites in mo		Four quantile spacing in mo			
Total 3 yr	A	11		(6, 16)			0.009
	B	16		(12, 19)			

Table 6 Clinical characteristics of the patients in survival rate and incidence of hepatic encephalopathy

Characteristics	Group	Survival		Survival rate, %	χ^2	*P* value
		Yes	No			
1 yr	A	237	18	92.9	6.98	0.008
	B	123	21	85.4		
2 yr	A	214	41	83.9	14.362	0.021
	B	98	46	68.1		
3 yr	A	177	78	69.4	7.701	0.018
	B	81	63	56.3		
		HE		Morbidity, %		
		Yes	Not			
HE	A	70	185	27.5	0.40	0.527
	B	35	109	24.3		

HE: Hepatic encephalopathy.

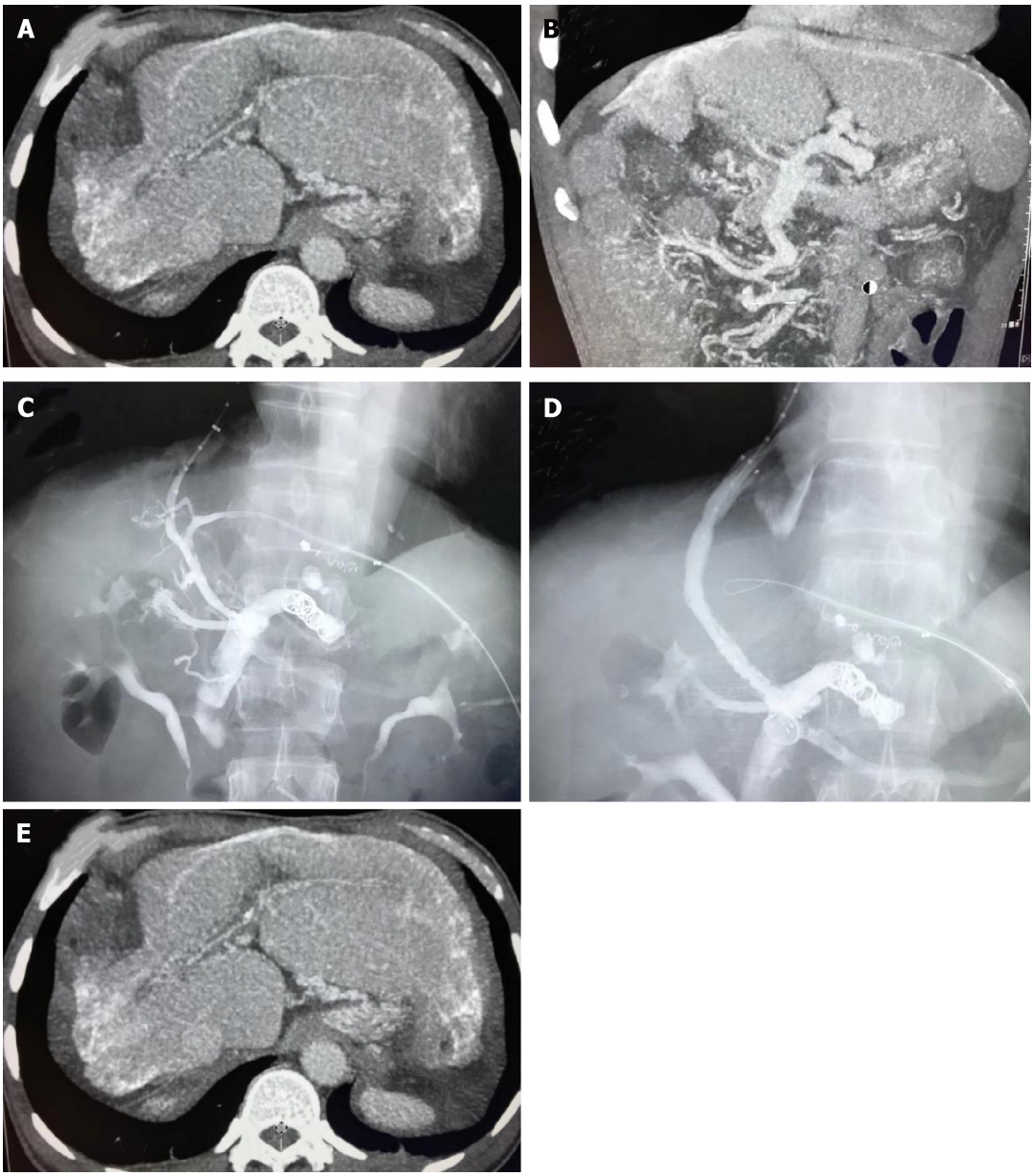

Figure 2 Decompensative liver cirrhosis and portal vein thrombosis treated with transjugular intrahepatic portosystemic shunt. A 67-year-old female with decompensative liver cirrhosis and portal vein thrombosis caused by Schistosoma was treated with transjugular intrahepatic portosystemic shunt. A, B: The right lobe of the liver atrophied, and the left lobe of the liver was compensatory. Calcified hepatic portal vein, portal vein thrombosis and occlusion of the main portal vein and the collateral circulation formed; C-E: Transjugular intrahepatic portosystemic shunt was performed through the collateral vessels of the hepatic portal vein, which decreased the pressure of portal vein and the collateral vessels were embolized by coils (arrows).

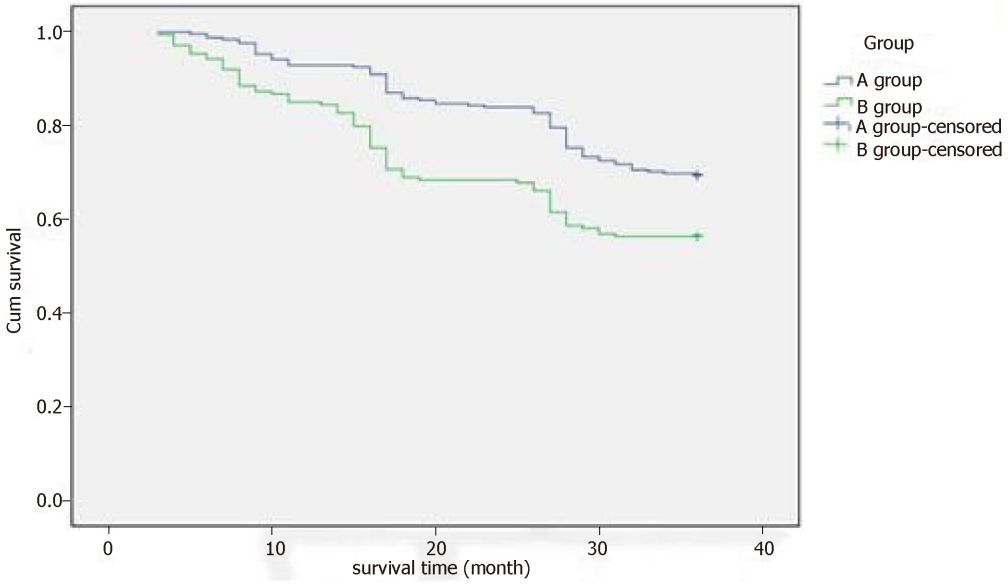

Figure 3 Survival time. During a 3-year follow-up, the 1-year (92.9% *vs* 85.4%), 2-year (83.9% *vs* 68.1%) and 3-year (69.4% *vs* 56.3%) survival rates in group A were higher than in group B.

ARTICLE HIGHLIGHTS

Research background

Splenectomy with pericardial devascularization (SPD) without liver transplantation has been widely accepted for the treatment of cirrhosis in patients with variceal bleeding and secondary hypersplenism in China. However, when compared with other treatments, simple splenectomy and SPD are associated with an increased incidence of postoperative complications, such as portal vein thrombosis (PVT). Transjugular intrahepatic portosystemic shunt (TIPS), as an alternative to surgery, is now commonly used for management of complications of portal hypertension. Patients with SPD had a high incidence of PVT, which can markedly affect TIPS stent patency and increase the risk of recurrent symptoms associated with shunt stenosis or occlusion.

Research motivation

SPD is one of the common treatment methods used in China for patients with cirrhosis and portal-hypertension-related complications and hypersplenism. It can correct hypersplenism and reduce PV blood flow and pressure within a short period of time. However, it may aggravate the portal hypertension, cause PVT, increase the probability of rebleeding and ultimately affects quality of life. In this study, we evaluated the incidence of PVT after splenectomy and its influence on the patency rate of TIPS in patients with cirrhosis and portal hypertension.

Research objectives

The main objective of this study was to investigate the effects of high incidence of PVT in patients with portal hypertension and prior SPD on the TIPS stent patency and the risk of recurrent symptoms associated with shunt stenosis or occlusion.

Research methods

We conducted a retrospective study to compare the incidence of PVT before TIPS for patients without prior SPD (group A) and those with prior SPD (group B). After TIPS placement, primary patency rate was compared using Kaplan-Meier analysis at 3, 6, 9 and 12 mo, and 2 and 3 years. The clinical outcomes were analyzed. Results are expressed as mean ± SD. Patency time was calculated using the Kaplan-Meier method, and the median time was compared by means of the log-rank test. Logistic regression analysis was performed on the variables. The differences between the groups were compared using one-way analysis of variance followed by least significant difference *t* tests. Differences were considered significant at $P < 0.05$. The statistical analysis was performed with SPSS version 20.0 (SPSS, Chicago, IL, United States).

Research results

The incidence of PVT in group B was higher than in group A, and the difference was significant between the two groups ($P = 0.003$). The success rate of TIPS in group A was higher than in group B, and the primary patency rate in group A tended to be higher than in group B at 3, 6, 9 and 12 mo, 2 years and 3 years. Recurrence of bleeding and ascites rate in group A were lower

than in group B at 3 mo, 6 mo, 9 mo, 12 mo, 2 years and 3 years. During the 3-year follow-up, the 1-, 2- and 3-year survival rates in group A were higher than in group B, but there was no difference of the incidence of hepatic encephalopathy.

Research conclusions

Patients with a SPD have a high incidence of PVT, which potentially increases the risk of recurrent symptoms associated with TIPS stenosis or occlusion.

Research perspectives

This study showed that patients with portal hypertension with prior splenectomy had a high incidence of PVT, which is an important determinant of TIPS stent patency and potentially increases the risk of recurrent symptoms associated with shunt stenosis or occlusion. Patients with portal hypertension may avoid splenectomy when they are undergoing TIPS treatment. However, this is only a retrospective study, and randomized controlled trials are needed to verify our results.

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ORIGINAL ARTICLE

Observational Study

Multiplex gene expression profile in inflamed mucosa of patients with Crohn's disease ileal localization: A pilot study

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Author contributions: Giudici F and Lombardelli L equally contributed to this work. Malentacchi C and Piccinni MP conceived the study. Giudici F, Cavalli T, Zambonin D and Bargellini T collected the samples. Lombardelli L, Logiodice F, Kullolli O, Russo E and Giusti L performed the experiments. Lombardelli L and Clemente AM performed the statistical analysis.

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Abstract

BACKGROUND

Crohn's disease (CD) is a complex disorder resulting from the interaction of genetic, environmental, and microbial factors. The pathogenic process may potentially affect any segment of the gastrointestinal tract, but a selective location in the terminal ileum was reported in 50% of patients.

AIM

To characterize clinical sub-phenotypes (colonic and/or ileal) within the same disease, in order to identify new therapeutic targets.

METHODS

14 consecutive patients undergoing surgery for ileal CD were recruited for this

Torcia MG and Piccinni MP partecipated in the writing of the study protocol and in the revision of the manuscript for important intellectual content with Ficari F, Tonelli F, Biancone L, Fazi M, Scaringi S and Delfino G. Perissi E and Russo E edited the manuscript. Malentacchi C, Giudici F, Russo E, Piccinni MP wrote the manuscript. Malentacchi C and Russo E provided funding acquisition. All authors read, commented, and approved the final manuscript.

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study. Peripheral blood samples from each patient were collected and the main polymorphisms of the gene *Card15/Nod2* (R702W, G908R, and 1007fs) were analyzed in each sample. In addition, tissue samples were taken from both the tract affected by CD and from the apparently healthy and disease-free margins (internal controls). We used a multiplex gene assay in specimens obtained from patients with ileal localization of CD to evaluate the simultaneous expression of 24 genes involved in the pathogenesis of the disease. We also processed surgery gut samples with routine light microscopy (LM) and transmission electron microscopy (TEM) techniques to evaluate their structural and ultrastructural features.

RESULTS
We found a significant increase of Th17 (IL17A and IL17F, IL 23R and CCR6) and Th1 (IFN-γ) gene expression in inflamed mucosa compared to non-inflamed sites of 14 CD patients. *DEFB4* and *HAMP*, two genes coding for antimicrobial peptides, were also strongly activated in inflamed ileal mucosa, suggesting the overwhelming stimulation of epithelial cells by commensal microbiota. IFN-γ and CCR6 were more expressed in inflamed mucosa of CD patients with ileal localization compared with patients with colonic localization suggesting a more aggressive inflammation process in this site. Morphological analysis of the epithelial lining of Lieberkün crypts disclosed enhanced release activity from goblet mucocytes, whereas the *lamina* propria contained numerous cells pertaining to various lines.

CONCLUSION
We observed that the expression of ileal genes related to Th1 and Th17 activity is strongly activated as well as the expression of genes involved in microbiota regulation.

Key words: Crohn's disease; Ileum; Colon; Messenger ribonucleic acid; Th1/Th17; Microbiota; Inflammation

Core tip: Multiplex Gene Assay in specimens obtained from patients with ileal localization of Crohn's disease (CD) allowed the simultaneous analysis of messenger ribonucleic acid levels for 24 genes, known to be involved in the inflammation processes of CD pathogenesis. The result showed that the expression of genes related to Th1 and Th17 immune response is strongly activated as well as the expression of genes deputized to interact with the commensal microbiota, such as DEFB4 and HAMP, which code for antimicrobial peptides.

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INTRODUCTION

The pathogenesis of Crohn's disease (CD), one of the major inflammatory bowel diseases (IBD) together with ulcerative colitis (UC), has been extensively investigated. It is generally accepted that both genetic and environmental factors contribute to the etiology of the disease. In CD patients, strong associations between genes involved in maintaining intestinal barrier function, epithelial anti- microbial defence, innate immune regulation, reactive oxygen species (ROS) generation, autophagy, and metabolic pathways have been identified[1,2].

Environmental risk factors involved in the progression of the disease include

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smoking, low-fiber and high-carbohydrate diet, gut microbiota (GM) alteration, and treatments with antibiotics or non-steroidal anti-inflammatory drugs[3].

CD is characterized by a transmural inflammation which can potentially affect any segment of the gastrointestinal tract[4]. However, recent studies reported a selective location in the terminal ileum in 50% of the patients and location in the colonic district in 20% of the patients. Ileum and colon district were involved in the remaining 30% of the patients. A different clinical course and surgical requirement was reported according to disease's localization but currently the reasons underlying the differences in the clinical course have not been defined. In addition, the immunological pathways involved in colonic inflammation are different from those involved in ileal inflammation[5].

The mutual interplay between GM and the immune system is involved in the pathogenesis and prognosis of intestinal diseases[6] as the GM is a key modulator of intestinal inflammation[7]. In CD patients, a reduced GM diversity and lower bacterial load in inflamed *vs* non-inflamed tissues was observed[8]. In addition, several evidences report that the small bowel is responsible for the systemic tolerance towards microbes. A recent study revealed that the ileum harbors a distinctive niche of the GM that differs more from the colonic[9]. This different GM composition could be attributed to the activation of distinctive immunological pathways.

In the present study, we used the multiplex gene assay[10,11] to analyze surgical specimens of CD patients with prevalent ileal localization.

MATERIALS AND METHODS

Patients

14 consecutive patients undergoing surgery for ileal CD aged 15 to 57 and hospitalized at the Surgery Unit of Azienda Ospedaliero-Universitaria Careggi, University of Florence, were recruited (Table 1). CD was diagnosed based on both histological and clinical/endoscopic criteria. Table 1 reports the clinical characteristics of the patients.

Peripheral blood samples from each patient were collected in EDTA tubes and genomic DNA was extracted using QIA-AMP DNA Blood Maxi Kit (Qiagen GmbH, Hilden, Germany). The main polymorphisms of the gene *Card15/Nod2* (R702W, G908R, and 1007fs) were analysed in each sample[12].

mRNA extraction and multiplex Gene Assay

Tissue samples were taken both from the tract affected by CD and from the apparently healthy and disease-free margins (internal controls). The surgical specimens were opened longitudinally.

All samples were stored in RNA later (Qiagen, Germany) before homogenization. Then each sample was weighed and the appropriate lysis solution was added to a final volume of 150 μL containing 50% Lysis Mixture (Thermo-Fisher, MA, United States) and 1 g/L proteinase. The mixture was agitated for 30 min at 65 °C to lyse the cells. The lysate was stored at -80 °C for later use. We used a microarray panel of 24 genes implicated in CD etiopathogenesis[10]. We evaluated the expression of these genes in both non-inflamed and inflamed ileal biopsies. Table 2 indicates the panel of the examined genes, the number of Mendelian Inheritance in Man (MIM) (used as a reference), accession number and their corresponding encoded product and function. To improve the analysis of the results, the selected genes were divided into four groups according to their biological role: (1) Transport across epithelia: *ABCB1*, *SLC40A1*, *SLC22A4*, *SLC22A5*, *HAMP*; (2) Immune response: *CCR6*, *IL*-17F, IL-*17A*, *MICA*, *MYD88*, *STAT3*, *IL-23R*, *JAK2*, *IFNG*, *NOD2;* (3) Antimicrobial activity: *HAMP*, *CAMP*, *LRRK2*.*DEFB4*; and (4) Physiological activities: *STAT3*, *ESR1*, *LRRK2*, *TNFSF15*, *CARD14*, *DLG5 BMP2 ATG16L1*.

The messenger ribonucleic acid (mRNA) expression for *CCR6*, *IL-17A*, *IL-17F*, *BMP2*, *TNFSF15*, *ABCB1*, *IL-23R*, *DEFB4*, *CARD14*, *STAT3*, *SLC40A1*, *JAK2*, *SLC22A5*, *ACTB*, *ATG16L1*, *CAMP*, *DLG5*, *ESR1*,*CARD15*, *MICA*, *MYD88*, *SLC22A4*, *IFN-γ*, *LRRK2*, *HAMP*, *ACTB* (high expression housekeeping gene), *HPTR1* (low expression housekeeping gene) was measured using the QuantiGene® Plex assay (Thermo-Fisher, MA, United States).

A panel of oligonucleotide capture probes was covalently linked to carboxylated fluorescently encoded beads (Luminex, Bio-Rad, MA, United States). Each probe has a unique sequence of 15 bases. Each sample lysate diluted at 1:1 and 1:2 was mixed with the pooled capture beads in a round-bottom assay well and hybridized for 16 h at 54 °C (final volume in each well was 100 μL). The assay mixture was moved to a MultiScreen® Filter Plate (Millipore, Billerica, MA, United States) and unbound

Table 1 Clinical characteristics of patients with ileal Crohn's disease

Patient	Pt1	Pt2	Pt3	Pt4	Pt5	Pt6	Pt7	Pt8	Pt9	Pt10	Pt11	Pt12	Pt13	Pt14
Localization of CDa	L1	L1	L1	L1	L1	L1	L3	L1	L3	L1	L3-L4	L1	L3	L1
Age of CD onset (yr)	57	15	53	55	25	31	39	42	16	24	19	18	46	30
Surgery / relapse	1st surgery	1st surgery	Relapse	1st surgery	Relapse	Relapse	Relapse	1st surgery	Relapse	Relapse	Relapse	Relapse	Relapse	1st surgery
Disease behaviorb	B2	B2, B3	B2	B3	B2, B4	B2	B3	B2	B2	B2	B2	B2	B3	B2
Therapyc	C, F, I, B	F, C	C	No	F, C, I	C, F, I	I, B	F, C	C, I, F, B	C	F, C, B	F, C, I	C, F, B, I	F, C, I
Smoking statusd	No	Cur 20/15.5	No	No	1010	No	No	20/30	1010	Cur 10	1020	No	No	No
Genotype	wt	R702	wt	hzG881R	wt	wt	wt	wt	hzG881R	R702	No seq	No seq	wt	wt

Localization of Crohn Disease: L1: terminal ileum; L2: colon; L3: ileum colon; L4: upper G (gastrointestinal); Disease behavior: B1: non-stricturing, non-penetrating; B2: stricturing; B3: penetrating; B4: perianal disease. Therapy: M: mesalazine; I: immunosuppressant; B: biologics; C: corticosteroids; Ab: antibiotics. Smoking status: No: non-smoker; Ex: ex-smoker; Cur: current smoker, no. cigs per day / no. yr. MIM: Mendelian inheritance in Man. 1: Transport across epithelia; 2: Immune response; 3: Antimicrobial activity; 4: Different physiological activities.

material was filter-washed from the wells by rinsing 3 times with wash buffer. The plate was hybridized with 100 μL/well of bDNA amplifier in Amplifier Diluent (Panomics, CA, United States) at 54 °C for 1 h. After the plate was filter- washed twice with wash buffer and incubated at 50 °C for 1 h with 100 μL/well of 5'-dT(Biotin)-conjugated label probe (Panomics, CA, United States) diluted in Label Probe Diluent (Panomics, CA, United States). After 2 washes, streptavidin-conjugated R-phycoerythrin diluted in SA-PE diluent (20 mmol/L Tris-HCl, 400 mmol/L lithium chloride, 1 mL/L Tween 20, 1 mL/L bovine serum albumin, and 5 mL/L Micr-O-protect) was added and the plate was shaken and incubated at room temperature for 30 min. We washed the beads to remove unbound SA-PE and then evaluated them with Bio-Plex® 200 system (Bio-Rad, MA, United States). The SA-PE fluorescence measured from each bead was proportional to the number of mRNA transcripts captured by the beads. Expression of target-specific RNA molecules was calculated as the mean values from triplicate cultures and normalized against *Actin* gene (high expression housekeeping gene).

Polymorphism analysis

A standard non-enzymatic method, using the QIA-AMP® DNA Blood Maxi Kit (Qiagen GmbH, Hilden, Germany) was used to extract Genomic DNA from peripheral blood leucocytes of all CD patients and healthy controls. In addition, DNA samples from 70 healthy Caucasian subjects (140 alleles) were analysed as controls. Three exon of the *CARD15/NOD2* gene (Exon 4, Exon 8, Exon 11), were amplified by PCR using pairs of primers derived from the published sequence of the gene (available upon request). Each exon is associated with the three main single-nucleotide polymorphisms (SNPs) (R702W-C2104T; G908R-G2722C; 1007fs-3020insC). These three main variants, associated with susceptibility to CD, represented 32%, 18%, and 31%, respectively, of the total CD mutations[13-15].

The BigDye® Terminator Cycle Sequencing kit (Applied Biosystems, CA, United States) was used to perform direct sequencing of PCR amplified products (SNPs rs87950, rs127951, and rs137955) of the *CARD15/NOD2* gene. The samples were analysed in an ABI Prism® 310 genetic analyzer (Applied Biosystems, CA, United States). The of the sequences were confirmed with the analysis of newly-amplified fragments and the sequencing of both DNA strands.

Statistical analysis

SSPS software vers. 10 (SPSS Inc., IL, United States) was used to perform the statistical analysis. All comparisons of genes mRNA expression in tissues (non-inflamed and inflamed areas) were performed by non-parametric assay (Mann-Whitney test, Wilcoxon test). Data are reported as mean and ranges unless otherwise stated. A P-value < 0.05 was accepted as statistically significant. Furthermore, to better characterize the different clinical CD phenotypes, we compared the results regarding the *CARD15*, *CCR6*, interferon gamma, and *IL-17A* genes to colonic CD patients previously examined for these same genes.

Table 2 Panel of the 24 genes investigated

Symbol	Complete name	Group	Accession number	mim	Gene product function (s)	Ref.
HPRT1	Hypoxanthine phosphoribosyltransferase 1	Low expression housekeeping gene	M26434	308000	It plays a central role in the generation of purine nucleotides, chosen as a low expression housekeeping gene	[39]
ACTB	Actin betaprovided	High expression housekeeping gene	M28424	102630	Is involved in the cell motility, structure, and integrity	[40]
SLC40A1	Solute carrier family 40 (iron-regulated transporter), member1	1	AF215636	604653	Exports iron from duodenal epithelial cells	[41]
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member1	1	M14758	171050	Transports various molecules across extra- and intra-cellular membranes. It belongs to a protein sub-family involved in multidrug resistance	[42]
SLC22A5	Solute carrier family 22 (organic cation/carnitine transporter), member 5	1	AF057164	603377	Transports several small organic cations in the liver, kidney, intestine. It is involved in elimination of drugs and environmental toxins	[43]
SLC22A4	Solute carrier family 22 (organic cation/ergothioneine transporter), member 4	1	AB007448	604190	Polyspecific transporter of organic cations in the liver, kidney, intestine, and involved in the elimination of these molecules.	[44]
CCR6	Chemokine (C-C motif) receptor6	2	U68030	601835	Induces B-lineage maturation and antigen-driven B-cell differentiation	[45]
IL17A	Interleukin 17A	2	U32659	603149	Produced by Th17-type CD4+ cells. Regulates the activities of NF-kB and mitogen-activated protein kinases	[26]
IL17F	Interleukin 17F	2	AF384857	606496	Produced by Th17-type CD4+ cells. Stimulates the production of other cytokines, including IL6,IL8.It also inhibits angiogenesis by endothelial cells.	[46]
STAT3	Signal transducer and activator of transcription 3 (acute-phase response factor)	2-4	BC014482	102582	Activates transcription of cell growth and apoptosis' genes asresponses to inflammation	[22,47]

MICA	MHC class I polypeptide-related sequence A	2	L14848	600169	Acts as a stress-induced antigen broadly recognized by intestinal intra-epithelial gamma delta T cells.	[48,49]
MYD88	Myeloid differentiation primary response gene (88)	2	U84408	602170	Acts as an essential signal transducer in the interleukin-1 and Toll-like receptor signaling pathways	[50]
IL23R	Interleukin 23 receptor	2	AF461422	607562	Expressed on Th17 cells. Involvedin the IL23A signaling pathways with the receptor molecule IL12RB1/IL12Rbeta1.	[20]
JAK2	Janus kinase 2	2	3717	147796	Is involved in cytokine receptor signaling pathways and is required for responses to gamma interferon	[51]
IFNG	Interferon, gamma	2	3458	147570	It encodes a cytokine with antiviral,immunoregulatory and anti-tumor properties and activates macrophages	[52]
CAMP	Cathelicidin antimicrobial peptide	3	BC055089	600474	It is an antimicrobial protein (defensin)	[53]
CARD15	Nucleotide-binding oligomerization domain containing 2	2	AF178930	605956	Induces immune response to intracellular bacterial by recognizing the muramyl dipeptide (MDP)	[54]
DEFB4	Defensin, beta 4A	3	AJ314835	602215	Acts as an antibiotic peptide locally regulated by inflammation.	[55,56]
HAMP	Hepcidin antimicrobialpeptide	1/2/3	AF309489	606464	It is involved in iron transport, antimicrobial, defence and inflammatory responses	[57,58]
LRRK2	Leucine-rich repeat kinase 2	3/4	AK026776	609007	It is involved in autophagy and implicated in clearance of intracellular bacteria.	[59,60]
TNFSF15	Tumor necrosis facto (ligand) superfamily, member 15	4	AF039390	604052	Induces apoptosis in endothelial cells	[61]
CARD14	Caspase recruitment domain family, member 14	4	AF322642	607211	Regulates the molecular scaffolding process and activates NF-kappa B	[62,63]
ATG16L1	ATG16 autophagy related 16-like 1	4	AK000897	610767	Induces autophagy processes involved in degradation of cell organelles	[64]

ESR1	Estrogen receptor 1	4	X03635	133430	Involved in the metabolic pathway of the hormones and in several diseases including osteoporosis	[65]
BMP2	Bone morphogenetic protein 2	4	650	112261	Induces bone and cartilage formation	[66]
DLG5	Discs, large homolog 5	4	U61843	604090	It encodes for scaffolding molecules involved in cell-cell contact and in the maintenance of epithelial cell integrity. Its products are also involved in the transmission of extracellular signals	[67]

MIM: Mendelian Inheritance in Man. 1: Transport across epithelia; 2: Immune response; 3: Antimicrobial activity; 4: Different physiological activities.

Histological analysis

Once removed, tissue samples were rinsed in 0.1 M, pH 7.0 cacodylate buffer, the same used in prefixation and further steps of histological preparation. Samples were then placed in Karnovsky (1965)[16], aldehyde solution, and after 3 h prefixation (4°C), underwent prolonged washing in the buffer. Surgery specimens were reduced into approximately 20 mm^3 fragments that were post-fixed (1 h 30 min, 4°C) with 1% OsO4 in cacodylate. These specimens were washed in the buffer, dehydrated in graded ethanol series, soaked in propylene oxide, and embedded in Epon 812. Flat blocks were obtained after polymerization, which were reduced into semi-thin sections (1.5 μm thick), using an 8800 ULTROTOME III LKB equipped with glass knives. Semi-thin sections were stained with borax buffered 1% toluidine blue, and observed with a LEITZ DMRB, in order to collect LM digital images (JPG) for structural analysis. Subsequent ultrastructural observations were carried out on ultrathin sections, obtained with an ULTROTOME NOVA LKB, using a DIATOME diamond knife. Ultrathin sections with gold yellow to silver gray interference colour were selected and collected on uncoated 200-300 mesh copper grids to be electron-dense stained with a hydroalcoholic saturated solution (25 mg/mL) of uranyl acetate, followed by alkaline lead citrate (2 mg/mL). These sections where finally observed (80 KV) with a PHILIPS 201 TEM (BIO, UNIFI), and analogic images were collected, which were later acquired and stored as digital TIFF files using a DIMAGE SCAN DUAL (MINOLTA).

RESULTS

Expression of CD susceptibility genes in the inflamed ileum tissue

The simultaneous expression of 24 genes involved in the pathogenesis of CD was studied in surgical specimens from 14 CD patients with ileal localization of disease. The expression of genes in inflamed ileal mucosa was compared to that of non-inflamed ileal sites collected from the same patient. We observed a significant increase in mRNA levels of twelve genes compared to internal control (Figure 1).

Figure 1 shows that genes related to innate immune response (*NOD* 2, *ATG16L1*, *DEFB4*), and to adaptive immune response (*CCR6*, *IL17*A, *IL17F*, *IL23R*, *IFN-γ*) were significantly increased in inflamed mucosa of CD patients compared with non-inflamed sites. Moreover, the levels of mRNA for genes involved in physiological functions of epithelial cells, such as *JAK2*, *TNFSF15*, and *SLC22A4* were higher in inflamed mucosa compared to non-inflamed mucosa and the differences in expression reached statistical significance.

Detection of CARD15 polymorphism

DNA samples obtained from peripheral blood were sequenced to investigate the presence of polymorphisms of *CARD15/NOD2* gene. The results of this analysis showed that four patients (28.5%) included in this study are carriers of at least one of the polymorphisms investigated, suggesting that genetic factors might contribute to the dysregulated expression of *CARD15/NOD2* gene[17-19].

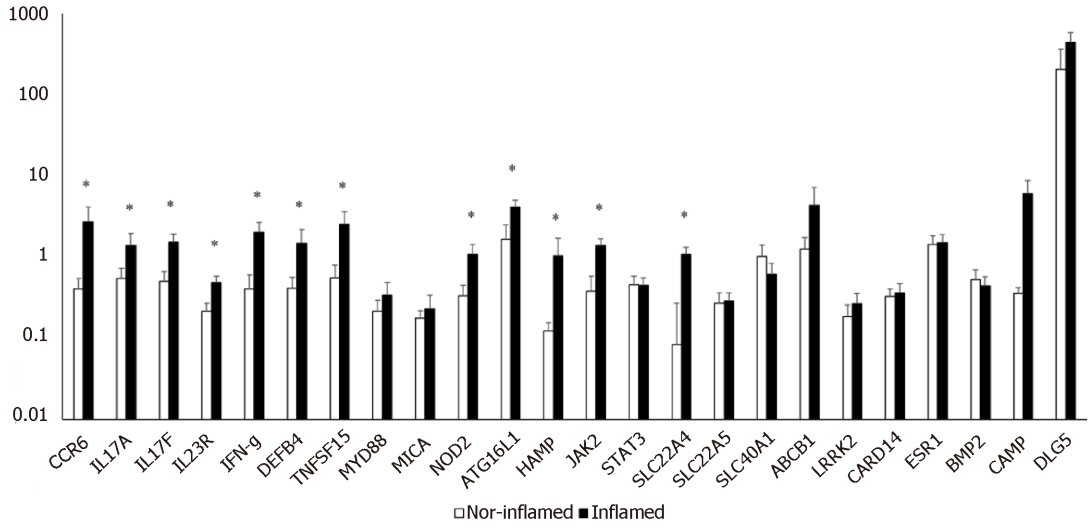

Figure 1 Quantitative evaluation of gene expression using multiplex gene assay in surgical ileum specimens of CD patients. The abscissa shows the genes evaluated in inflamed and not inflamed tissue; the axis of the ordinates shows the value of expression of the gene normalized to the housekeeping actin (gene/β actin ratio). The first seven genes are more closely related to immunity. *P* value is reported only when statistically significant ($P < 0.05$).

Morphological analysis

In order to observe the morphology of inflamed tissue samples, light microscopy (LM) and TEM micrographs were obtained. Both gut wall and Lieberkühn crypts retain usual features in both lining epithelium and *lamina propria*. Epithelial cells consist of constitutive enterocytes along with goblet mucocytes, whereas the underlying connective tissue contains large amounts of cells with wide morphological variety (Figure 2). Goblet cells are involved in impressive secretory processes, releasing a moderately opaque product into cryptal and gut lumen through gaps between enterocytes apices (Figure 3). As a consistent pattern, the lamina propria contains granulocytes and plasma cells.

DISCUSSION

Among the numerous genes that have been studied so far with respect to CD, strong and replicated associations have been identified with *NOD2*, *IL23R*, and *ATG16L1* genes[20]. Environmental factors like smoking, low-fiber and, high-carbohydrate diet, altered GM, and medications such as non-steroidal anti-inflammatory drugs interact with genetic background and induce abnormal inflammation and dysregulation of the immune response. Clinical symptomatology relates to such dysregulation.

The clinical course of CD is conditioned by several parameters such as disease location, extra-intestinal manifestation, and age at onset[21]. Strictures and fistulas are more frequent in patients with ileal disease, whereas Crohn's colitis remains uncomplicated for many years. On the whole, almost 80% of patients with CD require intestinal surgery, with a permanent stoma required by almost 10%. The presence of selected mutations in the *NOD2* gene (see, *e.g.*, 605956.0001-605956.0003) (IBD1; 266600) has been associated with susceptibility to ileum-localized CD[22]; patients homozygous for the 1007fs mutation had an early disease onset with long-segment ileal stenoses and entero-enteral fistulas; they frequently needed surgical intervention and had a high risk of recurrence[23,24]. Beside *NOD2* gene, huge genome-wide linkage-analyses and meta-analyses have described several CD susceptibility regions including IBD5 locus, DLG5, and autophagy- related 16-like 1 (ATG16L1) gene, JAK2, STAT3 interleukin-23 receptor (IL23R), SLC22A4 and SLC22A5 TNFSF15[14].

In this paper, we evaluated the expression of 24 genes that were associated to CD susceptibility[10]. mRNA was extracted from gut specimens obtained from patients with CD ileal localization of CD, undergoing surgery. We used a multiplex gene assay which directly quantifies the mRNA amounts without need of reverse transcription and gives a detailed picture of the inflammation process for each patient[11]. The same technique was used to quantify gene expression in colonic mucosa from surgical specimens or endoscopic bioptic fragments obtained by CD patients with predominant colonic (L2) location[10].

The analysis revealed a clear activation of immune-adaptive Th17 response in association with a Th1 response in inflamed mucosa of patients undergoing surgery

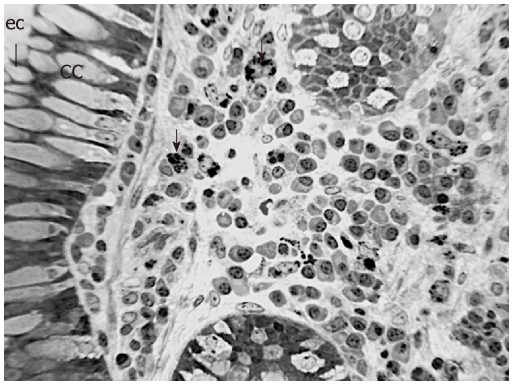

Figure 2 Representative Light microscope (LM) of the lamina propria between Lieberkühn crypts in inflamed ileal tissue of CD patient number 7b. Notice muciparous goblet cells in cryptal epithelium and large amount and variety of immune cells (arrows) in the connective tissue. Semithin (1 μm thick) section, toluidine blue staining; cc = goblet cell, ec = enterocyte. Scale bar (4 cm) = 70 μm.

suggesting a dysregulated and very aggressive immune-inflammatory response.

Here gene expression analysis of inflamed ileal mucosa revealed an increased expression of genes involved in adaptive immune response compared to non-inflamed tissue. In particular, we found a significant increase of *IL17A* and *IL17F*, *IL 23R* and *CCR6* gene expression suggesting an activation of a Th17 adaptive response[25,26] similar to that found in gut mucosa of patients with colonic localization. According with this hypothesis, three additional genes involved in Th17 differentiation as *JAK2*, *STAT3* and *TNFSF15*[27,28] were found to be overexpressed in inflamed ileal mucosa of CD patients compared to non- inflamed sites. Furthermore, as we expected, the expression of the antimicrobial peptides as defensin (DEFB4)[29] and Hepcidin 6 (HAMP)[30] were significantly increased in inflamed mucosa of CD patients compared with non-inflamed sites, suggesting the overwhelming stimulation of epithelial cells by commensal GM. Indeed, while the human β-defensin (HBD) 1 is constitutively expressed, other genes, like HBD2 (gene name DEFB4), show pathogen and/or inflammation dependent upregulation[31] while also being inducible by probiotic bacteria[32]. Conversely, HAMP transcription mediates the effects of host defence and inflammation. Shanmugam *et al*. provided persuasive evidence in support of an important role for the GM composition in influencing hepcidin expression during intestinal inflammation in mouse models of colitis[33].

As the position of the pathogenic tissue may condition not only the clinical course of the disease but also the probability to require surgery, we also compared with the same methodology (Quantigene 2.0) the expression of selected genes (IFN-γ, CCR6, IL17A, NOD2) involved in immune responses in inflamed mucosa with predominant ileal location with the one previously studied[10] in inflamed mucosa with colonic location. mRNA expression for IFN-γ γ and for the chemokine CCR6 appeared significantly higher in ileal site compared to colonic site (ileal CD = 2.7 ± 1.5; colonic CD = 0.2 ± 0.06; P = 0.01). The mRNA for IL-17 and NOD2 appeared to be expressed at higher levels in ileal site compared to colonic site, even if the difference is not statistically significant ($P \geq 0.05$). The significant differences in the expression levels of *IFN*-γ gene (higher expression in specimens from patients with ileal localization compared to patients with colonic localization) may suggest an increased damage of the ileal mucosa due to the simultaneous presence of Th1 and Th17 effector cells and/or the shift of Th17 cells to Th1 effectors functionally more aggressive than Th17 unshifted cells[34,35].

Furthermore, according to a worse clinical course of patient with ileal localization of CD compared with patient with colonic localization[36], the increased expression of IL17 and NOD2 in mucosal fragments from patients with ileal CD compared to patients with colonic CD is in agreement with the NOD2 –dependent regulation of immunity in mouse intestinal tract[37]. We suppose that the above differences between the two gut tracts (ileal and colonic) may be due to the Paneth cells at the bottom of the crypts of Lieberkühn in the small intestine, which produce antimicrobial peptides and hinder commensal GM and pathogenic bacteria to penetrate gut mucosa. Initially described as innate immune cells producing antimicrobial products, Paneth cells have recently been suggested to constitute a cardinal component of the intestinal stem cell niche. In fact, Paneth cells contribute to controlling the luminal flora as well as repairing the intestinal barrier following an insult. Genomic alterations that impede the Paneth cell compartment functionality can potentially increase the propensity to

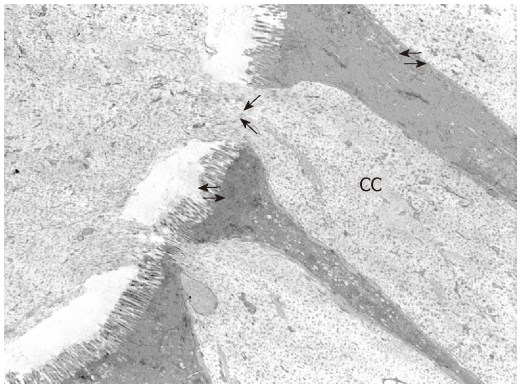

Figure 3 Representative TEM micrograph of Lieberkühn crypt wall and lumen that contains mucous product released (large arrows) by goblet cells (CC) in inflamed ileal tissue CD patient number 7b. Small arrows indicate transport processes involving apical and lateral surfaces of enterocytes. Scale bar (1 cm) = 1 μm.

develop CD[38].

As a consistent trait, cryptal globlet cells produce large amounts of mucus that performs the double role of barrier and holder of antimicrobial products. The microscopic anatomy analysis aims to provide some details that illustrate phenotypic features: the large cell variety in the *lamina propria* includes immune lines that represent a further defense tool. Although these morphological traits are not directly related to specific gene outputs, they illustrate the tissue responses to key gene deregulation.

As a pilot study, our study presents a low number of subjects investigated which may have influenced the statistical power of the results. To confirm these results, studies with a larger number of patients are needed. In addition, gene expression was evaluated with Multiplex Gene Assay only. This method directly quantifies the mRNA amounts without need of reverse transcription and gives a detailed picture of the metabolic processes for each patient but it should be validated by comparisons with additional techniques to evaluate gene expression.

One of the main purposes of our research is therefore to identify new molecules involved in metabolic pathways that could potentially represent new biological drugs to identify the appropriate therapy in relation to the clinical phenotype of the CD patient.

ARTICLE HIGHLIGHTS

Research background

The interplay of environmental, genetic and microbial elements influences the etiopathogenesis of Crohn's disease (CD). Differences in the clinical course of CD have recently been reported in patients with ileal or colonic localization of the inflammatory process.

Research motivation

Aim of this study was to define biochemical and histological differences in intestinal biopsies from patients with ileal or colonic localization of Crohn disease in order to identify new assays which can be useful for planning individual therapeutic strategies

Research objectives

Main objective of the current research was to investigate the expression of genes involved in immune-inflammatory pathways in gut mucosa from patients with ileal or colonic localization of CD and to correlate the results of gene expression with those obtained through a classical morphological analysis of surgical biopsies.

Research methods

A Multiplex Gene Assay was used to assess the simultaneous expression of 24 genes related to immune-inflammatory process and to CD pathogenesis. Structural and ultrastructural features of gut samples were also evaluated through Light microscopy (LM) and Transmission Electron Microscopy (TEM) techniques.

Research results

We observed a strong activation of genes involved in TH-1- and TH-17 immune response in patients with ileal localization of CD compared to patients with colonic localization. In addition, the expression of genes for antimicrobial peptides as DEFB4 and HAMP was found highly stimulated in ileal mucosa from CD patients suggesting a possible interference with microbial

commensals at this site.

Research conclusions

Our results indicate that patients with ileal localization of CD have a stronger activation of TH-1 and TH-17 immune-inflammatory responses compared with patients with colonic localization of the disease thus defining a clear subclinical phenotype of CD.

Research perspectives

These results may suggest that therapeutic strategies with biological drugs in CD patients can be differentiated depending on the location of the disease

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ORIGINAL ARTICLE

Prospective Study

Analysis of the postoperative hemostatic profile of colorectal cancer patients subjected to liver metastasis resection surgery

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Abstract

BACKGROUND

Liver resection surgery has advanced greatly in recent years, and the adoption of fasttrack programs has yielded good results. Combination anesthesia (general anesthesia associated to epidural analgesia) is an anesthetic-analgesic strategy commonly used for the perioperative management of patients undergoing surgery of this kind, though there is controversy regarding the coagulation alterations it may cause and which can favor the development of spinal hematomas.

AIM

To study the postoperative course of liver resection surgery, an analysis was made of the outcomes of liver resection surgery due to colorectal cancer metastases in our centre in terms of morbiditymortality and hospital stay according to the anesthetic technique used (general *vs* combination anesthesia).

METHODS

A prospective study was made of 61 colorectal cancer patients undergoing surgery due to liver metastases under general and combination anesthesia between January 2014 and October 2015. The patient characteristics, intraoperative variables, postoperative complications, evolution of hemostatic parameters, and stay in intensive care and in hospital were analyzed.

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RESULTS

A total of 61 patients were included in two homogeneous groups: general anesthesia (n = 30) and combination anesthesia (general anesthesia associated to epidural analgesia) (n = 31). All patients had normal coagulation values before surgery. The international normalized ratio (INR) in both the general and combination anesthesia groups reached maximum values at 2448 h (mean 1.37 and 1.45 *vs* 1.39 and 1.41, respectively), followed by a gradual decrease. There was less intraoperative bleeding in the combination anesthesia group (769 mL) than in the general anesthesia group (1200 mL) ($P < 0.05$). Of the 61 patients, 38.8% in the general anesthesia group experienced some respiratory complication *vs* 6.6% in the combination anesthesia group ($P < 0.001$). The time to gastrointestinal tolerance was significantly correlated to the type of anesthesia, though not so the stay in critical care or the time to hospital discharge.

CONCLUSION

Epidural analgesia in liver resection surgery was seen to be safe, with good results in terms of pain control and respiratory complications, and with no associated increase in complications secondary to altered hemostasis.

Key words: Hepatectomy; Epidural analgesia; Perioperative complications; Epidural hematoma; Multimodal rehabilitation; Outcomes

Core tip: This is a study of morbiditymortality and hospital stay according to the anesthetic technique used (general *vs* combination anesthesia) in liver resection surgery in patients with colorectal cancer metastases. Epidural analgesia in liver resection surgery was seen to be safe, with good results in terms of pain control and respiratory complications, and with no associated increase in complications secondary to altered hemostasis. The time to gastrointestinal tolerance was significantly correlated to the type of anesthesia, though not so the stay in critical care or the time to hospital discharge.

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INTRODUCTION

There is currently enough experience to consider liver resection as the treatment of choice for some colorectal cancer patients with liver metastases. Combination anesthesia (general anesthesia associated to epidural analgesia) is an anestheticanalgesic strategy commonly used for the perioperative management of liver surgery patients. Its inclusion in fasttrack liver surgery protocols has yielded good results in terms of morbidity and hospital stay[1-3]. However, there is some controversy regarding the use of combination anesthesia in liver resection surgery, due to the probable coagulopathy[4] that accompanies procedures of this kind, and its complications (*e.g.*, spinal hematoma). The anesthetist therefore must weigh the advantages of the epidural catheter against the possible complications associated with its placement and removal.

The present study examines the hemostatic changes in patients undergoing liver resection due to colorectal cancer metastases, their course, and whether the extent of liver resection is a predictor of postoperative coagulopathy.

Assessment is also made of intraoperative bleeding, associated respiratory complications, stay in critical care and time to hospital discharge according to the anesthetic technique used (general *vs* combination anesthesia).

MATERIALS AND METHODS

Following approval by the Ethics Committee, a prospective observational study was carried out involving 61 colorectal cancer patients undergoing surgery due to liver metastases in a tertiary hospital between January 2015 and June 2016. All patients gave their consent for inclusion in the study. In addition to demographic variables [age, gender and body mass index (BMI)], we recorded anesthetic risk, the patient medical history, previous continuous treatment with antiplatelet drugs or anticoagulants, preoperative hemostasis, type of liver resection (major, defined as the resection of ≥ 3 couinaud segments, or minor, defined as the resection of ≤ 2 segments), type of anesthesia (general or combination anesthesia), intraoperative central venous pressure (CVP), hepatic vascular exclusion, surgery time, estimated blood loss, intra and postoperative blood products administered, weight of the surgical piece and hemostasis values at the end of surgery and after 24, 48, 72, 96 and 120 h. All surgeries were performed by the same surgical team with extensive experience in liver surgery. A first descriptive analysis was made of the preoperative variables, followed by an analysis of the behaviour of the postoperative hemostatic parameters over time.

Rocuronium was used as neuromuscular blocker in all patients, and sugammadex was used as reversal agent at the end of surgery where required.

Statistical analysis

The statistical analysis of the data was carried out using R Statistical Programming Language®-Project for Statistical Computing® version 2.15.0 for MS Windows XP® and Linux Fedora 16 Kernel 3.4.111[5].

RESULTS

Of the total patients, 30 were subjected to general anesthesia and 31 to combination anesthesia (general anesthesia plus epidural analgesia).

There were no statistically significant differences between the groups in terms of the preoperative variables, with the exception of BMI (Table 1).

The international normalized ratio (INR) was analyzed at 0, 24, 48, 72, 96 and 120 h postsurgery (Table 2).

The maximum INR values were recorded between 24 and 48 h after surgery in both the general anesthesia and combined anesthesia groups, followed by a gradual decrease.

The type of surgical resection was seen to influence the behaviour of the INR values over time. Figure 1 shows the values recorded at 0, 24, 48, 72 and 120 h. In the case of major liver resection, the maximum INR value (recorded at 48 hpostsurgery) was 1.54. The values subsequently decreased at 72 and 120 h (1.28 and 1.12, respectively). In the case of minor liver resection, the maximum INR value (likewise recorded at 48 h postsurgery) was 1.17. The values subsequently decreased at 72 and 120 h (1.06 and 1.01, respectively). The INR values showed statistically significant differences between major and minor resection. The mean INR curves were entered in a model including the type of resection and the type of anesthesia as INR determining factors (Figure 1).

The evolution of prothrombin activity (PA) was evaluated 0, 24, 48, 72 and 120 h postsurgery (Table 3).

Figure 2 shows the mean PA values according to the type of anesthesia and surgical resection performed. The behaviour of this parameter over time coincided with that of the INR values.

Considering the type of anesthesia and type of surgical resection, the mean blood losses were found to be 919 ml and 585 ml respectively for major and minor resection with combination anesthesia, and 1254 ml and 1116 ml respectively for major and minor resection with general anesthesia. The statistical analysis showed blood loss to be significantly related to the type of anesthesia (P = 0.008) and type of resection (P = 0.016).

Respiratory complications in turn were seen to be related to the type of anesthesia used (P = 0.003). The patients subjected to combination anesthesia suffered fewer postoperative respiratory complications (6.6%) than the patients subjected to general anesthesia (38%). Similarly, the incidence of complications was greater in the major resection group (27.3%) than in the minor resection group (17.9%) (P < 0.01).

The time from the end of surgery to gastrointestinal tolerance was related to the type of anesthesia administered: 60.4 h in the case of combination anesthesia *vs* 83.5 h in the case of general anesthesia (P = 0.001).

The mean time to discharge from critical care was 2.77 da and 3.74 d in the case of

Table 1 Demographic and preoperative data of the study series

	Combination (SD) *n* = 30	General (SD) *n* = 31	*P*-value
AGE	61.7 ± 9.9	63.6 ± 9.7	0.520
BMI	24.2 ± 3.01	26.1 ± 3.3	0.111
Mean blood Pressure	91.3 ± 12.8	95.2 ± 15	0.276
Creatinine	0.86 ± 0.31	0.80 ± 0.27	0.427
Glucose	108.9 ± 24.3	103.9 ± 18.9	0.344
Hemoglobin	12.9 ± 1.51	13.2 ± 1.85	0.568
Hematocrit	38.8 ± 4.42	39.1 ± 5.33	0.817
Platelets	222 ± 77.2	220 ± 83.6	0.862
INR	0.97 ± 0.09	0.98 ± 0.10	0.885
PA	106.7 ± 17.6	105.1 ± 174.6	0.817
aPTT	29.1 ± 2.32	29.3 ± 2.73	0.976

BMI: Body mass index; PA: Prothrombin activity; aPTT: Activated partial thromboplastin time; INR: International normalized ratio; SD: Standart desviation.

combination and general anesthesia, respectively, and 4.06 d and 2.32 d in the case of major and minor resection, respectively. The statistical analysis showed the number of days to discharge from critical care to be significantly associated to the type of resection (P = 0.001) but not to the type of anesthesia (P = 0.069).

In turn, the mean time to patient discharge home was 10.53 d and 7.62 d respectively for major and minor resection with combination anesthesia, and 10.47 d and 10.07 d respectively for major and minor resection with general anesthesia. The number of days to discharge was not significantly related to the type of resection (P = 0.060) or the type of anesthesia (P = 0.129). Interaction of the type of resection with the type of anesthesia yielded a pvalue close to statistical significance (P = 0.052).

DISCUSSION

Epidural analgesia is an accepted procedure in major abdominal surgery[6] .Controversy regarding its use in liver surgery is due to the risk of postoperative coagulation disorders[7-9], with spinal hematoma being the most feared complication, even in patients with normal preoperative coagulation parameters[10,11]. The possibility of coagulation disorders after liver surgery and of an increased risk of bleeding complications requires the anesthetist to weigh the advantages of placing an epidural catheter against the possible complications of catheter placement and removal[12] .

The extent of liver resection, bleeding, and the functional capacity of the remaining liver tissue can affect the magnitude and duration of the postoperative coagulation disorders, and make the appropriate timing of epidural catheter removal an important issue[13]. In coincidence with the literature, our protocol considers that an INR value of 1.55 should not be exceeded either in performing the epidural technique or in catheter removal[14], and that a minimum prothrombin activity (PA) value of 60% should be observed[15]. Other authors further lower PA to 50%[16] and INR to 1.4[17]. Stamenkovic *et al*[12] established a maximum INR value of 1.2 for any type of resection.

Because of this controversy, many studies involving particularly live donors and liver resection procedures in general have evaluated the course of hemostasis after liver resection surgery. Most of them[7-9,12-15] reported normal hemostatic control values by the fifth postoperative day. This is the reason why followup in our study was extended to the fifth day after surgery, Although, we recorded alterations in hemostasis, they proved transient, with maximum levels between 24 and 48 h after resection surgery. Our findings in this regard are consistent with those of Kim *et al*[14] and Siniscalchi *et al*[15].

In all but two cases, the hemostatic controls performed after 72 h showed the parameters to be below the normal values for removing the epidural catheter. The mentioned two patients had an epidural catheter, and the parameters were seen to have normalized 120 h after surgery, thus allowing catheter removal without complications.

The literature recommends the transfusion of fresh frozen plasma when epidural catheter removal proves mandatory and the hemostatic parameters have not been normalized[7,12,16]. None of our patients required the transfusion of this blood product,

Table 2 International normalized ratio according to the type of anesthesia and type of resection

Time	Anesthesia	Resection	Mean	St. error	SD
0	Combi	Major	1.217	0.032	0.130
24	Combi	Major	1.516	0.053	0.219
48	Combi	Major	1.556	0.074	0.303
72	Combi	Major	1.265	0.042	0.173
120	Combi	Major	1.062	0.028	0.115
0	General	Major	1.207	0.035	0.134
24	General	Major	1.425	0.074	0.287
48	General	Major	1.542	0.099	0.385
72	General	Major	1.287	0.063	0.246
120	General	Major	1.124	0.052	0.203
0	Combi	Minor	1.048	0.049	0.154
24	Combi	Minor	1.171	0.057	0.182
48	Combi	Minor	1.160	0.098	0.309
72	Combi	Minor	1.065	0.074	0.233
120	Combi	Minor	0.979	0.048	0.153
0	General	Minor	1.142	0.121	0.271
24	General	Minor	1.220	0.027	0.060
48	General	Minor	1.174	0.078	0.175
72	General	Minor	1.040	0.071	0.160
120	General	Minor	1.018	0.088	0.197

Combi: Combined anesthesia; General: General anesthesia; SD: Standart desviation.

though Stamenkovic *et al*[12] had to perform such transfusion in a patient with an INR value of 1.5 on day four after surgery.

Possible factors underlying such coagulopathy after liver resection have been described[17], including the extent of resection, intraoperative bleeding and the functional capacity of the remaining liver tissue[12,18]. In our study, statistically significant differences were observed directly relating the type of liver resection to the subsequent development of hemostatic alterations, in coincidence with the findings of Matot *et al*[7]and Stamenkovic *et al*[12].

Liver surgery involves a high risk of intraoperative bleeding due to the anatomical characteristics of the liver, and consequently there is a greater potential need for transfusion, and higher patient morbidity and mortality[19].

Only a limited number of studies have contrasted surgical bleeding according to the type of anesthesia used. One such study was published by Page *et al*[20], involving patients undergoing liver resection due to any disease condition. One of the study variables was blood loss, and comparison of the epidural analgesia group (mean 709 mL) *vs* the nonepidural group (mean 780 ml) revealed no significant differences. Likewise, Revie *et al*[21], in their twoyear study of 177 patients undergoing liver resection due to any disease condition, recorded no significant differences in intraoperative bleeding according to the type of anesthesia used. In contrast to the above authors, our results indicate a mean intraoperative blood loss of 769 ml for combination anesthesia *vs* 1200 mL for general anesthesia the difference being statistically significant. However, since the aforementioned studies involved heterogeneous patient series, any comparative analysis entails a certain risk of bias.

Considering the characteristics of analgesia achieved with local anesthetics administered *via* the epidural route *vs* analgesia with intravenous opiates, such as possible block or attenuation of the entry of pain stimuli to the central nervous system, the literature indicates that epidural analgesia offers benefits in relation to postoperative respiratory morbidity with improved lung function and tissue oxygenation[22]. Pöpping *et al*[23] conducted a metaanalysis involving 58 studies with 5904 patients, of which 19 with 3504 patients analyzed respiratory complications. The authors concluded that the use of epidural analgesia was significantly associated to a decreased risk of postoperative pneumonia this being consistent with our own observations. Our study showed that 38.8% of the patients subjected to general anesthesia had some type of respiratory complication after surgery (pleural effusion, atelectasis, pneumonia), *vs* only 6.6% of those subjected to combination anesthesia.

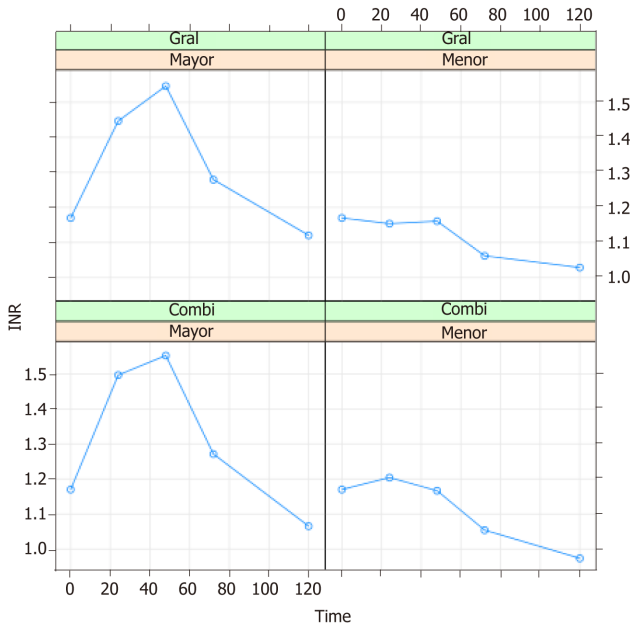

Figure 1 International normalized ratio according to the type of resection, type of anesthesia and time.

However, in the only identified study reporting results different from our own, Page *et al*[20] described a greater number of respiratory complications (without specifying which) in their patients subjected to liver resection under epidural *vs* nonepidural analgesia though the differences were not significant.

Postoperative ileus implies a delay in the resumption of oral food intake and thus prolongs hospital stay[24]. One of the main factors conditioning the accelerated recovery of intestinal function after abdominal surgery is the use of epidural analgesia[25]. Studies similar to our own, such as those published by Ahmed *et al*[26] and Hendry *et al*[27], evaluating the application of a fasttrack program in liver surgery, have found gastrointestinal tolerance in all patients to be resumed 4872 h after surgery, in coincidence with our own findings. In our series, of the same size as those of Ahmed *et al*[26] and Hendry *et al*[27], the time to gastrointestinal tolerance was found to be 60.4 h on average in the combination anesthesia group *vs* 83.5 h in the general anesthesia group the difference being statistically significant. Our findings are likewise consistent with those of Qi *et al*[28], who analyzed the outcomes of fasttrack liver surgery and observed a significant decrease in the time to tolerance (64 ± 17.9 h with fasttrack surgery *vs* 77.0 ± 26.4 h with the classical protocol).

Abu Hilal *et al*[29] published one of the few studies referred to liver surgery in which patient stay in critical care was analysed. Without mentioning the type of anesthesia used, these authors compared laparoscopic surgery *vs* open surgery. The mean stay in the case of open surgery was about four days, which is longer than in our study. Chhibber *et al*[30] in turn reported a threeday stay in critical care.

Our own findings were 3.7 d of stay on average in the general anesthesia group *vs* 2.7 d in the combination anesthesia group this indicating a tendency towards shorter stay in the latter group, though statistical significance was not reached (P = 0.060). However, on considering the type of liver resection performed (*i.e.*, major or minor), patient stay in critical care was seen to be significantly shorter in the minor resection group, with 2.3 d on average *vs* 4.3 d among the patients subjected to major liver resection.

Lastly, with regard to patient discharge home, Enhanced Recovery After Surgery protocols in liver surgery have been found to shorten the mean time to discharge (Pöpping *et al*[23] , Hendry *et al*[27] Savikko *et al*[31]. However, although we found combination anesthesia to result in a small reduction in time to discharge (9.3 d *vs* 10.3 d in the comparator group), the difference was not statistically significant. In any case, our stays were far longer than those recently published by Schultz *et al*[32]. These authors, after making changes to a successful protocol already implemented in 2011[2], including the administration of high dose corticosteroids before surgery (125 mg of methylprednisolone), recorded a median stay of two days for laparoscopic surgery *vs* four days in the case of open surgery.

In conclusion, epidural catheter placement and combination anesthesia constitute a safe alternative in patients undergoing liver resection due to colorectal cancer metastases. The coagulation alterations reach maximum levels at 24 and 48 h, with

Table 3 Evolution of prothrombin activity over time according to the type of anesthesia and type of resection

Time	Anesthesia	Resection	Mean	St. error	SD
0	Combi	Major	76.529	2.154	8.882
24	Combi	Major	58.824	2.661	10.973
48	Combi	Major	59.529	3.245	13.380
72	Combi	Major	76.353	3.240	13.360
120	Combi	Major	95.118	2.724	11.230
0	General	Major	78.133	3.275	12.682
24	General	Major	65.333	5.123	19.841
48	General	Major	60.200	5.206	20.164
72	General	Major	74.467	5.130	19.867
120	General	Major	87.533	4.916	19.041
0	Combi	Minor	95.800	5.781	18.281
24	Combi	Minor	81.600	5.053	15.981
48	Combi	Minor	82.500	5.905	18.674
72	Combi	Minor	94.000	7.335	23.195
120	Combi	Minor	101.600	4.960	15.686
0	General	Minor	88.800	8.540	19.097
24	General	Minor	75.000	2.408	5.385
48	General	Minor	79.000	6.716	15.017
72	General	Minor	92.800	9.019	20.167
120	General	Minor	99.000	9.555	21.366

Combi: Combined anesthesia; General: General anesthesia; SD: Standart desviation.

normalization of the parameters in all cases at 120 h after surgery. Statistically significant differences were observed in the evolution of the hemostatic parameters over time according to the type of liver resection involved. None of our patients required the transfusion of fresh frozen plasma for epidural catheter removal. There were no complications related to catheter placement.

There was less intraoperative bleeding in the combination anesthesia group. These patients moreover suffered fewer respiratory complications and showed a shorter time to oral tolerance.

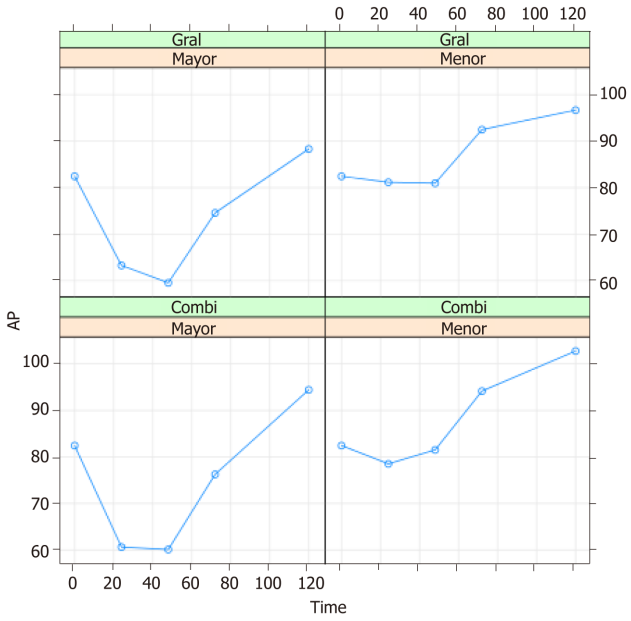

Figure 2 Prothrombin activity according to the type of anesthesia and type of resection.

ARTICLE HIGHLIGHTS

Research background

Epidural analgesia is a well-known technique use in thoracic and abdominal surgery for its benefits in stress response, pulmonary complications. Anesthesiologists are afraid of its use in patients with potentially haemostatics disorders. Liver surgery is an example of them. In literature is well described the use of epidural analgesia in hepatic surgery and others, with different opinions. So that, we wanted to study the behaviour haemostatic profile after a particular etiology of hepatic resection, colon-rectum liver metastases. We think are patients with particular peculiarities in liver function non comparable to others disease, thus the use of epidural analgesia could be safer than in others, with greater benefits than risks.

Research motivation

Patient wellness, patient comfort, patient care, minimize patient stress previous and following days after surgery is one of the goals for all health professionals. So that, in literature is well published the benefits of epidural analgesia in many patients under thoracic or abdominal surgeries. Is for that we started this study, because of the discrepancies existing in use or not use epidural techniques in patients under liver surgery with potentially haemostatic postoperative disorders.

Research objectives

To know the behaviour of haemostatic profile following a colon-rectum metastases liver resection, to considerer if benefits of epidural analgesia are greater than risks.

Research methods

The research methods (*e.g.*, experiments, data analysis, surveys, and clinical trials) that were adopted to realize the objectives, as well as the characteristics and novelty of these research methods, should be described in detail.

Research results

We found in both minor and major hepatic resections, there was oscillation in international normalized ratio (INR) and prothrombin time till 48th postoperative hours. These variations in minor resections were never greater than INR 1.5, instead in major resections existed at 48th postoperative hours haemostatic alteration that turn to normal range before postoperative day 5. We did not use fresh frozen plasma or prothrombin complex to improve the haemostasia prior to remove an epidural catheter.

Research conclusions

Haemostatic profile following colon-rectum hepatic metastases resection. Safety use an epidural catheter in patients under colon-rectum liver metastases resection. Benefits of epidural analgesia for patients under colon-rectum metastases liver resections are greater than risks, but if you chose use it, use it with care. Offer to anaesthesiologists another tool in anesthesia and analgesia management in patients with those characteristics.

Research perspectives

Never is enough when in terms of health recommendations is worked. More studies are always necessary to improve and certified your studies.

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SYSTEMATIC REVIEW

Systematic review of ablative therapy for the treatment of renal allograft neoplasms

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Abstract

BACKGROUND

To date, there are no guidelines on the treatment of solid neoplasms in the transplanted kidney. Historically, allograft nephrectomy has been considered the only reasonable option. More recently, nephron-sparing surgery (NSS) and ablative therapy (AT) have been proposed as alternative procedures in selected cases.

AIM

To review outcomes of AT for the treatment of renal allograft tumours.

METHODS

We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 Checklist. PubMed was searched in March 2019 without time restrictions for all papers reporting on radiofrequency ablation (RFA), cryoablation (CA), microwave ablation (MWA), high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE) of solid tumours of the kidney allograft. Only original manuscripts describing actual cases and edited in English were considered. All relevant articles were accessed in full text. Additional searches included all pertinent references. Selected studies were also assessed for methodological quality using a tool based on a

2009 Checklist and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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modification of the Newcastle Ottawa scale. Data on recipient characteristics, transplant characteristics, disease characteristics, treatment protocols, and treatment outcomes were extracted and analysed. Given the nature and the quality of the studies available (mostly retrospective case reports and small retrospective uncontrolled case series), a descriptive summary was provided.

RESULTS

Twenty-eight relevant studies were selected describing a total of 100 AT procedures in 92 patients. Recipient age at diagnosis ranged from 21 to 71 years whereas time from transplant to diagnosis ranged from 0.1 to 312 mo. Most of the neoplasms were asymptomatic and diagnosed incidentally during imaging carried out for screening purposes or for other clinical reasons. Preferred diagnostic modality was Doppler-ultrasound scan followed by computed tomography scan, and magnetic resonance imaging. Main tumour types were: papillary renal cell carcinoma (RCC) and clear cell RCC. Maximal tumour diameter ranged from 5 to 55 mm. The vast majority of neoplasms were T1a N0 M0 with only 2 lesions staged T1b N0 M0. Neoplasms were managed by RFA (n = 78), CA (n = 15), MWA (n = 3), HIFU (n = 3), and IRE (n = 1). Overall, 3 episodes of primary treatment failure were reported. A single case of recurrence was identified. Follow-up ranged from 1 to 81 mo. No cancer-related deaths were observed. Complication rate was extremely low (mostly < 10%). Graft function remained stable in the majority of recipients. Due to the limited sample size, no clear benefit of a single procedure over the other ones could be demonstrated.

CONCLUSION

AT for renal allograft neoplasms represents a promising alternative to radical nephrectomy and NSS in carefully selected patients. Properly designed clinical trials are needed to validate this therapeutic approach.

Key words: Ablative therapy; Cryoablation; Radiofrequency ablation; Microwave ablation; High-intensity focused ultrasonography; Irreversible electroporation; Neoplasm; Kidney transplant; Renal allograft; Systematic review

Core tip: Ablative therapy (AT) is a minimally invasive alternative to radical or partial nephrectomy for the treatment of renal allograft tumours. To date, limited data exist regarding long-term efficacy and safety. We performed a systematic review on radiofrequency ablation, cryoablation, microwave ablation, high-intensity focused ultrasound, and irreversible electroporation of neoplasms arising in the transplanted kidney and described treatment-specific and overall outcomes. In the considered cases, AT was successfully offered to all transplant recipients with benign tumours or with American Joint Committee on Cancer T1a N0 M0 renal cell carcinomas of the kidney allograft who were not suitable for more aggressive and demanding surgical treatments.

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INTRODUCTION

Kidney transplantation (KTx) is the best therapy for end-stage renal disease[1]. However, due to chronic exposure to immunosuppression, renal transplant recipients have higher incidences of malignancy than the general population[2-4]. Among cancer-related complications, neoplasms involving the allograft are particularly difficult to manage and deserve special consideration[5]. Ideally, optimal therapy should ensure tumour control while preserving as much transplant function as possible. In this complex group of patients, the benefit of complete allograft removal must be carefully

weighed against the substantial risk of death arising from renal failure and return to chronic dialysis[5-7].

Like in the non-transplant population, for many years nephrectomy has been considered the gold standard treatment[8]. More recently, recognition of the advantages of nephron-sparing surgery (NSS) and ablative therapy (AT) in native kidneys has led to an increasing use of such alternative options in renal allografts[9-12]. Radiofrequency ablation (RFA), cryoablation (CA), microwave ablation (MWA), high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE) have all shown promising results in selected cases but solid evidence supporting their role in the management of kidney allograft neoplasms and long-term follow-up data are still missing.

To date, no clinical guidelines, comprehensive meta-analyses, or systematic reviews addressing this topic have been published. The aim of the present study was to systematically review characteristics and outcomes of AT for the treatment of solid masses of the transplanted kidney.

MATERIAL AND METHODS

Literature search

We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 Checklist[13]. PubMed was searched in March 2019 for any papers reporting on AT of kidney allograft neoplasms. No time limits were applied. The following key word combinations were used: "thermal ablation", "kidney ablation", "renal ablation", "allograft ablation", "graft ablation", "transplant ablation", "allograft cancer", "allograft neoplasm", "allograft tumor", "allograft mass", "kidney transplant cancer", "kidney transplant neoplasm", "kidney transplant tumor", "kidney transplant mass", "renal transplant cancer", "renal transplant neoplasm", "renal transplant tumor", and "renal transplant mass". Only English manuscripts were considered.

Study selection and data extraction

Primary and secondary searches were performed by two independent groups of authors. Disagreements between the two groups were resolved by discussion with the lead author. Duplicate articles were removed. Remainder were screened out reading titles and abstracts. Manuscripts potentially describing cases of AT of kidney allograft tumours were assessed in full text. Only original studies actually reporting on AT of neoplasms in the transplanted kidney were included. Additional search of reference lists was performed. If available, the following data points were collected: recipient ethnicity, recipient gender, recipient age, donor type, donor gender, donor age, induction treatment, maintenance immunosuppression, time from transplant to tumour diagnosis, tumour type, tumour size, tumour histology, Fuhrman grade[14], diagnostic modality, staging modality, American Joint Committee on Cancer (AJCC) Tumour Nodes Metastasis (TNM) classification[15], treatment modality, primary treatment failure, secondary treatment failure, complications, allograft function before and after treatment, recurrence, cancer-specific survival, transplant survival, and length of follow-up. Extracted data were transferred to a dedicated database for analysis purpose.

Study quality assessment

Selected studies were assessed for methodological quality using a tool based on a modification of the Newcastle Ottawa scale as proposed by Murad *et al*[16]. As suggested by the authors, questions 4, 5, and 6 of the questionnaire were not considered since they were mostly relevant to cases of adverse drug events. Rather than using an aggregate score, we made an overall judgement considering the questions deemed most critical in the specific clinical scenario. Accordingly, quality of selected studies was classified as low, average or high.

Statistical analysis

Our review considers a large majority of single case reports and some small case series. No meta-analysis was performed as the small case series are composed of heterogeneous patients making any summary measures meaningless. In order to describe compactly the literature, we reported the number for the categorical variables and the range for the continuous ones. The tables must also be considered as a compact way of describing the results from the literature review. No inferences can be drawn from this study. The statistical methods were assessed by a senior biomedical statistician (Federico Ambrogi, Associate Professor from the Laboratory of Medical Statistics, Biometrics and Epidemiology of the Department of Clinical

Sciences and Community Health of the University of Milan).

RESULTS

Included studies

A flow diagram summarizing included articles and selection processes is depicted in Figure 1. The amount of reports preliminarily retrieved using each of the keyword combinations previously mentioned was 133206. More in details: thermal ablation, 5981; kidney ablation, 4130; renal ablation, 4374; allograft ablation, 172; graft ablation, 899; transplant ablation, 4205; allograft cancer, 6749; allograft neoplasm, 5502; allograft tumor, 7726; allograft mass, 1720; kidney transplant cancer, 13171; kidney transplant neoplasm, 11784; kidney transplant tumor, 14121; kidney transplant mass, 5495; renal transplant cancer, 14010; renal transplant neoplasm, 12406; renal transplant tumor, 14896; and renal transplant mass, 5865. After duplicates were removed (n = 87755), a pool of 45451 manuscripts remained for further evaluation. Following the inclusion criteria described above and after reviewing papers by title and abstract, 110 full text articles were identified. Articles not reporting original cases of AT of kidney allograft neoplasms were excluded (n = 82). No additional reports were found through searches of references. Eventually, 28 studies were selected[17-44]. No randomized clinical trials, prospective controlled studies or prospective uncontrolled studies were identified. At the end of the process, we included 12 retrospective case reports, 13 single-centre retrospective uncontrolled case series, 2 multi-centre retrospective uncontrolled case series, and 1 multi-centre retrospective controlled case series. Main characteristics and qualitative evaluations of the studies meeting the criteria for the systematic review are described in Table 1. In total, 100 KTx neoplasms in 92 recipients were treated by 100 primary AT procedures. This included 78 RFA, 15 CA, 3 MWA, 3 HIFU, and 1 IRE.

Patients' characteristics

Only a few articles reported on the total number of KTx performed over the same period in which allograft neoplasms were diagnosed and treated. Consequently, no reliable estimate of cumulative incidence of these tumours could be calculated. Nevertheless, according to Tillou *et al*[33], incidence and prevalence of KTx neoplasms are 0.19% and 0.5%, respectively. Information regarding donor type, donor gender, donor age, recipient ethnicity, induction treatment, and maintenance immunosuppression were seldom given. Gender details were available for 69/92 (75%) recipients undergoing AT. Data on recipient age were reported in 64/92 (69.6%) patients. Recipient age at the time of tumour diagnosis ranged from 21 to 71 years. Time between transplantation and diagnosis was adequately reported in 48/100 (48%) cases. Time interval range was 0.1-312 mo.

Neoplasms characteristics

Diagnosis was made by imaging in almost all the lesions. Albeit scarce (38/100, 38%), data showed that neoplasm distribution within the allograft was homogeneous. Tumour appearance was available in 48/100 (48%) cases. Most lesions were endophytic but both exophytic and mixed exo-endophytic masses were described. Size was reported in 73/100 (73%) neoplasms. Maximal tumour diameter ranged from 5 to 55 mm. The majority of the neoplasms showed a maximal diameter inferior to 20 mm. Only 2 cases exceeding 40 mm were reported. Biopsy was obtained for 93/100 (93%) masses. Final pathologist reports demonstrated: Papillary renal cell carcinoma (RCC), clear cell RCC, RCC not otherwise specified, chromophobe RCC, tubulo-papillary RCC, tubulo-cystic RCC, mixed clear cell and papillary RCC, and oncocytoma . Details on Fuhrman grading score were given for 38/100 (38%) neoplasms. Most lesions were grade I or grade II. No cases of locally advanced or metastatic disease were reported. Staging as per AJCC 2010 TNM classification was reported for 93/100 (93%) tumours. The vast majority were T1a N0 M0 with only 2 T1b N0 M0. Clinical presentation was described for 91/100 (91%) neoplasms. Most masses were asymptomatic and were diagnosed during routine ultrasound (US) follow-up or incidentally discovered during investigations carried out for other reasons. Symptoms not necessarily related to the tumour that prompted further assessment included haematuria, allograft dysfunction, abdominal pain, fever, flu-like syndrome, and asthenia. Characteristics of kidney allograft neoplasms treated by AT are summarized in Table 2.

Diagnostic modalities

Detailed descriptions of diagnostic work up were available in 95/100 (95%) cases. Most lesions were initially detected by Doppler-US scan with or without contrast

Table 1 Characteristics of studies meeting the criteria for the systematic review

Study	Design	Period	Total sample size (P/N)	Ablation sample size (P/N)	Ablation technique	Quality
Charboneau *et al*[18]	R-CR	2002	1/1	1/1	RF	L
Shingleton *et al*[17]	R-CR	2002	1/1	1/1	CA	L
Baughman *et al*[19]	R-CR	2004	1/1	1/1	RF	L
Hruby *et al*[22]	R-CR	2006	1/1	1/1	CA	L
Goeman *et al*[21]	R-CR	2006	1/1	1/1	RF	L
Aron *et al*[23]	R-CR	2007	1/1	1/1	RF	L
Matevossian *et al*[24]	R-CR	2008	1/1	1/1	RF	L
Sanchez *et al*[26]	R-CR	2009	1/1	1/1	RF	L
Chakera A *et al*[27]	R-CR	2010	1/1	1/1	HIFU	L
Olivani *et al*[29]	R-CR	2011	1/1	1/1	RF	L
Silvestri *et al*[36]	R-CR	2014	1/1	1/1	CA	L
Christensen *et al*[38]	R-CR	2015	1/1	1/1	RF	L
Roy *et al*[20]	S-U-R-CS	2005	2/2	1/1	RF	L
Veltri *et al*[25]	S-U-R-CS	2009	3/3	3/3	RF	L
Elkentaoui *et al*[28]	S-U-R-CS	2010	39/42	2/2	RF	L
Leveridge *et al*[31]	S-U-R-CS	2011	47/53	3/3	RF	L
Ploussard *et al*[32]	S-U-R-CS	2012	12/17	2/2	CA	L
Swords *et al*[34]	S-U-R-CS	2013	4/4	1/1	RF	L
Vegso *et al*[35]	S-U-R-CS	2013	9/9	5/5	RF	L
Su *et al*[37]	S-U-R-CS	2014	4/5	1/2	RF	L
Hernàndez *et al*[39]	S-U-R-CS	2015	4/4	1/1	RF	L
Cool *et al*[41]	S-U-R-CS	2017	10/12	10/12	RF	A
Iezzi *et al*[42]	S-U-R-CS	2018	3/3	3/3	RF	L
Di Candio *et al*[43]	S-U-R-CS	2019	3/4	3/4	RF, HIFU	L
Gul *et al*[44]	S-U-R-CS	2019	6/6	6/6	CA, MW, IRE	L
Tillou *et al*[33]	M-U-R-CS	2012	79/79	5/5	RF	A
Cornelis *et al*[30]	M-U-R-CS	2011	20/24	20/24	RF, CA	A
Guleryuz *et al*[40]	M-C-R-CS	2016	92/92	14/14	RF, CA	H

P: Patient; N: Neoplasm; R: Retrospective; CR: Case report; RF: Radiofrequency ablation; L: Low; CA: Cryoablation; HIFU: High-intensity focused ultrasound; S: Single-centre; U: Uncontrolled; CS: Case series; A: Average; MW: Microwave ablation; IRE: Irreversible electroporation; M: Multi-centre; C: Controlled; H: High.

enhancement. The remaining masses were diagnosed by contrast-enhanced computed tomography (CT) scan, magnetic resonance imaging (MRI) with or without contrast dye, a combination of different imaging modalities or kidney allograft biopsy.

Staging modalities

Information regarding staging modality could be retrieved for 49/100 (49%) tumours. Preferred imaging technique was contrast-enhanced CT scan followed by MRI with or without contrast dye and Doppler-US scan with or without contrast enhancement.

Access for AT

Technical details were obtained for 84/100 (84%) ablative treatments. A percutaneous approach was used in most of the procedures. Other access modalities were: Transosseous (n = 1), laparoscopic (n = 1), and open (n = 1).

Imaging guidance for AT

Guidance modality was described for 71/100 (71%) procedures. US-guided and CT-guided procedures were the most frequently reported.

Follow-up modalities

Follow-up protocol was mentioned for 69/100 (69%) treatments. In most cases, a combination of different imaging modalities was used. In one study an US-guided

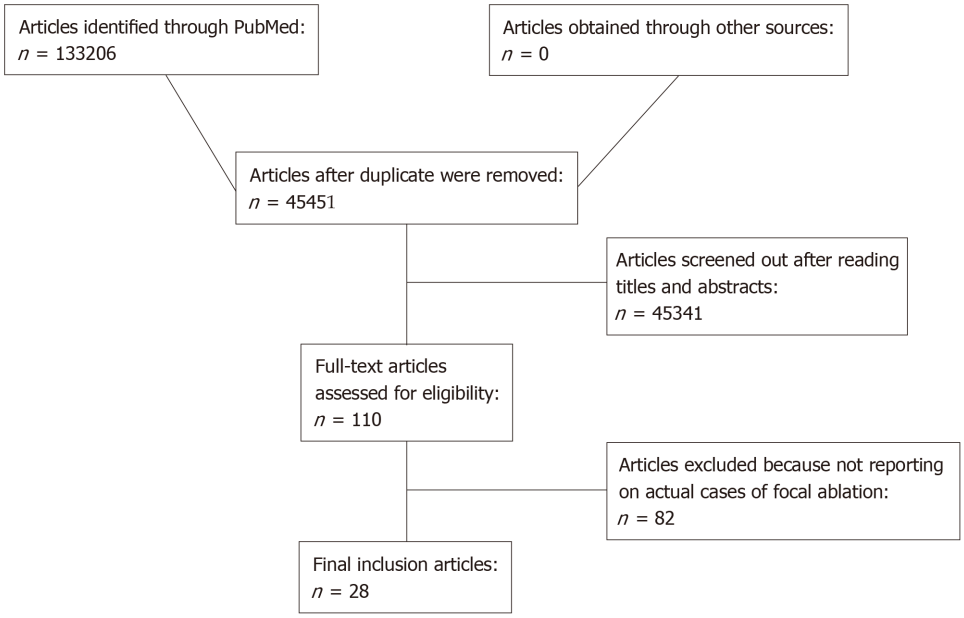

Figure 1 Flow diagram of the systematic review.

allograft biopsy was also obtained as a part of the routine surveillance program.

Overall outcome of AT

Twenty-eight studies describing 100 AT of KTx neoplasms in 92 patients were considered[17-44]. Patients and tumours characteristics as well as technical details of the procedures (access to the allograft and guidance modality) have been described above. Overall, 3 episodes of primary treatment failure (residual tumour present following treatment) were reported. In 2 cases, repeat AT was performed with successful ablation of the lesion. Follow-up range was 1-81 mo. One local recurrence which was successfully treated with further AT was described. One patient developed regional lymph node metastases without local recurrence 4 years after treatment. This recipient died from a cardiovascular event a few months later. No kidney allograft cancer-specific deaths were recorded. Eleven patients experienced peri-operative complications. Transplant function remained stable in the majority of the patients. In 5 recipients, there was a progressive deterioration of function eventually leading to allograft loss. Overall characteristics and outcome of AT are summarized in Table 3.

Outcome of RFA

RFA was by far the most widely used treatment modality with 22 studies reporting on 78 procedures in 70 patients[18-21,23-26,28-31,33-35,37-43]. Recipient age ranged from 21 to 77 years. Histological evaluation was obtained in 73/78 (93.6%) cases and it demonstrated papillary RCC (n = 41), clear cell RCC (n = 10), chromophobe RCC (n = 2), tubulo-papillary RCC (n = 2), tubulo-cystic RCC (n = 1), and RCC not otherwise specified (n = 17). Tumor size ranged from 5 to 40 mm. All lesions were T1a N0 M0. Almost all the procedures were executed percutaneously under US or CT guidance. Overall, 2 cases of primary treatment failures were identified. Both patients underwent repeat RFA obtaining successful tumour ablation. Post-operative follow-up range was 3-71 mo. Local recurrence was observed in one treatment. Recurrent disease was successfully managed by repeat RFA. No cancer-related deaths were recorded. Peri-operative complication rate was less than 15% in all the reports. Complications were: Transient leg pain due to thermal injury to the genitofemoral nerve (n = 3), urinary leakage (n = 1), cruralgia due to thermal injury to the ileopsoas muscle (n = 1), ablative site infection (n = 2), and post-infarction syndrome (n = 1). Renal function remained consistently stable in most cases. However, a few recipients developed irreversible allograft dysfunction. Characteristics and outcome of RFA are summarized in Table 4.

Outcome of CA

CA of a renal allograft neoplasm has been described in 7 studies treating 15 patients[17,22,30,32,36,40,44]. Recipient age at the time of intervention ranged from 35 to 71 years. Histology was available in 13/15 (86.7%) cases. Treated tumours comprised clear cell RCC (n = 7), papillary RCC (n = 3), mixed clear cell and papillary RCC (n =

Table 2 Summary of the characteristics of the case reports and the case series of kidney allograft neoplasms treated by ablative therapy[1]

Variables	Range or number
Neoplasms	100
Imaging-based diagnosis	
RCC	94
Cystic mass	4
Oncocytoma	1
Not available	1
Localization	
Interpolar	16
Lower pole	12
Upper pole	10
Not available	62
Growth pattern	
Endophytic	27
Exophytic	16
Mixed exo-endophytic	5
Not available	52
Size	
Maximal diameter (mm)	5-55
Maximal diameter 0-20 mm	37
Maximal diameter 21-30 mm	26
Maximal diameter 31-40 mm	9
Maximal diameter > 40 mm	1
Not available	27
Histology-based diagnosis	
Papillary RCC	48
Clear cell RCC	20
Chromophobe RCC	2
Tubulo-papillary RCC	2
Tubulo-cystic RCC	1
Mixed clear cell and papillary RCC	1
RCC not otherwise specified	17
Oncocytoma	1
Indeterminate	1
Not available	7
Fuhrman grading score	
Grade I	10
Grade II	24
Grade I-II	3
Grade III	1
Not available	62
AJCC TNM classification	
T1a N0 M0	91
T1b N0 M0	2
Not available	7
Ablative treatment	
RFA	78
CA	15
MWA	3
HIFU	3)
IRE	1/100 (1)

[1]Summaries based on individual cases should not be considered as an estimate of the "real world". RCC:

Renal cell carcinoma; AJCC: American Joint Committee on Cancer; TNM: Tumor nodes metastasis; RFA: Radiofrequency ablation; CA: Cryoablation; MWA: Microwave ablation; HIFU: High-intensity focused ultrasound; IRE: Irreversible electroporation.

1), oncocytoma (n = 1), and indeterminate (n = 1). Neoplasm size range was 15-41 mm. One lesion was stage T1b N0 M0 with the reminder T1a N0 M0. Cryoablation was predominantly performed using a percutaneous approach under US or CT guidance. There were no primary treatment failures and no local recurrences after a follow-up ranging from 1 to 59 mo. One patient developed regional lymph node metastasis 4 years after the procedure and died from cardiovascular accident a few months later. No episodes of cancer-related death were recorded. Overall, there were 2 peri-operative complications: An abdominal wall hematoma and a retroperitoneal hematoma requiring surgical drainage. No significant changes in allograft function were noted before and after treatment. Characteristics and outcome of cryoablation are summarized in Table 4.

Outcome of MWA

Three cases of MWA of a KTx tumour were reported. In their retrospective case series, Gul *et al*[44] described successful treatment of 1 clear cell (28 mm, Fuhrman grade I-II, T1a N0 M0) and 2 papillary (22 mm, Fuhrman grade I-II, T1a N0 M0 and 31 mm, Fuhrman grade II, T1a N0 M0) RCC in 3 transplant recipients. All the procedures (2 percutaneous and 1 transosseous) were carried out under CT guidance and led to complete tumour ablation. During follow-up (range, 8-61 mo), no primary treatment failures or recurrences were observed and graft function remained consistently stable. One of the patients experienced transient leg pain due to thermal injury to the genitofemoral nerve. Characteristics and outcome of MWA are summarized in Table 4.

Outcomes of HIFU

Two studies reporting on HIFU for the treatment of renal allograft tumours were identified, reporting 3 AT treatments in 3 patients. In the first report, Chakera *et al*[27] described how they treated a symptomatic 55 mm clear cell RCC (Fuhrman grade II, T1b N0 M0) in a 58-year old recipient. The procedure was performed percutaneously under US guidance with no intra- or post-operative complications. Despite 3 ablations to the lesion, treatment was not successful and the patient required a partial graftectomy. Percutaneous US-guided HIFU was also used by Di Candio *et al*[43] to ablate two small (22 mm and 8 mm) papillary RCC (T1a N0 M0). Treatment was effective in both cases with no signs of relapse after 6 years of follow-up. Peri-operative course was uneventful and no loss of graft function was observed. Characteristics and outcome of HIFU are summarized in Table 4.

Outcome of IRE

We found only one study describing IRE[44]. The procedure was carried out under CT guidance via a percutaneous approach to treat an asymptomatic 16 mm clear cell RCC (Fuhrman grade III, T1a N0 M0) arising in a 57-year-old patient. There were no intra- or post-operative complications, graft function remained stable over time, and no signs of recurrence were observed after 34 mo of follow-up. Characteristics and outcome of IRE are summarized in Table 4.

DISCUSSION

An increased susceptibility to primary malignancies and lymphoproliferative disorders is a well-recognized complication of KTx[2-4]. For renal transplant recipients, cancer currently represents the third leading cause of mortality[45] and overall cancer rates as high as 40% at 20 years have been reported[46]. In comparison to the general population, this group of patients have been shown to have higher incidences of non-melanoma skin cancers[47] and RCC[48]. Most renal neoplasms detected after transplant occur in the native kidneys[48]. However, solid tumours involving the allograft are being increasingly identified[5,7]. Reported prevalence of de novo neoplasms in the transplanted kidney is between 0.2% and 0.5%, depending on the series[33,49,50]. The exact incidence of these tumours is difficult to determine because available data predominantly comes from retrospective registry analyses and refer to RCC. As the majority of the studies included in our systematic review did not report the total number of transplants performed during the same time in which the lesions were treated, incidence or prevalence of the disease could not be estimated. Nevertheless,

Table 3 Summary of the overall outcomes of ablative therapy of kidney allograft neoplasms from the case reports and the case series examined[1]

Variables	Range or number
Procedures	100
Patients	92
Interventional access	
Percutaneous	81
Open	1
Laparoscopic	1
Transosseous	1
Not available	16
Guidance modality	
US	31
CT	20
MRI	1
US and CT	19
Not available	29
Primary treatment failure	3
Secondary treatment failure	1
Recurrence	1
Disease-specific mortality	0
Overall renal allograft loss	5
Peri-operative complication	11
Urinary leakage	1
Post-infarction syndrome	1
Hematoma	2
Infection of the ablation site	2
Leg pain due to nerve injury	4
Leg pain due to muscle injury	1
Follow-up (mo)	1-81

[1]Summaries based on individual cases should not be considered as an estimate of the "real world". US: Ultrasound; CT: Computed tomography; MRI: Magnetic resonance imaging.

considering the increased use of kidneys from elderly donors[51], the progressive aging of the population on the transplant waiting list[52], the improvement in long-term recipient and graft survival[45], and the widespread application of systematic imaging-based screening protocols during the post-transplant follow-up[49], it is likely that the incidence of kidney allograft tumours will, in the near future, rise considerably.

Specific risk factors for KTx neoplasms have been poorly investigated[33]. It is generally accepted that well established risk factors for RCC in the native kidney may be responsible for carcinogenesis in the renal allograft[53]. Chronic kidney disease, prolonged renal replacement therapy, and long-term immunosuppression also play a role[48,53,54]. Deceased donor recipients seem to be at higher risk than those receiving a kidney from a living donor, representing approximately 90% of the cases[55]. A possible explanation is that deceased donors are generally older than living donors and therefore more prone to develop malignancies. Differences in cancer screening protocols before organ retrieval may also contribute. Tillou *et al*[55] showed that among affected patients, there was a disproportionate number of men . An association between primary renal disease (*i.e.* glomerulopathies and uropathies) and kidney allograft neoplasms has been also suggested but evidence remain weak[55]. It has been demonstrated that the majority of renal allograft tumours originate from donor-derived cells. However, whether these neoplasms are de novo transformations or a transplanted disease is often difficult to discriminate[7,56]. Primary RCC of recipient origin has been also reported[57]. Although not routinely undertaken, discerning between donor-derived and recipient-derived neoplasms may have important implications as different cancer behaviours may be expected suggesting tailored therapeutic strategies.

Time interval between transplantation and diagnosis is variable[7,58]. In our review

Table 4 Summary of the different ablative therapies described in the case reports and the case series examined[1]

Variables	Range or Number				
	RFA	CA	HIFU	MWA	IRE
Procedures	78	15	3	3	1
Patients	70	15	3	3	1
Tumor size (mm)	5-40	15-35	8-55	21-28	16
Tumor histology					
Clear cell	10	7	1	1	1
Papillary	41	3	2	2	0
Mixed RCC	0	1	0	0	0
Chromophobe	2	0	0	0	0
Tubulo-papillary	2	0	0	0	0
Tubulo-cystic	1	0	0	0	0
RCC NOS	17	0	0	0	0
Oncocytoma	0	1	0	0	0
Indeterminate	0	1	0	0	0
Not available	5	2	0	0	0
Interventional access					
Percutaneous	67	8	3	2	1
Open	0	1	0	0	0
Laparoscopic	0	1	0	0	0
Transosseous	0	0	0	1	0
Not available	11	5	0	0	0
Guidance modality					
US	24	4	3	0	0
CT	12	4	0	3	1
MRI	0	1	0	0	0
US and CT	18	1	0	0	0
Not available	24	5	0	0	0
Primary treatment failure	2	0	1	0	0
Re-treatment failure	0	-	1	-	-
Recurrence	1	0	0	0	0
Disease-specific mortality	0	0	0	0	0
Renal allograft loss	5	0	0	0	0
Complications	8	2	0	1	0
Follow-up (mo)	3-71	1-59	12-81	8-61	34

[1]Summaries based on individual cases should not be considered as an estimate of the "real world". RCC: Renal cell carcinoma; NOS: Not otherwise specified; US: Ultrasound; CT: Computed tomography; MRI: Magnetic resonance imaging.

the considered cases showed a range between 0.1 and 312 mo. In contrast to Penn *et al*[50] it also suggests that the interval can be extremely long. Such a finding not only confirms the importance of age and duration of immunosuppression as risk factors for tumour development[59] but also supports long-term US-based screening protocols after transplantation[49].

It is commonly believed that neoplasms arising in a transplanted kidney are more aggressive than those originating in the native kidney or in patients not exposed to immunosuppression but significant differences in tumour growth dynamics or metastatic behaviours have not been consistently demonstrated[7]. Like in native kidneys, renal allograft neoplasms are generally asymptomatic and mostly discovered at an early stage during routine surveillance imaging studies or diagnostic work up performed for other reasons[60]. Our analysis focused on small KTx tumours treated by AT. The vast majority of lesions considered amenable to focal ablation were asymptomatic. It is reasonable to expect that symptomatic lesions may more often

present at an advanced stage thus limiting therapeutic options[7,61]. This observation further underlines the importance of periodic US evaluation of the allograft for the detection of silent KTx neoplasms[60,62].

US scan undoubtedly represents the cornerstone of kidney allograft imaging not only in the early post-transplant phase but also in the long-term[63]. Cost-effectiveness of annual US screening remains debated but many centres worldwide perform US evaluation of the allograft as a part of their routine follow-up. Such a policy allows detecting transplant tumours at a very early stage and therefore increases the possibility of using conservative treatments like NSS and AT. We found that Doppler-US and contrast-enhanced US (CEUS) were the preferred first line imaging modalities for tumour diagnosis[49,55,60]. Lesions with indeterminate characteristics at US were evaluated using CT scan, MRI or a combination of both, mostly with contrast enhancement. In patients with suboptimal renal function, Doppler-US and CEUS offer several advantages as CT scan and MRI may expose the patient to contrast induced nephropathy or nephrogenic systemic sclerosis. Studies comparing CEUS to contrast-enhanced CT scan for the differentiation between benign and malignant renal tumours have shown encouraging results[64]. In particular, CEUS seems to be superior to Doppler-US and contrast-enhanced CT scan in case of complicated cystic lesions or small solid masses[64].

As for any other neoplasms, accurate staging is paramount for proper treatment planning. Since indication for AT is currently limited to small allograft tumours with no signs of local invasiveness or metastatic disease (AJCC T1a N0 M0 and T1b N0 M0), careful pre-operative evaluation is mandatory. Overall, there is a lack of information regarding staging work up of renal allograft tumours but our review showed that lesions were frequently assessed by contrast-enhanced CT scan or a combination of contrast-enhanced CT scan and MRI with or without contrast dye.

Like tumours arising in the native kidney, renal allograft neoplasms can be benign or malignant. Four main variants could be identified: Clear cell RCC, papillary RCC, chromophobe RCC, and oncocytoma. Clear cell type and papillary carcinomas represent most of the cases. Clear cell type is more often unifocal and aggressive whereas papillary type is generally indolent and multifocal[20,65]. A disproportionate number of papillary carcinoma over clear cell carcinoma has been noticed in kidney allografts compared to native kidneys[33]. In our review papillary type was the most represented lesion treated with AT. This is an important epidemiological data with relevant clinical implications. Due to its multifocality, for many years papillary carcinoma has been considered as an indication for radical nephrectomy or graftectomy. More recently, positive outcomes obtained with NSS have cautiously allowed to extend indications for conservative therapeutic options also to patients with papillary carcinoma[66,67]. We detected several reports in the literature describing successful ablation of papillary lesions in the renal allograft[18,20,23,25,30,38-41,43,44]. Therefore our review further supports the use of AT in recipients with papillary carcinoma as current literature showed similar primary treatment failure, secondary treatment failure, recurrence, graft survival, and disease-free survival for papillary, clear cell, and chromophobe RCC.

Pre-operative histology is crucial for the assessment of solid masses in the transplanted kidney as it provides information on tumour type, grading, and origin thus helping clinicians choose the best therapy. Proper characterization of renal allograft neoplasms also allows to obtain important epidemiological and clinical data that may favour the construction of specific tumour registries and the analysis of specific treatment outcomes. Given the fact that renal allografts are generally located in the iliac fossa, in the retroperitoneum, and in a relatively superficial position, US-guided biopsy is considered the procedure of choice[68].

Current treatment of KTx tumours mostly reflects the evolution observed in the management of neoplasms of the native kidney. Historically, radical nephrectomy and graftectomy have been considered the only acceptable options. Over years, improvements in surgical technique and peri-operative care as well as a better understanding of cancer biology and behaviour have progressively favoured the use of nephron sparing strategies. Current evidence show that for RCC up to 4 cm in maximal diameter, cancer-specific survival at 5 years is 95%[7,69]. The risk of death arising from transplantectomy and return to dialysis is much higher with a reported 5-year survival rate of 34%[6]. Therefore, radical nephrectomy and transplantectomy are now indicated only for malignant lesions with features of advanced local (AJCC stage III) or metastatic (AJCC stage IV) disease, in case of large masses exceeding 7 cm (AJCC stage II), for sarcomatoid RCC, for lesions infiltrating the hilum, and in patients with irreversible kidney failure or a non-functioning allograft. For the remainder (mostly AJCC stage I T1a N0 M0), NSS represents the most widely used therapeutic option. NSS includes several procedures such as enucleation, wedge resection, and polar resection. After partial nephrectomy, excellent oncological outcomes can be

achieved with resection margins of 5 mm and for T1a lesions, local recurrence rates of less than 5% have been reported. The risk of new cancer development in the resected kidney is also minimal (< 5%)[7] and successful reoperation with allograft salvage in case of local recurrence or metachronous disease has been described[70]. Given the technical difficulty of the procedures and the risk of intra-operative and post-operative complications, perfect candidates for NSS are relatively healthy uninephric or chronic kidney disease subjects with a small unifocal tumour located in a favourable position[8]. Such an ideal patient is seldom encountered among KTx recipients as most of them present with advanced age, complex comorbidities, increased risk of infection, and impaired healing response. Decise adhesions from previous operation, short vascular pedicles, and increased tissue fragility may represent a surgical challenge in case of NSS limiting the chances of organ mobilization, vasculature control, and adequate tumour resection[9].

In the last decade, for non-transplant patients with contraindications to general anaesthesia, high surgical risk, or in a need for maximum renal function preservation, AT have been increasingly recognized as a valuable alternative to NSS. Compared to NSS, focal ablation offers several advantages: It can be performed under local anaesthesia, is less invasive, allows to spare more renal parenchyma, does not require vascular clamping, and has minimal or absent blood loss. Initial experience showed comparable mid-term oncological outcomes, lower complication rates, and better preservation of renal function than radical nephrectomy and NSS[71]. These encouraging results have favoured the acceptance of AT also in the transplant community. Moreover, specific characteristics of the renal allograft such as superficial location and greater susceptibility to ischemia-reperfusion injury in case of vascular occlusion, make it even more suitable for ablation than the native kidney.

Available AT for the treatment of renal allograft neoplasms are RFA, CA, MWA, HIFU, and IRE. To date, RFA is the most widely used AT in both native and transplanted kidney (78% of the procedures included in our review). It utilizes a high frequency, alternating electrical current to generate heat in the target lesion. The current is transmitted to the tissues through an electrode with a non-insulated tip. Cellular and extracellular ions in which the current flows are forced to follow the same path as the alternating current determining agitation and frictional heating eventually leading to coagulative necrosis. This procedure is particularly indicated for small exophytic lesions distant from the hilum[72,73]. CA is the second most frequently used AT (15% in our analysis) and basically utilizes argon gas to freeze and damage the tumour. Cooled and thermally conductive fluids are transmitted to the lesion via hollow needles. Once the probes are in place, a cryogenic freezing unit removes heat from the target causing ice crystal formation, membrane disruption, cell lysis, apoptosis, and ischemic necrosis due to intravascular coagulation. A theoretical advantage of CA over other AT is the greater selectiveness and therefore the possibility to safely treat parenchymal lesions located in critical areas of the organ[73]. Overall experience with MWA in kidney allografts is limited (3% of the cases). It is a thermal ablation modality using microwaves to generate oscillation of polar molecules within the target tissues with subsequent frictional heating and coagulative necrosis. Since multiple applicators can be utilized simultaneously, MWA allows to treat larger lesions compared to other AT and also to ablate several masses during the same procedure[73]. HIFU represents another thermal ablation modality more recently introduced in clinical practice. Available reports in KTx neoplasms are still scarce (3% of the procedures) but results in native kidneys are promising[74]. This AT uses multiple US beams converging into a focus to produce inertial cavitation, micro streaming, and radiation forces eventually causing localized heating and coagulative necrosis. HIFU does not require needles or probes and as such represents the least invasive technique currently available. It is also extremely selective with an excellent safety profile. The need for adequate acoustic windows to successfully operate remains the major limitation of the technique. Nevertheless, such an issue may be more theoretical than practical in the case of renal allograft lesions as transplanted kidneys are almost always in a superficial plane, relatively distant from sensible organs, and not surrounded by adipose tissue[75,76]. IRE is a non-thermal AT utilizing electrical pulses to generate nanopores in the cell membrane thus leading to irreversible disruption of cell homeostasis and apoptosis[77]. Only one report could be identified in the transplant setting (1%).

As previously mentioned, in our review, papillary RCC was the most frequent neoplasms treated by AT. The outcomes were overall similar for patients with different tumour types. The vast majority of these lesions were less than 4 cm in maximal diameter and staged T1a N0 M0. It is worth noticing that among the 2 tumours exceeding 4 cm (T1b N0 M0), one could not be successfully treated by AT and required partial nephrectomy to achieve complete removal. Available data showed that neoplasms were mostly Fuhrman grade I or II but information on

grading score were overall insufficient for proper inferential analysis. Multifocality and unifocality were also seldom reported. Most lesions treated were actually endophytic. This is particularly interesting because focal ablation has been more often restricted to exophytic masses. One of the arguments in favour of AT over radical nephrectomy and NSS is that it is less invasive. Almost all the procedures included in our review were performed using a percutaneous approach. Moreover, patients were mostly treated under local anaesthesia, there were no intra-operative complications, and hospital stay was mostly less than 3 d. Post-operative complication rate was also reassuring with only 2 cases requiring further surgical intervention. Allograft function was preserved in the vast majority of the patients. These results show that AT is safely offered to elderly and frail transplant recipients who may not be suitable for more demanding surgical procedures. It can also offer a valuable alternative to active surveillance in carefully selected candidates[71]. We found that preferred guidance modalities were Doppler-US and CEUS. CEUS has been increasingly recognized as the technique of choice for percutaneous interventional procedures. It can be easily utilized for diagnostic, guidance, and follow-up purposes. There is no exposure to ionizing radiations and particularly in patients with impaired renal function, it has also the advantage of avoiding the administration of toxic contrast agents[64]. Overall, in our review AT was effective and safe. Only 3 primary treatment failures were reported with a single episode of local recurrence. Persisting and relapsing tumours could be all treated with further AT or NSS with excellent oncological outcomes and preservation of allograft function. No cancer-related deaths were observed. Whilst limited by the lack of long-term follow-up these reports are encouraging and suggest that AT can be considered a valuable alternative to radical nephrectomy and NSS not only for critically ill patients but also for the majority of the recipients with a renal allograft neoplasms staged T1a N0 M0. Comparison with NSS supports this point of view. After partial graftectomy, an overall recurrence rate as high as 9% has been reported with higher rates of severe post-operative complications and allograft dysfunction (15%)[7-9,55].

Despite the numerous advantages, AT has some limitations. First of all, percutaneous procedures do not allow to obtain definitive histological diagnosis and staging of the lesion treated. There is also the possibility that pre-operative imaging and ablation itself may miss very small satellite lesions or multifocal neoplasms. Finally, which is the optimal strategy for the assessment of complete tumour ablation and the detection of local recurrence remains debated[78]. In our review, follow-up modalities were very heterogeneous among transplant centres. In most cases, multiple imaging techniques such as US, CT scan, and MRI were used. Such an observation confirms the difficulty in discriminating between necrosis, vital parenchyma, and neoplastic tissue and underlines the importance of strict and diligent surveillance strategies after AT. Especially in difficult cases, protocol ablation site biopsy may help rule out the presence of residual tumours or local recurrences and prompt timely and effective treatment[23].

Details on post-ablation immunosuppression were not routinely reported in the studies included in our review. To date, there is no consensus regarding the best immunosuppressive strategy for cancer prevention and control after KTx. In case of tumours amenable of NSS or AT, the use of a proliferation signal inhibitor such as sirolimus or everolimus may be considered but evidence are still limited[79-81].

To the best of our knowledge, this is the first systematic review on AT for the treatment of renal allograft neoplasms. All principal focal ablation techniques were explored describing treatment-specific and overall outcomes. The main limitation of the review is the impossibility to perform any sort of meta-analysis due to the small case series considered with heterogeneous patients. Nevertheless, our work offers a comprehensive and updated reference which may provide the basis for further studies and help clinicians counselling their patients. In order to improve the quality of further research, systematic use of proper ablation terminology and current reporting standards is recommended[82-84]. As suggested by Su *et al*[37], patients and neoplasms should be also stratified according to the R.E.N.A.L. nephrometry scoring system, probably the most appropriate tool to describe tumours arising in the transplanted kidney[85].

Results of AT are overall encouraging but long-term follow-up data remain limited. AT is generally offered to all transplant recipients with benign neoplasms or AJCC stage I T1a N0 M0 RCC of the kidney allograft who are not suitable for more aggressive and demanding surgical treatments. The inability to obtain definitive histological diagnosis represents the main limitation of AT. Therefore, strict and diligent follow-up strategies are mandatory. All the AT modalities currently available can be considered a valuable option but tailored treatment may help achieve the best outcomes. Properly designed prospective randomized clinical trials are needed.

ARTICLE HIGHLIGHTS

Research background

Kidney allograft tumours represent a challenging complication of renal transplantation. Optimal treatment should ensure adequate oncological results while preserving as much renal function as possible. For many years, graftectomy has been considered the gold standard. In the last decade, improved surgical techniques and technological advances have favoured the use of nephron-sparing alternatives such as partial nephrectomy and focal ablation. Preliminary reports on ablation treatment of solid masses of the kidney allograft have shown promising results. However, solid evidence supporting widespread application of ablation therapy are lacking and there is still concern in the transplant community regarding efficacy and safety in the long term. To date, no guideline, meta-analysis or systematic review on the topic have been published.

Research motivation

The rarity of the disease and the multiple options available (radiofrequency ablation, cryoablation, microwave ablation, high-intensity focused ultrasound, and irreversible electroporation) make it extremely difficult to assess results of ablation therapy for the treatment of kidney allograft neoplasms. A better insight into this complex topic would help clinicians choose the best treatment and provide the basis for further research.

Research objectives

We performed a systematic review of ablation therapy for the treatment of solid neoplasms of the transplanted kidney. All major ablation techniques were considered. Overall and treatment-specific outcomes were extensively reported in order to offer a comprahensive overview on currently availbale data and remark the need for properly designed clinical trials.

Research methods

We conducted a systematic review according to the PRISMA 2009 Checklist. PubMed was extensively searched in March 2019 for any papers reporting on ablation therapy of kidney allograft neoplasms. Only English manuscripts were considered. No time limits were applied. Multiple key word combinations were used. Duplicate articles were removed. Remainder were screened out reading titles and abstracts. Manuscripts potentially describing cases of ablation of kidney allograft tumours were assessed in full text. Only original studies reporting on actual cases of ablative treatment of neoplasms in the transplanted kidney were included. Additional search of reference lists was performed. Selected studies were also assessed for methodological quality using a tool based on a modification of the Newcastle Ottawa scale. Data were extracted and transferred to a dedicated database for analysis purpose. Given the nature of the studies and the large heterogeneity of the patients included, we decided not to meta-analyze data. To the best of our knowledge, this is the first systematic review on the topic.

Research results

Preliminary search identified 133206 articles. After duplicate were removed (n = 87755), a pool of 45451 manuscripts remained for further evaluation. Reviewing articles by title and abstract, 110 full text papers were selected. Articles not reporting on original cases of ablation of kidney allograft tumours were excluded (n = 82). No additional cases were found through references lists. At the end of the process, 28 studies were included in the systematic review: 12 retrospective case reports, 13 single-centre retrospective non-comparative case series, 2 multi-centre retrospective non-comparative case series, and 1 multi-centre retrospective comparative study. In total, 100 kidney transplant neoplasms in 92 recipients were treated by 100 ablation procedures: 78 radiofrequency ablation, 15 cryoablation, 3 microwave ablation, 3 high-intensity focused ultrasound, and 1 irreversible electroporation. According to our review, incidence of renal allograft neoplasms is approximately 0.2%. Recipient age at the time of tumour diagnosis ranged from 21 to 71 years whereas time between transplant and diagnosis ranged from 0.1 to 312 mo. Most represented lesions were papillary and clear cell renal cell carcinomas. Considered neoplasms were more often endophytic with a maximal tumour diameter ranging from 5 to 55 mm. The vast majority were asymptomatic masses staged T1a N0 M0. Ablation was predominantly performed using a percutaneous route under ultrasound or computed tomography guidance. Overall, retrieved reports showed that ablation therapy was effective with only 3 episodes of primary tratment failures and 1 episode of local recurrence. Safety was also satisfactory. There were no intra-operative complications or cancer-related deaths. Post-operative complications were rare and allograft function was preserved in most of the recipients. Follow-up range was 1-81 mo.

Research conclusions

Our systematic review, shows that ablation therapy has been increasingly used as an effective and safe alternative to graftectomy and nephron-sparing surgery in carefully selected recipients with kidney allograft neoplasms. In particular, ablation was successfully offered to all patients with benign tumours or with T1a N0 M0 malignant lesions not suitable for more demanding surgical procedures. Main advantages of ablation therapy were easy feasibility, mini-invasiveness, short intra-operative time, reduced risk of bleeding, low post-operative complication rate, preserved allograft function, and short hospital stay. The inability to obtain definitive histological diagnosis and the difficult follow-up represented the main limitations of ablation therapy.

Research perspectives

Overall results of ablation therapy are encouraging but there is still a lack of long-term efficacy and safety data. Current evidence do not allow to safely extend indications to more advanced cancer stages. Radiofrequency ablation is the most widely used ablative modality. Proper comparison between different ablation therapies is limited by the small experience gained with cryoablation, microwave ablation, high-intensity focused ultrasound, and irreversible electroporation. In theory, tailored treatments might help achieve the best outcomes. Properly designed multi-centre prospective randomized clinical trials are needed.

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CASE REPORT

Subcutaneous sarcoidosis of the upper and lower extremities: A case report and review of the literature

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Abstract

BACKGROUND

Sarcoidosis is a granulomatous disease of unknown etiology that most often impacts the lungs. Cutaneous manifestations of sarcoidosis are seen among 9%-37% of patients. Subcutaneous sarcoidosis is a rare presentation of cutaneous sarcoidosis with estimates of frequency ranging from 1.4%-16%. To date, very few articles and case reports have been written about this subject. In this paper, we describe a case of subcutaneous sarcoidosis and perform a review of the literature to determine if there are commonalities among patients who present with subcutaneous sarcoidosis.

CASE SUMMARY

A 38-year-old female, with a past medical history of arthritis and recurrent nephrolithiasis, presents with an 8-mo history of 4 firm, asymptomatic, skin-colored nodules on her left and right upper extremities and neck. Needle biopsy and post-excisional pathology report both revealed well-formed, dense, non-caseating granulomas localized to the subcutaneous tissue. Chest computed tomography revealed mild mediastinal lymphadenopathy. A diagnosis of subcutaneous sarcoidosis was made, and the lesions were surgically removed.

CONCLUSION

Commonalities among patients presenting with subcutaneous sarcoidosis include: middle-aged female, lesions localizing to the upper or lower limbs, lymphadenopathy or pulmonary infiltration on chest imaging, elevated serum angiotensin-converting enzyme.

Key words: Subcutaneous sarcoidosis; Upper extremity; Granulomatous disease; Case report

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Core tip: Recognizing patterns of subcutaneous sarcoidosis is important for hand surgeons and other surgical specialties that do not commonly see this patient population in order to rapidly identify and diagnose a disease that has extra-cutaneous manifestations and can lead to greater morbidity and mortality when not diagnosed or treated early.

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INTRODUCTION

Sarcoidosis is a chronic systemic granulomatous disease of unknown etiology characte-rized by the presence of non-caseating granulomas in affected organs[1]. he non-caseating granulomas of sarcoidosis can be found anywhere on the body and involve many different organs. In the head and neck, sarcoidosis typically impacts the cervical lymph nodes, globe, parotid, and larynx with up to 5% of patients demonstrating facial nerve involvement[2]. Ocular involvement is also seen, presenting as uveitis, scleritis, and chorioretinitis[2]. Typically, the lungs are the primary site of disease with cutaneous manifestations being the second most common site. Cutaneous manifestations of Sarcoidosis are seen in up to 9%-37% of patients[3,4]. One particular manifestation of cutaneous involvement, subcutaneous sarcoid nodules, is a rare finding. Previous estimates of the frequency of subcutaneous sarcoidosis ranged from 1.4%-6%, with more recent studies suggesting an occurrence rate of 11.8%-16% among patients presenting with cutaneous sarcoid involvement[3,5-7]. This variant of Sarcoidosis is defined clinically by asymptomatic, non-tender, flesh colored nodules usually ranging between 0.5-2.0 cm[6,8]. Histologically, subcutaneous sarcoidosis is defined by the presence of non-caseating granulomas present in the subcutaneous tissue[6]. On ultrasound imaging these lesions present as an irregularly defined mass with hyper and hypoechoic areas[9]. Fludeoxyglucose (FDG) positron emission tomography (PET) / computed tomography (CT) has also been used to identify sarcoid lesions and presents as increased uptake in subcutaneous areas[10]. While helpful, FDG PET/CT may not be able to differentiate between connective tissue diseases as Sjrogen's Syndrome also presents as increased uptake[11]. Additionally, many soft tissue diseases can look similar on magnetic resonance imaging (MRI) making defining imaging characteristics of each disease important to diagnosis. On MRI imaging Sarcoid lesions involving the face and neck will appear with high signal intensity on T2-weighted images and enhancement on contrast-enhanced images[2]. Given that Wegener's Granulomatosis can mimic Sarcoidosis in the head and neck, MRI imaging helps differentiate these two soft tissue diseases as Wegener's Granulomatosis will appear as hypodense on T1 and T2-weighted images with variable degrees of enhancement with contrast[2]. Similarly, both sarcoidosis and Scleroma can impact the cervical lymph nodes making diagnosis difficult. MR imaging is again a useful tool in differentiating these two diseases in the lymph nodes as Scleroma will appear as low signal intensity on T1 and high signal intensity on T2 imaging with homogeneous pattern of contrast enhancement, and Sarcoidosis will have a foamy appearance on T1 weighted imaging[2,12]. Lupus Both Sarcoidosis and another soft tissue disease like scleroderma can impact the lymph nodes in the neck Recent literature has suggested a strong correlation between subcutaneous sarcoidosis and evidence of systemic sarcoid involvement, and that sarcoid lesions may be an early finding indicative of systemic disease[7,13,14]. Given its correlation with systemic illness, the ability to correctly identify subcutaneous sarcoid lesions is an important diagnostic tool for physicians in the early stages of sarcoidosis. We describe here a case of subcutaneous sarcoidosis and review the literature to determine if there are any commonalities in the presentation of this disease among patients, and to better assist clinicians with diagnosing this rare disorder.

A literature search was performed of the MEDLINE and PubMed database using keywords as "Subcutaneous sarcoidosis" and "Subcutaneous Sarcoidosis", combined with "hand", "hand surgery", "Upper extremity surgery", yielding 202 results. The search includes all articles published since 2000. The search was limited to studies

published in English and performed on humans. Cases without either a serum angiotensin-converting enzyme (ACE) level or a chest imaging study for all patients reported were excluded. Ultimately 29 articles were selected using the diagnostic criteria of subcutaneous sarcoidosis first proposed by Vainsencher *et al*[6]. These 29 articles represent 82 cases of subcutaneous sarcoidosis dating back to 1966.

CASE PRESENTATION

Chief complaints

A 38-year-old Caucasian female was referred to Plastic Surgery from Dermatology after presenting with an 8-mo history of 4 firm, asymptomatic, skin-colored nodules on her left and right upper extremities and neck.

History of past illness

A past medical history of arthritis and recurrent nephrolithiasis.

Personal and family history

She denied any family history of soft tissue masses or autoimmune disorders.

Physical examination upon admission

The mass on the posterior aspect of her neck measured 0.5 cm x 5 cm. The nodule on her left forearm measured 2 cm x 3 cm (Figure 1A and B). On the extensor surface of her right forearm were two masses measuring 1 cm x 1.4 cm and 3.5 cm x 4.5 cm respectively (Figure 1C and D). The overlying skin was normal. At the time of the plastic surgery consult, the patient was compliant with her medication regimen of dextroamphetamine-amphetamine 30 mg by mouth once daily, and acetaminophen 500 mg Tab as needed for arthritic pain.

Laboratory examinations

The complete blood count with differential was normal. Comprehensive metabolic panel was normal. Erythrocyte sedimentation rate, C-Reactive Protein, Anti-SCL, Rheumatoid Factor, and antinuclear antibody were all within normal limits. Her Serum ACE level was also within normal limits with a value of 53 U/L (normal 9-67 U/L). While chest radiograph was normal, chest computed tomography revealed mild mediastinal lymphadenopathy.

FINAL DIAGNOSIS

Based on the histopathological findings of the cutaneous nodules and the computed tomography finding of mediastinal lymphadenopathy, a diagnosis of subcutaneous sarcoidosis was made.

TREATMENT

Patient was advised on various treatment options and chose to have the lesions surgically excised by a plastic surgeon.

OUTCOME AND FOLLOW-UP

Needle biopsy and post-excisional pathology report both revealed the presence of well-formed, dense, non-caseating granulomas located in the subcutaneous tissue. There was no evidence of organisms with Acid-Fast and Grocott's Methamine Silver staining.

Among the articles selected for this literature review, 4 were hospital based retrospective chart reviews.

DISCUSSION

The largest study was conducted by Ahmed *et al*[14] in 2006 out of the Mayo Clinic[14]. The authors reviewed all cases filed under the diagnosis of sarcoidosis, nonspecific granulomas and granulomatous panniculitis between 1966-2001. Ultimately 21 cases

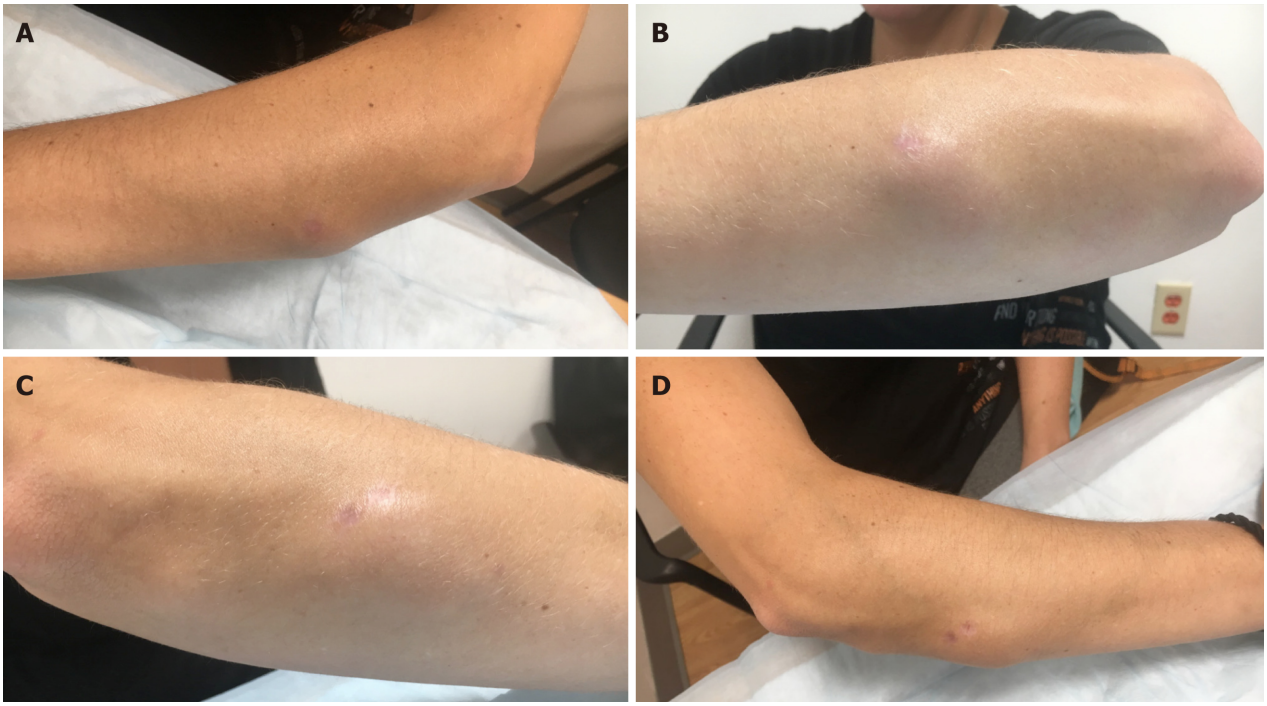

Figure 1 Subcutaneous nodule with normal overlying skin on the left forearm (A and B), subcutaneous nodules with normal overlying skin on the right forearm (C and D).

of subcutaneous sarcoidosis were reviewed. Among the 21 patients diagnosed with subcutaneous sarcoidosis, 15 were female and 6 were male. The mean age was 46.3. In 20/21 patients, lesions were located on more than one anatomical site. The most common anatomical site was the upper extremity with all 21 patients presenting with a lesion in this area. Lower extremity lesions were also common as they were found in 16/21 patients. In 15/21 patients, other types of cutaneous lesions of sarcoidosis co-existed with the subcutaneous lesion with plaques presenting in 6 patients, papules in 4 patient, erythema nodosum in 4 patients, and scar sarcoidosis in 1 patient. Out of the 20 patients who were evaluated for systemic involvement, 16 had pulmonic involvement evidenced by an abnormal chest radiograph. 15/16 patients exhibited bilateral hilar lymphadenopathy, with 6 of these cases exhibiting an additional finding of paratracheal and pulmonary infiltrates. The most common systemic involvements, other than the lung, included arthritis, peripheral neuropathy and renal dysfunction. Out of the 11 patients tested for Serum ACE, 3 patients had elevated levels.

In 2016, Ando *et al*[15] reviewed the charts of 130 patients diagnosed with systemic sarcoidosis between 2000-2012 out of Oita University of Japan medical center. 37/130 patients presented with cutaneous sarcoid lesions with 9/37 presenting with subcutaneous sarcoidosis. Among their cohort were 8 female patients and 1 male patient with an average age of 52.5 years. Six of the patients only had lesions on their lower extremities. The other 3 patients had lesions on their upper extremity and trunk, upper and lower extremities, and hip respectively. Two patients presented with sarcoid plaques and scars in addition to their subcutaneous nodules. All 9 patients were found to have lung involvement with 4 of these patients presenting with an additional involvement of their eyes, and 3 patients with an involvement of their muscles. On chest radiograph 3 patients had lymphadenopathy, and 6 patients had lymphadenopathy with pulmonary infiltrates.

In 2005, Marcoval *et al*[7] conducted a retrospective chart review analyzing 480 patients admitted with systemic sarcoidosis from 1974-2002 at the University Hospital of Bellvitge in Barcelona, Spain. A total of 85/480 patients demonstrated sarcoid cutaneous involvement with 10/85 demonstrating subcutaneous sarcoidosis. 9/10 of the patients were female, and the average age of presentation was 52.6 years. All of the patients presented with nodules on their upper extremities with 5 patients presenting with additional nodules on their lower extremities. In addition to subcutaneous nodules, 4 patients presented with erythema nodosum, and 1 patient presented with sarcoid plaques and papules. 8 patients presented with lymphadenopathy on chest radiograph, and 1 patient presented with lymphadenopathy and pulmonary infiltrate.

In 2011 the same lead author, Marcoval *et al*[3], conducted a similar retrospective chart review analyzing 86 patients with systemic sarcoidosis who presented with cutaneous involvement to the Sarcoid Clinic of Bellvitge University Hospital in Barcelona, Spain. A total of 14/86 patients presented with subcutaneous nodules. Among the 14 patients, 11 were female and 3 were male. All 14 patients had nodules limited to the upper and lower extremities with 6 patients presenting with lesions on their arms, 1 patient presenting with lesions on their legs, and 7 patients presenting with lesions on both their upper and lower extremities. 13/14 patients were found to have abnormal chest radiograph findings with 11 patients exhibiting hilar lymphadenopathy, and 2 exhibiting hilar lymphadenopathy and lung infiltrate. Among the 14 patients, 12 had systemic involvement with arthritis being the most common presentation in 6 of the patients (Table 1).

In our literature review we found 25 case reports representing 28 unique cases of subcutaneous sarcoidosis between 2000-2019. Notable features of these cases are listed in Table 2. The average age of patients among all reports was 53 years old and 21/28 of the patients were female.

Out of the 20 reported cases that checked for serum ACE, elevated levels were found in 18 patients. Abnormal Chest Computed Tomography results were found in 16/21 patients. Abnormal Chest Radiograph results were found in 12/19 patients. The most common site of lesion seemed to be the upper and lower limbs with 17/25 patients presenting with subcutaneous sarcoid nodules in one or both of these locations. Most reports did not comment on extracutaneous involvement other than the lung, but those did reported a range of systemic findings including arthritis, renal dysfunction, uveitis, dactylitis, and limb weakness. Sarcoidosis is a chronic systemic granulomatous disease of unknown etiology[1]. Although the lungs are typically the primary site of disease, cutaneous manifestations of the Sarcoidosis can be seen in up to 9-37% of patients[3,4]. Subcutaneous sarcoid nodules, is a rare cutaneous sarcoidosis finding that typically presents as asymptomatic, non-tender, flesh colored nodules ranging in size between 0.5-2.0 cm[6,8]. Histological examination of a subcutaneous sarcoid nodule reveals the presence of non-caseating granulomas present in the subcutaneous tissue[6].

Our patient, a 38 year old female, presented with an 8 month history of 4 subcutaneous nodules ranging in size from 0.5cm-5cm. Her past medical history was significant for arthritis and recurrent nephrolithiasis. Upon testing we found that she had a normal chest radiograph and her serum ACE levels were within normal limits. On chest computed tomography we found evidence of mild mediastinal lymphadenopathy, pathognomonic for sarcoidosis.

In analyzing the 29 publications from 2000-2019 along with our own case, we reviewed 83 cases of subcutaneous sarcoidosis. Among the 83 patients, 65 (78.3%) were female and the average age of presentation was 51.1 years old. The upper and lower extremities were the most common site of subcutaneous sarcoidosis development with 76/83 (91.6%) patients presenting with at least one lesion in these anatomical areas. In our analysis we learned that findings of lymphadenopathy or lymphadenopathy with pulmonary infiltrate was a very common chest radiograph finding among patients presenting with subcutaneous lesions. In total, 58/69 (84.1%) patients had abnormal chest radiograph findings. Among the 22 patients that received a chest computed tomography scan, abnormal findings of lymphadenopathy or pulmonary infiltrate were found in 17/22 (77.2%) patients. Elevated levels of serum ACE is also a common finding, although not as prevalent as lung involvement. In total, among the cases that measured serum ACE, 28/41 (68.3%) patients presented with elevated levels. Instances of sarcoidosis organ involvement other than the lung seems to be a rarer finding presenting in only 29/49 (59.1%) patients. Assessment of the number of patients with systemic involvement other than the lung, however, was difficult as some articles did not include this information within their study. In conclusion, our literature review shows that subcutaneous sarcoidosis primarily impacts middle-aged women, is most frequently found on the upper or lower limbs, and commonly presents with abnormal findings of lymphadenopathy or pulmonary infiltration on chest imaging as well as elevated levels of serum ACE. These patterns and findings are important for hand surgeons and other surgical specialties that do not commonly see this patient population to be able to rapidly identify and diagnose a disease that has extra-cutaneous manifestations and can lead to greater morbidity and mortality when not diagnosed and treated early.

Table 1 Subcutaneous sarcoidosis retrospective chart reviews

Authors	Sex	Average age	Serum angiotensin-converting enzyme	Chest X-ray	Most common site of lesion	Most common site of systemic involvement other than the lungs
Ahmed *et al*[14], 2006	15F/6M	46.3	3/11 Elevated	9/16 Lymphadenopathy, 6/16 Pulmonary infiltration	Upper extremities	Joints-arthritis
Ando *et al*[15], 2016	8F/1M	52.5	7/9 Elevated	3/9 Lymphadenopathy, 6/9 Lymphadenopathy with pulmonary infiltration	Upper extremities	Eyes
Marcoval *et al*[7], 2005	9F/1M	52.6	NA	8/10 Lymphadenopathy, 1/10 Lymphadenopathy with pulmonary infiltration	Upper extremities	NA
Marcoval *et al*[3], 2011	11F/3M	N/A	NA	11/14 Lymphadenopathy, 2/14 Lymphadenopathy with pulmonary infiltration	Upper and lower extremities	Joints-arthritis

Table 2 Features of 25 case reports from 2000-2019

Authors	Sex	Average age	Serum angiotensin-converting enzyme	Chest computed tomography	Chest X-ray	Site of lesion	Extracutaneous involvement other than the lungs
Barnadas *et al*[16], 2000	F	38	Normal	Normal	Normal	Upper and lower limbs	Malaise, joint pains
Girão *et al*[17], 2000	M	37	Elevated		Lymphadenopathy	Lower limb	Hands and feet arthralgia
Dalle Vedove *et al*[18], 2011	1F/1M	75	2/2 Elevated	1/2 Mediastinal Lymphadenopathy, 1/2 Lymphadenopathy with pulmonary infiltration	2/2 Normal	Upper and lower limbs	1/2 Uveitis
Kim *et al*[19], 2014	M	61	Elevated	Normal		Trunk	Renal
Fichtel *et al*[20], 2006	F	42	Elevated		Normal	Upper and lower limbs	None
Bosnic *et al*[21], 2010	F	51	Elevated	Normal		Face	None
Kim *et al*[22], 2017	M	33		Lymphadenopathy with pulmonary infiltration		Face, toe	None
Won *et al*[23], 2016	F	54			Normal	Lower limb	None
Marcoval *et al*[24], 2008	F	49	Elevated		Lymphadenopathy	Upper and lower limbs	None
Dulgueroy *et al*[25], 2015	F	34	Elevated	Lymphadenopathy with pulmonary infiltration		Face	None
Ruangchaijatuporn *et al*[26], 2016	M	56		Normal		Lower limb	None
Watanbe *et al*[27], 2007	F	70	Elevated		Lymphadenopathy	Lower limb	Polyneuropathy of limbs

Janegova *et al*[28], 2016	F	59		Lymphadenopathy with pulmonary infiltration		Foot	None
Yamaguchi *et al*[29], 2013	F	85	Elevated	Lymphadenopathy with pulmonary infiltration	Lymphadenopathy	Upper and lower limbs	Joints arthralgia
Mori *et al*[30], 2018	F	72	Elevated			Lower limb	Renal and cardiac dysfunction
Kwan *et al*[31], 2015	F	53	Elevated	Lymphadenopathy		Upper and lower limbs	None
Miida *et al*[32], 2009	F	62	Elevated	Lymphadenopathy with pulmonary infiltration	Lymphadenopathy	Upper limbs	Uveitis, renal dysfunction, splenic nodules
Bianchini *et al*[33], 2010	F	38	Elevated	Normal	Normal	Face	None
Kerner *et al*[34], 2008	F	53		Lymphadenopathy	Lymphadenopathy	Upper and lower limbs	Facial nerve palsy, arthralgia
Kim *et al*[35], 2013	F	52	Elevated	Lymphadenopathy with pulmonary infiltration	Lymphadenopathy	Upper and lower limbs	None
Guccione *et al*[36], 2017	M	40		Lymphadenopathy		Upper limbs, trunk	None
Meyer-Gonzalez *et al*[37], 2011	3F	52.6	1/3 Normal, 2/3 Elevated	1/3 Lymphadenopathy, 2/3 Lymphadenopathy with pulmonary infiltration	3/3 Lymphadenopathy	Upper and lower limbs	Dactylitis, lower limb weakness
Moscatelli *et al*[38], 2011	M	41		Lymphadenopathy with pulmonary infiltration	Normal	Hand	None
Shigemitsu *et al*[39], 2008	F	65			Lymphadenopathy	Upper extremity	None
Celik *et al*[40], 2010	F	53	Elevated	Lymphadenopathy with pulmonary infiltration	Lymphadenopathy	Foot	None

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CASE REPORT

Atypical cutaneous lesions in advanced-stage Hodgkin lymphoma: A case report

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Abstract

BACKGROUND

Cutaneous involvement in Hodgkin lymphoma (HL) is a rare finding. Few cases have been reported in literature, most describing paraneoplastic manifestations. Only very few papers have described primary HL skin infiltration, reporting a wide range of clinical presentations that frequently include ulcers; plaques, nodules and papules have also been noticed.

CASE SUMMARY

We report the case of a 56-year-old man who presented fever, multiple adenomegalies of neck and axilla and thick serpiginous skin lesions involving bilateral pectoral regions. After an initial diagnostic workup for a suspected active infectious disease, a lymph node biopsy was performed, which showed a neoplastic invasion from a mixed cellularity classical HL. The same histological pattern was described in a cutaneous biopsy of the chest lesions. The other staging procedures performed revealed an advanced disease, with unfavourable clinical prognostic features. The patient was prescribed 6 cycles of ABVD chemotherapy scheme (doxorubicin, bleomycin, vinblastine, dacarbazine), a regiment that requires demonstration of metabolic response achievement at the interim PET/CT scan to confirm continuation or to change therapeutic strategy.

CONCLUSION

Skin involvement in HL is a rare finding and may represent a challenging clinical presentation due to extremely various types of lesions observed.

Key words: Hodgkin lymphoma; Skin lesions; Advanced stage; ABVD; Case report

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Core tip: We report the case of a 56-year-old man presenting with neck and armpits swelling, fever and thick cutaneous chest lesions. Active infectious disease was ruled out and a lymph node biopsy was carried out, diagnostic for Hodgkin lymphoma (HL). Histological examination of pectoral cutaneous serpiginous plaques resulted positive for the same haematological malignancy infiltration. Skin involvement in HL is a rare finding, with main clinical manifestations being ulcers, papules and nodules. We describe this peculiar finding to underline the need for a correct differential diagnosis, especially for other malignancies and infectious disorders.

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INTRODUCTION

Hodgkin lymphoma (HL) is a B-cell neoplasm accounting for 10%-15% of all lymphomas in Europe and the United States[1,2]. The disease is characterised by nodal infiltration, typically involving cervical, mediastinal and axillary regions (accounting for almost 90% of HL presentations), while extranodal involvement occurs in almost a quarter of cases, more often secondary to contiguous spreading from bulky masses [3]. Skin involvement is rare in HL (< 1%) and has been reported both in specific and non-specific presentations[4,5]. Specific lesions are related to the histological demonstration of HL cutaneous infiltration secondary to direct, lymphatic or haematogenous spread and usually occurs in advanced stage diseases, despite the rare finding of a primary cutaneous HL (PCHL) having been reported in literature[6,7]. Non-specific lesions have several clinical types of presentation (pityriasis-like, psoriatic, erythema nodosum, eczematoid) and must be considered as paraneoplastic events[8].

We describe the case of a 56-year-old male patient, who came to our attention for the onset of fever, multiple cervical and axillary lymphadenopathy and bilateral cutaneous pectoral lesions.

CASE PRESENTATION

Chief complaints

A 56-year-old male patient, born in Pakistan and of Pakistani ethnicity, was admitted to the Emergency Room of our hospital for fever and multiple adenomegalies.

History of present illness

The patient referred a 20-d history of fever and the appearance of bilateral neck and axillary adenomegalies, showing no signs of improvement after a broad-spectrum antibiotic treatment prescribed by his general practitioner.

History of past illness

Past medical history did not reveal any relevant illness.

Personal and family history

The patient was unmarried and had been working as a cook since he moved to Italy from Pakistan 7 years earlier.

Physical examination upon admission

Physical examination showed enlarged lymphadenopathy in the supradiaphragmatic regions, with the largest lesions measuring 2.5 cm in the left subclavian area and 3 cm in the left axilla. Moreover, the patient presented with erythematous and serpiginous nodules and plaques on the chest, with a cobblestone-like surface. Few faint erythematous macules and plaques were distributed near the nodules (Figures 1 and 2).

Laboratory examinations

Laboratory data reported an increased white blood count (22600/μL) with

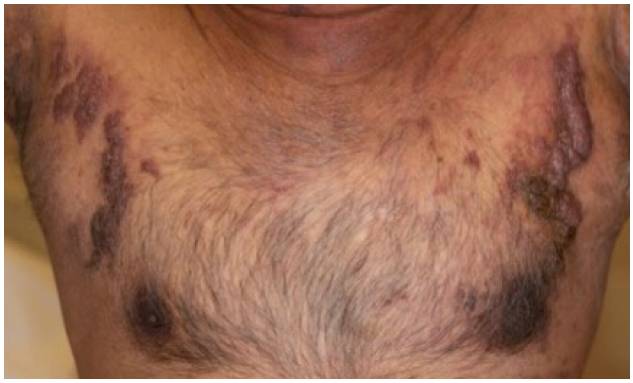

Figure 1 Nodular plaques involving bilateral pectoral districts.

neutrophilia (21000/μL), hypoalbuminemia (2.7 g/dL), increased hyperuricemia (12.6 mg/dL), LDH (230 U/L; normal range: 125-220 U/L), Beta 2 microglobulin (3.6 mg/L), C-reactive protein (CRP; 8.18 mg/dL) and erythrocyte sedimentation rate (ESR; 120 mm). A Quantiferon-TB gold assay revealed positive response to *Micobacterium tuberculosis* antigens.

Imaging examinations

An ultrasound scan of the described adenopathies revealed multiple round and hypoechogenic nodes; a chest X-ray did not show any significant finding. A whole-body CT scan revealed a dimensional increase of nodal lesions, the largest measuring 3 cm in the left supraclavicular area, 5 cm in the homolateral subclavian district and 4.3 cm in the right axilla. Positron emission tomography (PET) scan showed diffuse 18-fluorodeoxyglucose (FDG) uptake involving bilateral cervical, supraclavicular, subclavian, intrapectoral, axillary, mediastinal, celiac, retrocaval, para-aortic and iliac regions. A suspiciously increased uptake also involved skin thickening lesions in bilateral pectoral areas.

Final diagnosis

A lymph node biopsy was performed, revealing an immunohistochemical staining positive for CD30, CD15 +/-, PAX5 +/-, OCT2 -/+ and negative for CD20 and CD3, and a morphological pattern diagnostic for a mixed cellularity classical HL. A fluorescence in situ hybridization (FISH) assay excluded the presence of Epstein Barr virus (EBV) in analysed cells. The same neoplastic infiltration was detected in the cutaneous lesions through the execution of an incisional biopsy (Figures 3 and 4). Nodal tissue was also examined for microbiological testing, which excluded the presence of active tubercular infection.

Treatment

In the clinical and epidemiological suspicion of an active tubercular infection, a 4-drug regimen including ethambutol, rifampicin, isoniazid and pyrazinamide was started. However, after two weeks the patient returned to the Emergency Room due to worsening of both fever and lymphadenomegalies. Dermoscopy of a cutaneous nodular lesion offered no specific clinical clues. A lymph node biopsy was diagnostic for HL. The bone marrow biopsy did not show lymphoma infiltration. The patient was classified as stage IV A with an International Prognostic Score of 5 points (age, sex, stage, leukocytosis and hypoalbuminemia) and started on conventional treatment with ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine).

Outcome and follow-up

To date, the patient has completed the first of six planned cycles, showing significant clinical improvement in both lymphadenomegalies and in skin lesions.

DISCUSSION

HL is a lymphoproliferative disorder usually characterised by supradiaphragmatic nodal involvement and infrequent extranodal localisations, generally developing due to contiguous spread (especially for bulky presentations). The involvement of distant organs is usually limited to spleen, liver, bone or lung, and rarely to other districts. The incidence of cutaneous lesions associated with HL infiltration have been reported

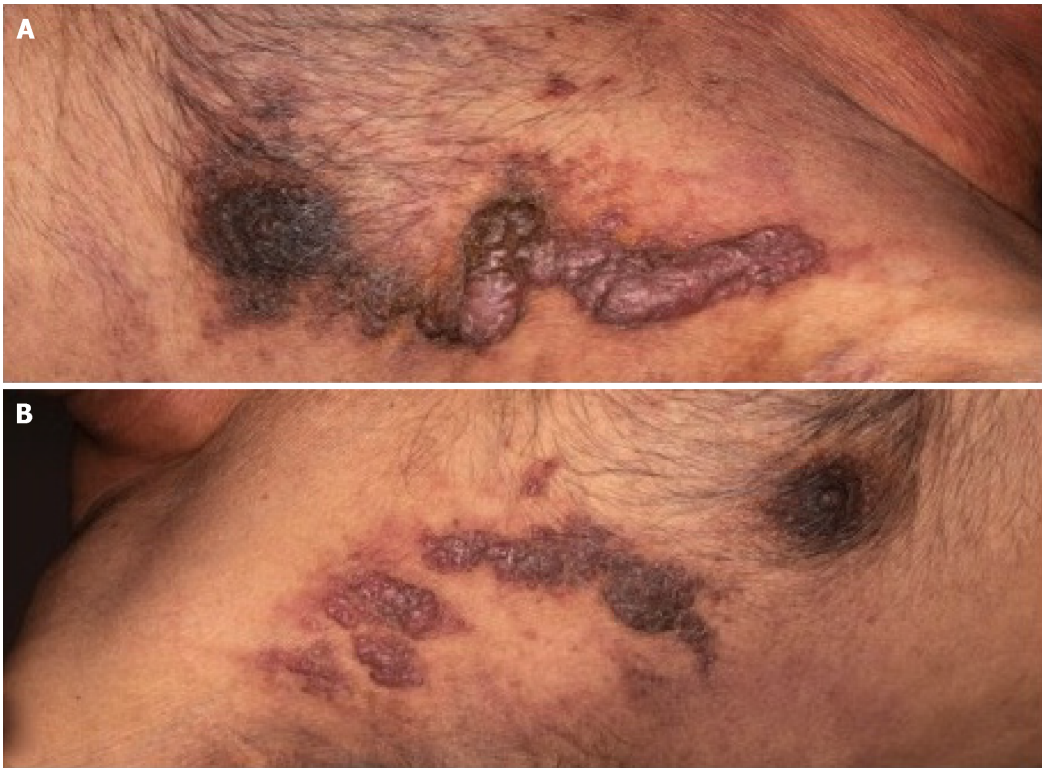

Figure 2 Close-up of left (A) and right (B) chest skin lesions.

as 0.5%-3.4% in several clinical records; lesions are often related to advanced stage disease[9,10]. Plaques, nodules, papules and ulcers are the most common findings[11]. Skin involvement might be explained by different mechanisms of tumour dissemination: the most common is thought to be the retrograde lymphatic diffusion starting from pathologic lymph nodes. Two other pathophysiological patterns are the direct extension due to contiguity and haematogenous spread[5,8]. Differential diagnosis between HL skin involvement and other histological subtypes such as mycosis fungoides, lymphomatoid papulosis, anaplastic large cell lymphoma and granulomatous slack skin disease must be performed[12]. We report a peculiar clinical presentation characterised by serpiginous nodular plaque lesions related to axillary lymphadenopathies in a patient presenting with a diagnostic delay probably related to poor sociocultural conditions. In fact, considering disease biology and size, it is plausible that adenopathies developed several months before ER admission. Furthermore, after the first clinical evaluation an active tubercular infection was suspected, due to fever, a positive Quantiferon-TB gold assay, increased blood CRP and ESR and epidemiological data identifying Pakistan as a country where tuberculosis remains endemic. Cutaneous tuberculosis is a rare but well-known finding that could have explained the skin lesions that we observed in our patient[13]. It is interesting to note that, despite the wide surface area covered by this cord-like lesion, the wall integrity of lesions was preserved without evidence of ulceration, which is a common finding in these clinically HL advanced conditions[8]. There is no specific treatment for cutaneous HL localisation: for advanced stage disease, the patient is prescribed six ABVD cycles. However, this schedule must be confirmed by the achievement of an early metabolic response, documented by a PET/CT scan after the first two chemotherapy cycles[14].

The patient has received the first chemotherapy cycle, with good tolerance to treatment, and has shown initial response both in the adenopathies and in the cutaneous localisations.

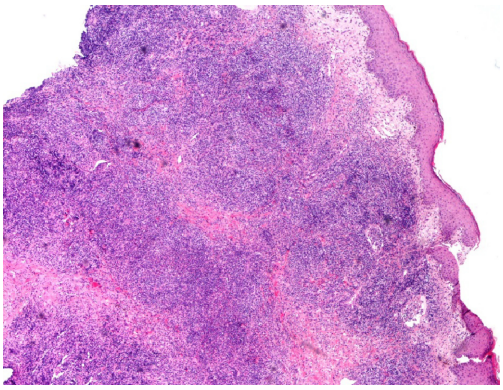

Figure 3 Dense dermic and hypodermic infiltration of lymphocytes, granulocytes (often eosinophils) and scattered Reed-Sternberg cells.

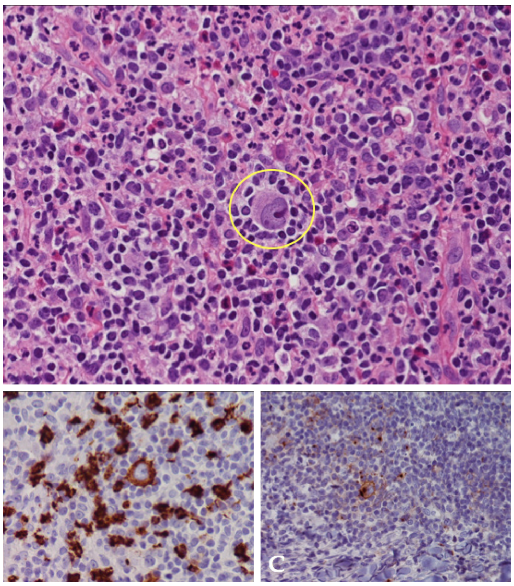

Figure 4 High power views highlighting a Reed-Sternberg large mononucleated cell (inset) in a background rich in eosinophils (A), CD30 (B) and CD15 (C) stains (HE 40 x).

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CASE REPORT

Characteristics of multiple nodules in a patient with pulmonary Langerhans cell histiocytosis: A case report

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Author contributions: Kanaji N carried out the diagnosis and followed up the patient, designed and drafted the manuscript; Tokunaga Y carried out the diagnosis; Ishikawa R collected pathological sections; Watanabe N and Kadowaki N revised the manuscript; all authors read and approved the final manuscript.

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Abstract

BACKGROUND

The common computed tomography findings of pulmonary Langerhans cell histiocytosis (PLCH) are multiple cysts and micronodules predominantly in middle to upper lung lobes. Non-cystic nodules and large nodules are atypical findings of PLCH.

CASE SUMMARY

The patient was a 48-year-old Japanese man with a smoking history (20 cigarettes/d, 28 years) and no symptoms. Multiple nodules existed in all lung lobes, predominantly in the right lower lobe. Some nodules seemed to be distributed randomly, and others were adjacent to bronchus. Most nodules were solid; some small ones were cystic. The largest nodule was 22 mm in diameter. Although metastatic lung tumors were suspected, thoracoscopic lung biopsy led to the diagnosis of PLCH. At 6 months after he quit smoking, all nodules had almost disappeared. We investigated the characteristics of nodules at diagnosis in detail. Of 349 nodules in total, 116 were in upper and 199 were in lower lobes. Ninety-six (27.5%) were cystic; the remaining 253 (72.5%) were non-cystic. The prevalence of cystic nodules was higher in upper lobes than in lower lobes (right upper 37.5% *vs* lower 18.2%, $P = 0.0068$; left upper 48.1% *vs* lower 24.4%, $P = 0.0078$). The average size (dia.) of cystic nodules was smaller than that of non-cystic nodules (5.03 mm *vs* 7.40 mm, respectively, $P < 0.0001$).

CONCLUSION

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Although multiple non-cystic nodules including large nodules (over 20 mm) are atypical, PLCH should be included in differential diagnoses. The presence of small cystic nodules predominantly in upper lobes and asymptomatic situation are also important for differential diagnoses to distinguish from metastatic cancers.

Key words: Langerhans cell histiocytosis; Multiple; Non-cystic; Nodule; Distribution; Size; Case report

Core tip: The common computed tomography findings of pulmonary Langerhans cell histiocytosis (PLCH) are multiple cysts and micronodules predominantly in middle-to-upper lung lobes. We present herein a rare case of PLCH with non-cystic multiple large nodules. Of 349 nodules in total, 116 were in upper and 199 were in lower lobes. The prevalence of cystic nodules was higher in upper lobes than in lower lobes. The average size (dia.) of cystic nodules was smaller than that of non-cystic nodules. Knowledge of such characteristics of nodules may help the pulmonologists consider PLCH in differential diagnoses of multiple nodules.

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is characterized by accumulations of large mononuclear cells named Langerhans cells that form granulomas in various organs such as bone, skin and lung[1-3]. LCH can be clinically classified into three groups: Single-system, low-risk multisystem, and multisystem with risk-organ involvement[4,5]. Pulmonary Langerhans cell histiocytosis (PLCH) is a diffuse lung disease whose clinical manifestations may involve a single organ or multisystem[4]. The common findings of PLCH on chest computed tomography (CT) scan are multiple cysts predominantly in upper lung zones and a micronodular pattern of the middle-upper lobes[4]. Non-cystic nodules and large nodules are rare in PLCH. Such characteristics of multiple nodules are common in metastatic cancers.

We here present a case of PLCH with multiple nodules including the non-cystic nodules > 20 mm in dia. We assessed the characteristics of multiple nodules including the number, distribution and sizes of cystic and non-cystic nodules.

CASE PRESENTATION

Chief complaints

A medical examination revealed an abnormal shadow on the chest radiograph of a 48-year-old Japanese man with no symptoms.

History of present illness

He visited to our hospital immediately after an abnormal shadow was pointed out.

History of past illness

He had been diagnosed with primary aldosterone disease and hypertension and had continued with treatment with tablets of potassium chloride, spironolactone, telmisartan and amlodipine besilate. He had no other notable medical history.

Personal and family history

He was a care assistant in a hospital and a current smoker (20 cigarettes/d for the past 28 years). He had no serious family history.

Physical examination

The physical examination revealed no remarkable abnormalities. Normal breath sounds and no adventitious sounds were auscultated.

Laboratory examinations

Laboratory examinations revealed a low concentration of serum potassium (3.0 mmol/L). The C-reactive protein level was 0.58 mg/dL. There were no other abnormal findings, including circulating blood cell counts, blood biochemistry and routine urine tests.

Imaging examinations

The chest radiograph and CT showed multiple nodules in both lung fields (Figure 1). Although the nodules seemed to be distributed randomly, fewer nodules were adjacent to the pleura, and some were adjacent to bronchus (Figure 1B and C). Nodules existed from upper to lower lobes, dominantly in the right lower lobes (Figure 1B and C). Most of the nodules were non-cystic, and the small nodules were cystic (Figure 1C). The largest nodule was 22 mm in dia., in the right middle lobe (Figure 1D). Mediastinal lymph nodes were approx. 10 mm in size (not shown). The differential diagnosis included metastatic lung tumors, lymph proliferative disorder, granulomatous polyangiitis, and PLCH.

FINAL DIAGNOSIS

Transbronchial biopsy specimens showed non-specific features; only inflammatory cells (not shown). Several nodules in the right lower lobe were resected under thoracoscopic surgery, and tissue specimens showed abnormal cells with notched nuclei with the infiltration of many eosinophils (Figure 2A and B). Abnormal cells were positive for CD1a and S-100 (Figure 2C and D) and negative for CD68 and CD21 (not shown). Based on these findings, we made the diagnosis of PLCH.

TREATMENT

The patient began to quit smoking after we encountered him. He received no additional medical treatment.

OUTCOME AND FOLLOW-UP

He continued the smoking cessation, and 6 months later, all nodules had almost disappeared (Figure 3).

INVESTIGATION OF CHARACTERISTICS OF MULTIPLE NODULES

To investigate the patient's CT findings at the diagnosis in detail, we counted the number of nodules in all lung lobes and classified the nodules into cystic and non-cystic nodules (Figure 4). Of the total of 349 nodules, 116 were in upper lobes and 199 were in lower lobes (right plus left lobes). Ninety-six (27.5%) were cystic, and the remaining 253 (72.5%) were non-cystic. The prevalence of cystic nodules was higher in upper lobes than in lower lobes (Figure 4A; right upper 37.5% *vs* lower 18.2%, $P = 0.0068$; left upper 48.1% *vs* lower 24.4%, $P = 0.0078$). The average size (dia.) of cystic nodules was smaller than that of non-cystic nodules (5.03 mm *vs* 7.40 mm, respectively; $P < 0.0001$, Figure 4B).

DISCUSSION

Our patient was diagnosed with PLCH and exhibited the following rare patterns on CT scans: (1) Multiple nodules dominantly in lower lobes; (2) Nodules > 20 mm in dia. Our investigation of the CT findings in detail revealed that (3) The prevalence of cystic nodules was higher in upper lobes than in lower lobes; and (4) The cystic nodules were smaller than the non-cystic nodules.

The two common CT findings of PLCH are multiple cysts and micronodules

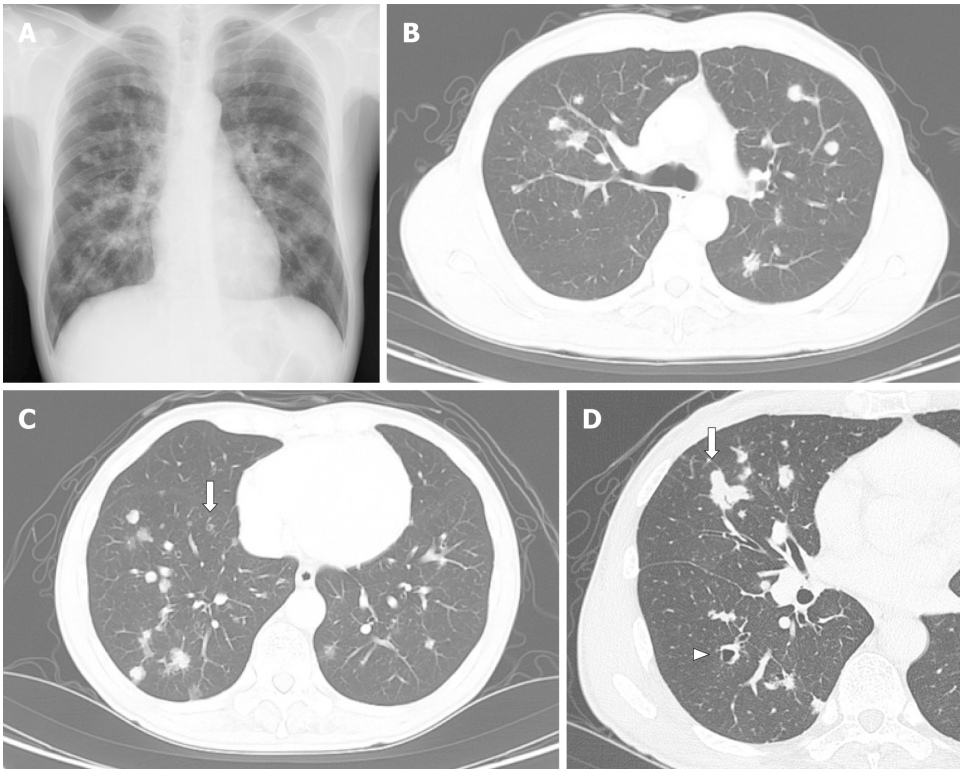

Figure 1 Radiological findings at the initial diagnosis. A: Chest X-ray at the diagnosis showed multiple nodules in bilateral lung fields; B and C: Chest computed tomography showed multiple nodules, adjacent to the pleura or bronchus, predominantly in the right lower lobe. Some small nodules showed cystic formation (arrow); D: Largest nodule was in the right middle lobe; 22 mm dia. (arrow). Arrowhead: A dilated bronchus, but not a cystic nodule.

predominantly in middle-to-upper lung zones[4]. Either one or both of the findings were recognized in all 40 of the reported cases[4]. Other abnormal findings include patchy or cord shadows, pleural thickening, pleural effusion, and mediastinal lymph node enlargement[5]. PLCH cases with multiple nodules without cystic formation have also been reported[6-8]. However, the sizes of the nodules in those cases were usually < 10 mm[6-8]. Thus, the non-cystic large nodules observed our patient are rare in PLCH. In addition, a greater number of nodules were found in lower lobes than in upper lobes. Such characteristics are common in metastatic lung tumors (cancers) because they usually develop *via* a hematogenous route and the bloodstream is more abundant in lower lobes, although transbronchial dissemination in lung cancer was also occasionally reported[9].

Many studies have shown that a subset of LCH has genetic mutations including V-Raf murine sarcoma vial homolog B1 (BRAF)[3,10]. BRAF V600E was detected in approximately one-half of patients with LCH[10]. MAPKK1 mutations were detected in 6 of 13 (46%) BRAF-negative cases[3]. These findings suggest that LCH has some genetic monoclonality, which was considered to be a type of tumor.

Langerhans cells can develop in organs such as bone, skin, brain, liver and lung[1-3], suggesting that they can spread to the whole body hematogenously. It is possible that some of the nodules observed in the present case developed as a result of hematogenous metastases. Consistent with this, the CT findings in several prior cases with multiple nodules showed a distribution pattern mimicking hematogenous pulmonary metastases[7,8]. We speculate that the distribution pattern as hematogenous lung metastases is consistent with PLCH as well as metastatic cancers.

There are several notable points for the differential diagnosis of PLCH from metastatic cancers in the present case. First, the distribution pattern of multiple nodules was not a completely hematogenous pattern, and some nodules were distributed around or adjacent to bronchi. It was reported that many small nodules were distributed in the centers of secondary lobules around small airways in PLCH[11]. It is quite unusual for a plurality of primary tumors to occur simultaneously. However, the existence/non-existence of a transbronchial dissemination of Langerhans' cells remains unclear.

Second, there were small cystic nodules. In cases of metastatic cancers, cystic changes tend to appear in larger nodules rather than in smaller nodules. Based on the follow-ups of PLCH cases, it was reported that nodular lesions transform into cysts[6]. In progressed cases, cystic changes fuse and develop emphysema-like lesions.

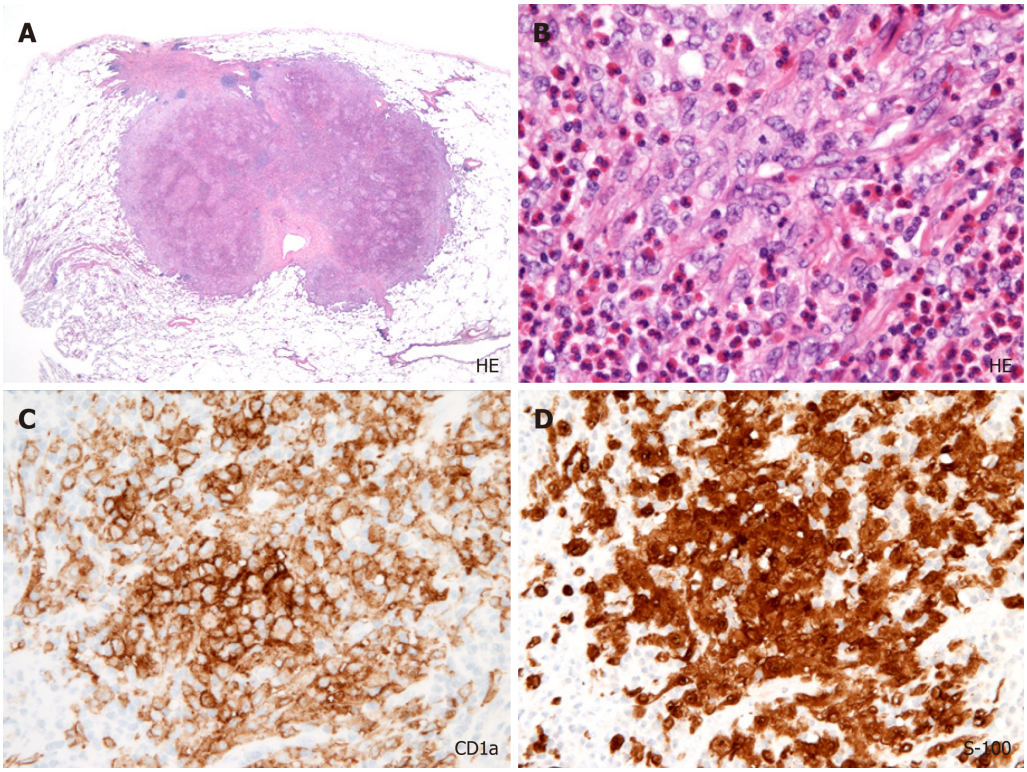

Figure 2 Histopathological findings obtained from a nodule in right lower field. A and B: Hematoxylin-eosin staining showing abnormal cells with notched nuclei with the infiltration of many eosinophils; C and D: Abnormal cells were positive for CD1a and S-100.

However, in our patient's case, the cystic nodules were smaller than the non-cystic nodules, and there were no fused cystic nodules. On the other hand, some non-cystic nodules fused and formed a snowman-like shape. In the present case, cystic changes inside nodules might appear at an early phase and disappear at a late phase at which Langerhans' cells proliferate and form a large, filled nodule.

Third, another important finding concerning the differential diagnosis between PLCH and metastatic malignant tumors is the patient's symptoms. Patients with advanced cancer often present subjective symptoms such as anorexia, body weight loss, fever, and fatigue. Our patient had no symptoms. PLCH as well as pulmonary alveolar proteinosis[12] and sarcoidosis[13] is a disease by which a symptom may relatively lack even though the evidence of the extensive radiological findings.

We counted the number of nodules and evaluated the ratio of cystic to non-cystic nodules visually. However, the computer-aided automatic evaluation of radiological findings may bring the diagnosis that is more exact than a human evaluation. Recently, trials of deep learning-based diagnosis of pulmonary nodules have been reported[14,15]. The introduction of such artificial intelligence in the medical settings will be realized in the near future.

CONCLUSION

Multiple non-cystic nodules including large nodules (> 20 mm) can occur in PLCH. Knowledge of atypical findings in PLCH, taken together with other findings (*e.g.*, cystic formation in small nodules dominantly in upper lobes and no symptom) may help pulmonologists consider PLCH in differential diagnoses.

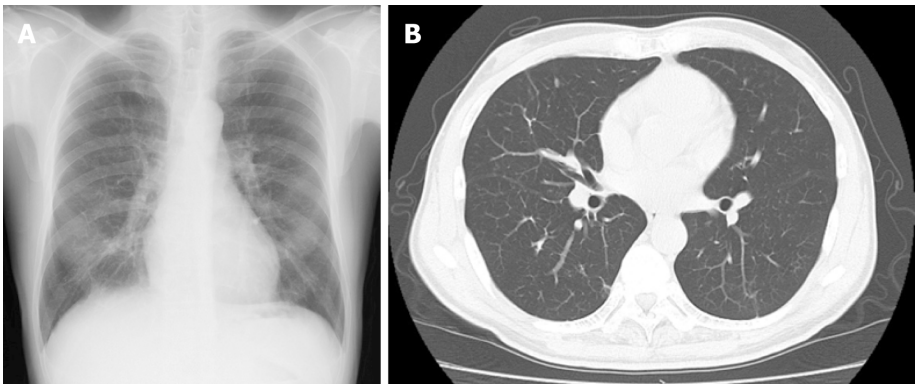

Figure 3 Radiological findings at 6 mo after the patient quit smoking. A: Chest X-ray; B: Computed tomography scan.

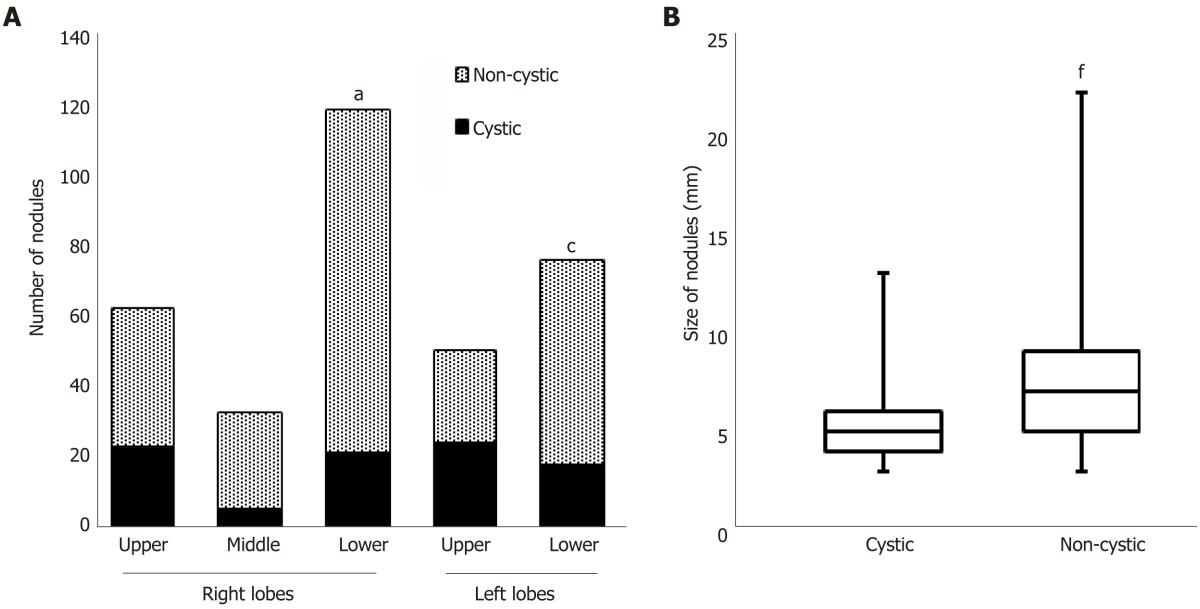

Figure 4 Numbers and sizes of cystic and non-cystic nodules. A: Number of nodules in each lobe. The prevalence of cystic nodules is compared. [a]*P*<0.01 *vs* the right upper lobe, [c]*P* < 0.01 *vs* the left upper lobe; B: Sizes of the nodules. The data summarize the results of all lung lobes. [f]*P* < 0.0001 *vs* the cystic nodules.

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CASE REPORT

Impact of continuous local lavage on pancreatic juice-related postoperative complications: Three case reports

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Author contributions: Hori T performed the surgeries, wrote the report, and created all original illustrations and schemas; all authors assisted with surgical and endoscopic therapies, assessing important papers, and providing academic opinions; Zaima M supervised this research.

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Abstract

BACKGROUND

Postoperative pancreatic leakage readily results in intractable pancreatic fistula and subsequent intraperitoneal abscess. This refractory complication can be fatal; therefore, intensive treatment is important. Continuous local lavage (CLL) has recently been reevaluated as effective treatment for severe infected pancreatitis, and we report three patients with postoperative intractable pancreatic fistula successfully treated by CLL. We also discuss our institutional protocol for CLL for postoperative pancreatic fistula.

CASE SUMMARY

The first patient underwent subtotal stomach-preserving pancreaticoduodenectomy, and pancreatic leakage was observed postoperatively. Intractable pancreatic fistula led to intraperitoneal abscess, and CLL near the

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pancreaticojejunostomy site was instituted from postoperative day (POD) 8. The abscess resolved after 7 d of CLL. The second patient underwent distal pancreatectomy. Pancreatic leakage was observed, and intractable pancreatic fistula led to intraperitoneal abscess near the pancreatic stump. CLL was instituted from POD 9, and the abscess resolved after 4 d of CLL. The third patient underwent aneurysmectomy and splenectomy with wide exposure of the pancreatic parenchyma. Endoscopic retrograde pancreatic drainage was performed on POD 15 to treat pancreatic fistula; however, intraperitoneal abscess was detected on POD 59. We performed CLL endoscopically *via* the transgastric route because the percutaneous approach was difficult. CLL was instituted from POD 63, and the abscess resolved after 1 wk of CLL.

CONCLUSION
CLL has therapeutic potential for postoperative pancreatic fistula.

Key words: Surgery; Pancreas; Pancreatic fistula; Pancreatic juice; Postoperative complications; Case report

Core tip: Pancreatic fistula after pancreatic surgery is a potentially fatal refractory complication. We describe the typical findings based on three patients who survived, and two patients who died of fatal complications. We also discuss the importance of intensive treatment for postoperative pancreatic fistula, with a literature review. Continuous local lavage (CLL) has been reevaluated as an effective treatment for severe infected pancreatitis, and our findings show that CLL shortened the therapeutic duration for postoperative pancreatic fistula. We suggest that CLL has therapeutic potential for postoperative pancreatic fistula. We also introduce our institutional protocol for CLL for postoperative pancreatic fistula.

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INTRODUCTION

Postoperative complication related to pancreatic juice leakage is a major clinical problem[1]. Pancreatic surgeries are inherently accompanied by postoperative pancreatic leakage[1,2], which readily results in intractable pancreatic fistula and subsequent intraperitoneal abscess[1,2]. This refractory complication may be fatal by inducing sepsis secondary to leakage from the digestive tract and shock hemodynamics secondary to sudden rupture of a pseudoaneurysm[3,4].

In pancreatitis therapy, minimally-invasive drainage (*e.g.*, percutaneous and transluminal approaches) is currently considered useful, especially for necrotizing and infected pancreatitis[5-7]. Recently, continuous local lavage (CLL) has been reevaluated as effective treatment for severe infected pancreatitis[8-11].

We present findings for three thought-provoking cases of postoperative intractable pancreatic fistula with bacterial infection that were successfully treated by CLL. We also discuss the typical findings of potentially fatal complications associated with intractable postoperative pancreatic fistula based on our patients' data, and we discuss the importance of intensive treatment for postoperative pancreatic fistula, with a literature review. We suggest that CLL has therapeutic potential for postoperative pancreatic juice-related complications and discuss our institutional protocol for CLL for postoperative pancreatic fistula.

CASE PRESENTATION

Case 1

A 66-year-old man suffered from cholangitis. Contrast computed tomography (CT) revealed a hypovascular tumor in the pancreatic head and biliary dilatation. His locally-advanced pancreatic cancer was categorized as stage IIB in the tumor-node-metastasis classification[12]. Obstructive jaundice was successfully treated by endoscopic nasobiliary drainage. Thereafter, he underwent subtotal stomach-preserving pancreaticoduodenectomy with extended lymph node and nerve plexuses dissection. Operative time was 433 min, and blood loss was 950 mL. Reconstructions were performed by modified Child's method with Braun's anastomosis, and pancreaticojejunostomy was performed using modified Blumgart's technique. We placed an intraductal stent (pancreatic duct tube, 7 Fr, burled; Sumitomo Bakelite Co., Ltd., Tokyo, Japan) and performed duct-to-jejunal anastomosis with 12 interrupted sutures (polydioxanone: 6-0 PDS II, violet; Ethicon, Inc., Cincinnati, OH, United States). Intentional approximation of the pancreatic stump and jejunal wall was performed using four interrupted sutures (polypropylene: 3-0 Prolene; Ethicon, Inc.). We closed all mesenteric gaps and placed three drains near the anastomoses of the pancreaticojejunostomy, choledochojejunostomy, and gastrojejunostomy sites (Figures 1 A and B). For the pancreaticojejunostomy, we ran two drains intentionally through the ventral and dorsal sides.

Pancreatic leakage was observed early postoperatively, and the peak amylase level in the drainage discharge was 23480 U/L (Figure 1C). Although drainage discharge gradually decreased to 1 wk postoperatively, high amylase levels in the drainage discharge (8980 U/L) were still observed on postoperative day (POD) 8 (Figure 1C). Contrast CT on POD 8 revealed that intractable pancreatic fistula had resulted in an intraperitoneal abscess around the pancreaticojejunostomy (Figure 1D). Fistulography *via* both drains revealed an abscess cavity around the pancreaticojejunostomy. Artificial fistulas along these drains had matured as accessible pathways for drain replacement, and the abscess cavity could be lavaged by injecting saline through one drain. We replaced both drains with red vulcanized rubber tubes. Fluoroscopic examination confirmed that the recovery rate of injected contrast dye was approximately 85%, and that uncollectible dye never spread, even under high-pressure administration.

Via the ventral tube to the pancreaticojejunostomy, we irrigated 1000 mL of saline per day slowly but continuously into the abscess cavity beginning on POD 8 (Figure 2). We used the dorsal tube to the pancreaticojejunostomy only to drain irrigated saline (Figure 2). Saline volume was increased on POD 12 to 1500 mL/d because the amylase level in the drainage discharge was relatively high (2880 U/L). Thereafter, amylase level in the drainage discharge decreased dramatically (Figure 1C). Fistulography on POD 15 revealed that the abscess had resolved after 7 days of CLL. The irrigation tube was removed on POD 15 because the amylase level in the discharge was 120 U/L (Figure 1C); we removed the drainage tube on POD 17. The patient's postoperative course was categorized as Clavien–Dindo grade II[13]. He was discharged on POD 22, and no recurrence was observed as of 4.3 years after surgery.

Case 2

A 45-year-old man suffered refractory pancreatitis, although he had no history of alcohol abuse, and autoimmune pancreatitis was excluded. He began suffering repeat episodes of acute pancreatitis from 21 years of age, and underwent pseudocystojejunostomy at 35 years of age. Metabolic disorders (*e.g.*, hyperlipidemia and gout) were present, but diabetes was not observed. Pancreatic stones and peripancreatic edema were seen at 42 years of age. Although stones were previously removed endoscopically, recurrent stones and peripancreatic abscess appeared in the pancreatic body and tail at 45 years of age. Collateral vessels were well-developed secondary to venous-flow occlusion related to the chronic pancreatitis, and splenomegaly was also confirmed. Therefore, we performed distal pancreatectomy and removal of the pseudocystojejunostomy. Operative time was 272 min. Blood loss was 429 mL, and transfusion of 280 mL packed red blood cells was required. Pancreatectomy was performed using a linear stapler (Endo GIA black cartridge, Reinforced Reload with Tri-Staple technology; Medtronic, Dublin, Ireland), and we placed a drain near the staple line (Figure 3A). To prevent drain dislocation, we fixed the drain to the surrounding tissue using absorbable suture (3-0 Coated Vicryl Rapide; Ethicon, Inc.).

Pancreatic leakage occurred early postoperatively, and the peak amylase level in the drain discharge was 18846 U/L. Although drainage decreased gradually over 8 d, high amylase levels in the drain discharge (14469 U/L) were still present on POD 9. Contrast CT on POD 9 revealed that intractable pancreatic fistula led to

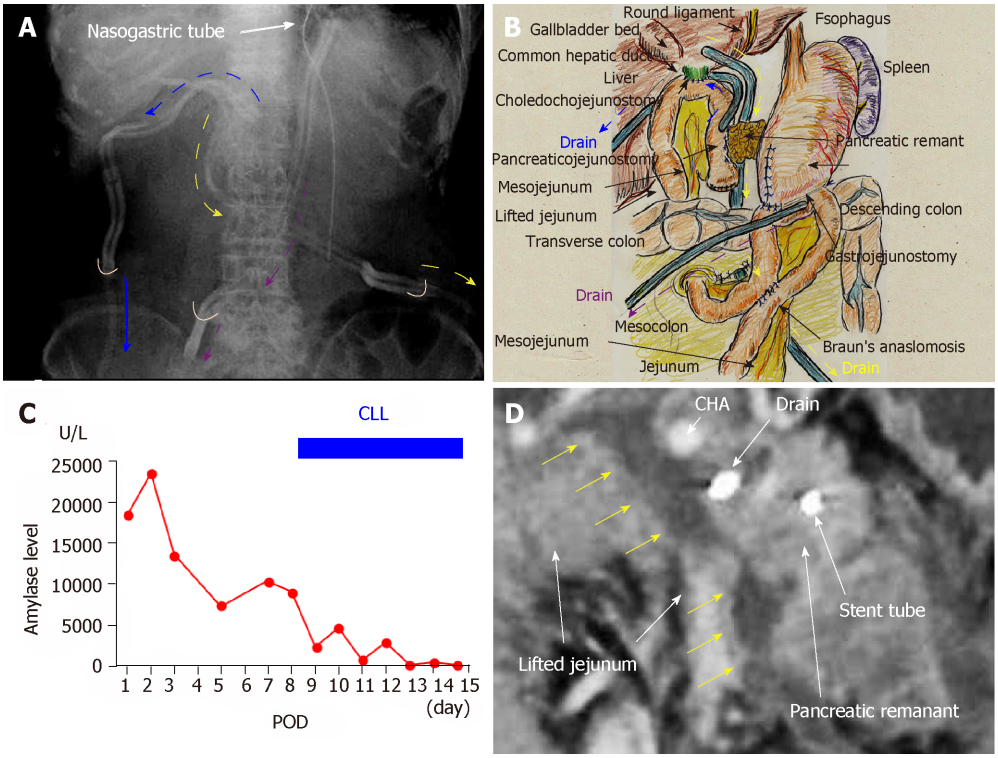

Figure 1 Case 1. A and B: We placed three drains near the anastomoses of the pancreaticojejunostomy (yellow arrows), choledochojejunostomy (blue arrows), and gastrojejunostomy (purple arrows). For the pancreaticojejunostomy, we ran two drains intentionally through the ventral and dorsal sides (yellow and blue arrows, respectively); C: Pancreatic leakage began early postoperatively, and peak amylase level in the drainage discharge was 23480 U/L. High amylase levels in the drainage discharge were still seen on postoperative day (POD) 8 continuous local lavage (CLL) was initiated on POD 8, and saline volume was increased on POD 12. We continued CLL for 7 d, and amylase levels in the drainage discharge decreased dramatically during that time; D: Contrast computed tomography on POD 8 revealed intractable pancreatic fistula had led to an intraperitoneal abscess around the pancreaticojejunostomy (yellow arrows). CHA: Common hepatic artery; CLL: Continuous local lavage; POD: Postoperative day.

intraperitoneal abscess near the staple line (Figure 3B). Fistulography *via* the drain on POD 9 identified the pancreatic fistula and abscess cavity (Figure 3C). The abscess cavity could be lavaged, and the recovery rate of injected contrast dye was approximately 90%; uncollectible dye never spread. Artificial fistulas along the drain had matured as accessible pathways for drain replacement, and we replaced the original drain with a two-way tube (Salem Sump, 14 Fr: Medtronic). To effectively lavage the pancreatic fistula and abscess cavity, the tip position of this two-way tube was appropriately adjusted during fluoroscopic examination (Figure 4).

From POD 9, saline irrigation was continuously injected *via* the two-way tube that followed the drainage route. A total of 1000 mL of saline per day was slowly irrigated into the abscess cavity, and amylase levels in the drainage discharge decreased immediately (767 U/L). Fistulography on POD 12 revealed that the abscess had resolved after 4 d of CLL (Figure 3D), and we removed the two-way tube on POD 13. The patient's postoperative course was categorized as Clavien–Dindo grade II[13]. He was discharged on POD 18, and 3 months after surgery, no metabolic disorders were identified.

Case 3

A 70-year-old man was being followed for myasthenia gravis and diabetes. Periodic CT incidentally detected a splenic arterial aneurysm that had enlarged over time. The true aneurysm extended almost the full length of the splenic artery, arising from the root to the splenic hilum. Interventional radiology was excluded from the therapeutic options because of risks associated with arterial recanalization, ischemic complications, and cost effectiveness. Therefore, we performed elective surgery with aneurysmectomy and splenectomy. The splenic artery was cut at its root without disturbing celiac arterial flow. After dissecting the pancreatic parenchyma to detect the intact portion of the dorsal pancreatic artery branching from the aneurysm, this artery was also cut. Because dense pancreatic capsule was adherent to the calcified aneurysmal wall, the aneurysm required dissection from the pancreatic parenchyma. The pancreatic parenchyma was preserved with its drainage vein, although the pancreatic parenchyma was widely exposed secondary to the aneurysmectomy

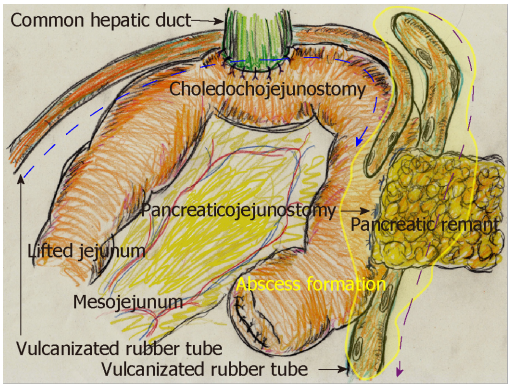

Figure 2 From the ventral tube to the pancreaticojejunostomy (blue arrow), saline was slowly and continuously irrigated into the abscess cavity (yellow area). In contrast, we used the dorsal tube to the pancreaticojejunostomy (purple arrow) only to drain the irrigated saline.

(Figure 5A). Operative time was 250 min, and blood loss was 1907 ml.

The patient subsequently developed postoperative intractable pancreatic fistula, and refractory symptoms affected his postoperative course. Peak amylase level in the drainage discharge was 32197 U/L. Although intraperitoneal drainage continued, optimal tube drainage (*i.e.*, intentional placement along the distal pancreas) was not an option because a percutaneous approach was too difficult. Fistulography *via* the intraperitoneal drain on POD 13 revealed intractable pancreatic fistula in the distal pancreas (Figure 5B); therefore, we performed endoscopic retrograde pancreatic drainage on POD 15. Intraperitoneal drainage with retrograde pancreatic drainage was continued for 36 days with intermittent antibiotics until POD 40. However, intractable pancreatic fistula resulted in an abscess and localized peritonitis secondary to bacterial infection. Contrast CT on POD 59 detected an intraperitoneal abscess in the distal pancreas (Figure 5C).

On POD 63, we initiated CLL of the abscess cavity *via* the transgastric route. The abscess cavity was punctured endoscopically under ultrasound guidance, and a transgastric path into the abscess cavity was made. Transnasal infusion was initiated, and transgastric drainage tubes were placed endoscopically (Figure 5D). CLL was instituted *via* transnasal continuous infusion and endoscopic transgastric drainage (Figure 6). The abscess cavity could be effectively lavaged, and the recovery rate of injected contrast dye was approximately 70% because of the concurrent transgastric drainage tube.

From POD 63, saline irrigation was continuously injected *via* the transnasal infusion tube. A total of 1000 ml of saline per day was slowly irrigated into the abscess cavity, and amylase levels in the drainage discharge decreased immediately (139 U/L). Fistulography on POD 70 revealed that the abscess resolved after 1 wk of CLL, and the refractory pancreatic fistula was no longer identifiable. Therefore, we removed the transnasal infusion and retrograde pancreatic drainage tubes. The patient was discharged on POD 72 with only the transgastric drainage tube remaining in place. His postoperative course was categorized as Clavien–Dindo grade IIIa[13], and he was in good health 9 moafter surgery.

DISCUSSION

Pancreatic fistula is one of the most common complications after pancreatic surgery[1,2], and diagnostic criteria and nosological classification have been established[14]. Although pancreatic diseases may cause associated pancreatitis, pancreatic parenchyma with an intermediate or normal consistency produces more pancreatic juice and has a higher rate of pancreatic leakage[15]. Any pancreatic surgery may lead to intractable pancreatic fistula unless the pancreatic parenchyma has been destroyed secondary to the primary disease[15]. Unfortunately, pancreatic stimulation and bacterial infections trigger a vicious cycle[1,16]. Activated pancreatic juice and accelerated bacterial infection destroy digestive anastomosis sites and create arterial pseudoaneurysm; anastomotic leakage and arterial rupture can be fatal[3,4]. Based on our patient experience, Figure 7 shows the typical findings of anastomotic leakage and arterial rupture associated with intractable pancreatic fistula. These potentially fatal complications are grave concerns for hepatobiliary-pancreatic surgeons; therefore, many focus on reconstructive techniques to reduce the development of

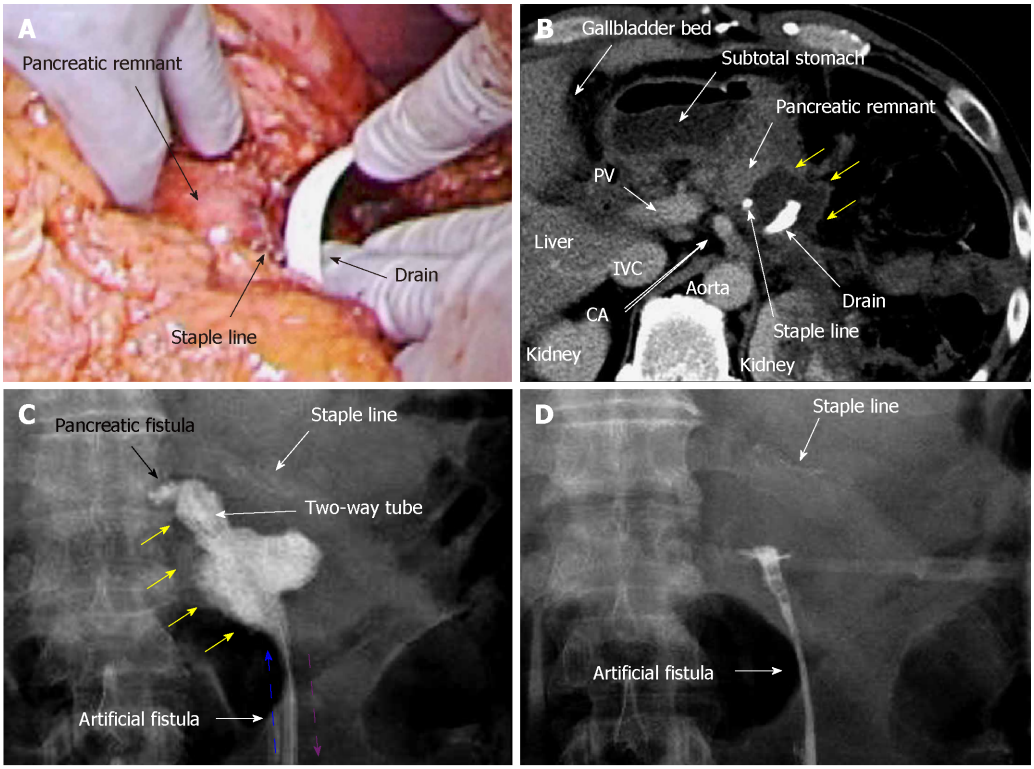

Figure 3 Case 2. A: Pancreatectomy was performed using a linear stapler, and we placed a drain near the staple line; B: Contrast computed tomography on postoperative day (POD) 9 revealed that intractable pancreatic fistula had led to an intraperitoneal abscess near the staple line (yellow arrows); C: Fistulography *via* the drain on POD 9 revealed intractable pancreatic fistula (black arrow) and the abscess cavity (yellow arrows). From POD 9, saline irrigation (blue arrow) was continuously injected into the abscess cavity *via* a two-way tube with the drainage route (purple arrow). Thereafter, amylase levels in the drainage discharge decreased immediately; D: Fistulography on POD 12 revealed that the abscess resolved after 4 d of continuous local lavage. CHA: Common hepatic artery; CLL: Continuous local lavage; IVC: Inferior vena cava; POD: Postoperative day.

refractory pancreatic fistula[2].

Pancreatic fistula is sometimes inevitable complication after pancreatic surgery. Soft pancreatic parenchyma with normal consistency produces more pancreatic juice[15], even though pancreatic diseases may cause associated pancreatitis. In cases with a higher risk of pancreatic leakage, intraoperative placement of two-way tube or irrigation drainage tube may be a good solution.

Minimally-invasive drainage is a standard therapeutic option for necrotizing and infected pancreatitis [5-7], although, historically, only a surgical approach was recommended[17-21]. Recently, CLL has been reevaluated as a therapeutic option for severe infected pancreatitis[8-11], and in our three patients, intractable pancreatic fistulas with bacterial infection gradually resolved after CLL. However, CLL is currently being reevaluated as an effective treatment specifically for severe infected pancreatitis[8-11]; therefore, we suggest that CLL may have therapeutic potential for postoperative pancreatic juice-related complications.

Our institutional protocol for CLL for postoperative pancreatic fistula is summarized in the Table 1. Key points and pitfalls for successful CLL are as follows: (1) Maturity of the artificial fistula(s) is important. An accessible pathway is required for drain replacement; therefore, tube replacements for CLL should be delayed until sufficient maturity of the artificial fistulas has developed along the intraperitoneal drains. Red vulcanized rubber tubes are advantageous for creating artificial fistulas. Also, injected saline should never spread outward from a mature artificial fistula because extension of the abscess cavity secondary to CLL should be avoided. Therefore, we recommend high-pressure administration of contrast dye during fistulography; (2) The optimal setting is crucial for effective CLL. The abscess cavity and pancreatic fistula should be effectively lavaged, and therefore, appropriate tube placement is required. A recovery rate of injected fluid > 80% should be guaranteed; and (3) Toxic amylase levels should decrease dramatically after CLL. Amylase levels in the drainage discharge are extremely important to evaluate pancreatic leakage after surgery[22]. Amylase levels in the draining discharge within the lower triple-digits (*i.e.*, approximately 100–500 U/L) are ideal after CLL induction. CLL generally begins with 1000 ml of saline per day. Tubes may be dislocated during CLL, and dysfunction of the sphincter of Oddi worsens pancreatic leakage[23]. CLL should be reconsidered if a

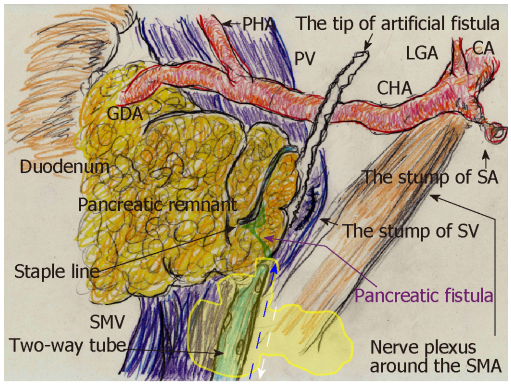

Figure 4 We replaced the drain passing almost through the abscess cavity (yellow area) with a two-way tube. Saline was continuously injected through the irrigation route (blue arrow), and this two-way tube followed the drainage route (white arrow). To effectively lavage the intractable pancreatic fistula and abscess cavity, the tip position of this tube was appropriately adjusted during fluoroscopic examination. CA: Celiac artery; CHA: Common hepatic artery; GDA: Gastroduodenal artery; LGA: Left gastric artery; PHA: Proper hepatic artery; PV: Portal vein; SA: Splenic artery; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein; SV: Splenic vein.

saline volume > 1500 mL per day is required to decrease amylase levels in the drainage discharge; positional change in the tube location or endoscopic pancreatic drainage may be required.

Waiting until the fistulas along the intraperitoneal drains mature is important for CLL induction (Table 1). Injected contrast dye should never spread outward from the mature fistula during fistulography. We have an impression that approximately one week after surgery is required for maturity of the artificial fistula.

In our patients, CLL shortened the therapeutic duration of postoperative pancreatic fistula and subsequently prevented fatal complications related to pancreatic juice leakage. CLL may be a powerful tool to overcome pancreatic juice-related complications with bacterial infection following pancreatic surgery.

CONCLUSION

Intensive treatment for postoperative pancreatic fistula is important to avoid fatal outcomes. CLL has therapeutic potential for postoperative pancreatic fistula. We hope that our thought-provoking cases will be informative for physicians working with patients with pancreatic disorders.

Table 1 Institutional protocol for continuous local lavage for postoperative pancreatic fistula

Maturity of the artificial fistula for CLL induction
Wait until the fistulas along the intraperitoneal drains mature because an accessible pathway for drain replacement is needed
Injected saline should never spread outward from the mature fistula
No extension of contrast dye should be confirmed during fistulography
Optimal setting for effective CLL
The abscess cavity and pancreatic fistula should be effectively lavaged
Appropriate tube placement is required
A recovery rate of injected fluid of > 80% should be confirmed
Decreased toxicity after CLL
Amylase level in the drainage discharge within the lower triple-digits is ideal
CLL should be reconsidered if ≥ 1500 mL/d saline is insufficient to decrease amylase levels in the drainage discharge

CLL: Continuous local lavage.

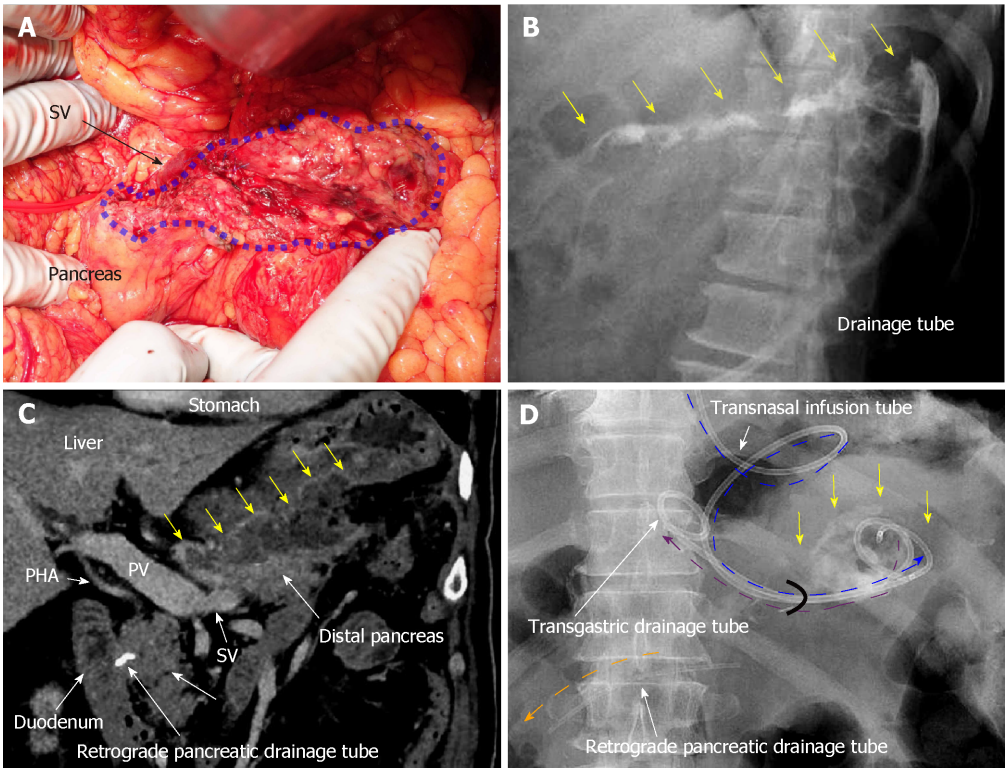

Figure 5 Case 3. A: Pancreatic parenchyma was preserved with the splenic vein, although the pancreatic parenchyma was widely exposed secondary to the aneurysmectomy (blue area); B: Optimal tube drainage (*i.e.*, intentional placement along the distal pancreas) could not be established because of difficulty using a percutaneous approach, and intractable pancreatic fistula along the distal pancreas (yellow arrows) was seen during fistulography on postoperative day (POD) 13; C: Intractable pancreatic fistula resulted in an abscess and localized peritonitis secondary to bacterial infection, and contrast computed tomography on POD 59 revealed an intraperitoneal abscess along the distal pancreas (yellow arrows); D: A retrograde pancreatic drainage tube (orange arrow) was placed endoscopically on POD 15. On POD 63, continuous local lavage (CLL) of the abscess cavity (yellow arrow) was initiated endoscopically *via* the transgastric route. Transnasal infusion was initiated and transgastric drainage tubes (purple and blue arrows) were placed endoscopically. From POD 63, saline irrigation was continuously injected *via* the transnasal infusion tube, and amylase levels in the lavaged fluid began to decrease immediately. Fistulography on POD 70 revealed resolution of the abscess after 1 wk of CLL. CLL: Continuous local lavage; PHA: Proper hepatic artery; POD: Postoperative day; PV: Portal vein; SV: Splenic vein.

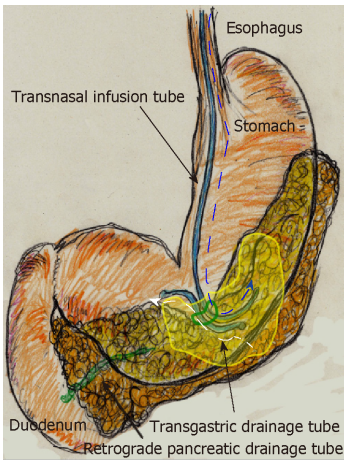

Figure 6 Continuous local lavage into the abscess cavity (yellow area) was instituted *via* transnasal continuous infusion (blue arrow) and endoscopic transgastric drainage (white arrow).

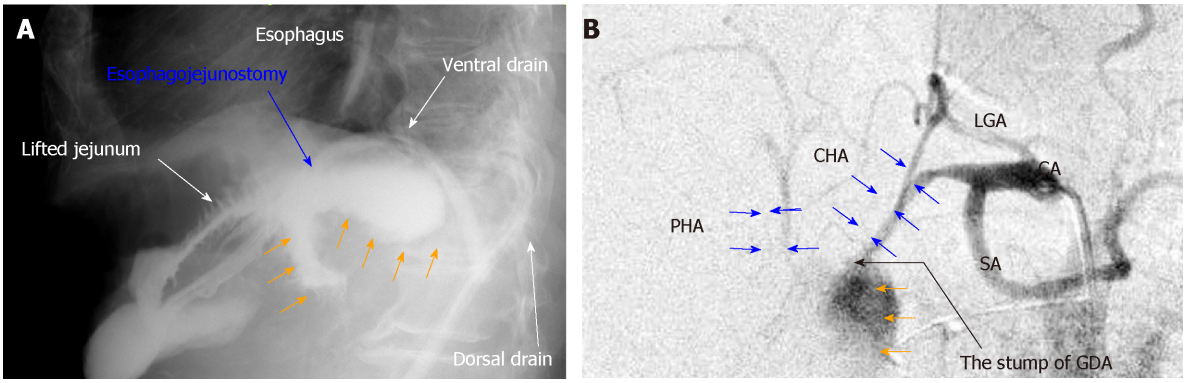

Figure 7 Typical findings of anastomotic leakage and arterial rupture associated with intractable pancreatic fistula. A: Anastomotic leakage is a potentially fatal complication related to pancreatic juice leakage. Typical findings in postoperative examinations for digestive tract leakage secondary to anastomotic failure caused by intractable pancreatic fistula are shown; B: Arterial rupture of a pseudoaneurysm is a fatal complication related to pancreatic juice leakage. Typical angiographic findings for arterial pseudoaneurysm rupture caused by intractable pancreatic fistula are shown. CA: Celiac artery; CHA: Common hepatic artery; GDA: Gastroduodenal artery; LGA: Left gastric artery; PHA: Proper hepatic artery; POD: Postoperative day; SA: Splenic artery.

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CASE REPORT

Adult intussusception caused by colonic anisakis: A case report

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Abstract

BACKGROUND

Colo-colonic intussusception is an uncommon phenomenon in an adult. Adult intussusception accounts for < 5% of total cases, and the colo-colonic type is < 30% of cases. Although surgical management has been the treatment of choice for intestinal intussusception in adults, because most frequent causes for adult intussusception are malignant in origin, the importance of the roles of preoperative colonoscopic evaluation has recently been emerging.

CASE SUMMARY

We report an extremely rare case of adult colo-colonic intussusception caused by colonic anisakiasis and successfully treated by endoscopic removal of the Anisakis body. A 59-year-old man visited the emergency department due to 1 day of lower abdominal colicky pain. Abdominopelvic computed tomography (APCT) revealed the presence of mid-transverse colon intussusception without definite necrosis, which was possibly related with colorectal cancer. Because there was no evidence of necrosis at the intussusception site, a colonoscopy was performed to target the colonic lesion and obtain tissue for a histopathological diagnosis. An Anisakis body was found when inspecting the suspicious colonic lesion recorded by APCT. The Anisakis body was removed with forceps assisted by colonoscopy. The patient's symptoms improved dramatically after removing the Anisakis. A reduced colon without any pathological findings was seen on the follow-up APCT. Without any further treatment, the patient was discharged 5 d after the endoscopy.

CONCLUSION

When colonic intussusception without necrosis occurs in an adult, physician should consider a colonoscopy to exclude causes cured by endoscopy.

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Core tip: We report an extremely rare case of adult colo-colonic intussusception caused by colonic anisakiasis and successfully treated by endoscopic removal of the Anisakis body. When colonic intussusception occurs in an adult patient and there is no evidence of necrosis of the colon, it is necessary to consider a colonoscopy to exclude causes that can be cured by endoscopy.

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INTRODUCTION

Eating raw marine food is popular not only in Asian countries but also in Europe and the United States, which has allowed parasitic diseases, such as anisakiasis, to emerge worldwide[1-3].

Anisakiasis is a parasitic disorder that occurs after ingesting the larval stages of ascaridoid nematodes[4]. Anisakids use aquatic mammals as their definitive hosts, while humans are the incidental host after eating raw marine food infected with Anisakis third-stage larvae[4,5]. The disease of anisakiasis presents after direct penetration of larvae into the gastrointestinal wall (invasive) and/or an allergic reaction (noninvasive form)[6]. The invasive form of Anisakis larvae is usually found in the mucosa or submucosa of the gastric and small bowel walls, and causes problems, such as nausea, vomiting, hematemesis, and abdominal pain within a few hours after ingesting the larvae[6]. Colonic anisakiasis is rare, and induces symptoms that mimic other diseases, such as acute appendicitis, ileitis, diverticulitis, cholecystitis, inflammatory bowel disease, and small bowel obstruction[7-10].

Colo-colonic intussusception is also an uncommon phenomenon in an adult[11]. Adult intussusception accounts for < 5% of total cases, and the colo-colonic type is < 30% of cases, while the intestinal type accounts for most of the cases[11].

We report an extremely rare case of adult colo-colonic intussusception caused by anisakiasis, which was successfully treated by a colonoscopic intervention.

CASE PRESENTATION

Chief complaints

A 59-year-old male visited the emergency department presenting with new onset left-sided lower abdominal pain.

History of present illness

He has abdominal pain for 1 day with no febrile sense.

History of past illness

He has no known medical history.

Personal and family history

He had no specific personal or family history of cancer or cancer related disease.

Physical examination on admission

Physical examination on admission revealed that he has upper abdominal tenderness but without rebound tenderness.

Laboratory examinations

Laboratory findings, including a blood cell count, chemistry, electrolytes, C-reactive protein (CRP), and carcinoembryonic antigen (CEA) levels were within normal ranges (hemoglobin, 12.9 g/dL; white blood cell count, 7.04 × 10^3/mm^3; CRP, 0.04 mg/dL;

and CEA, 0.69 mg/dL).

Imaging examination

He underwent a contrast enhanced abdominopelvic computed tomography scan (APCT) that showed colo-colonic intussusception in the mid-transverse colon (Figure 1). After an interdisciplinary approach on the part of the radiology, surgery, and gastroenterology departments, intussusception induced by descending colon cancer was highly suspected even though there was no definite evidence of cancer on the APCT, given that the most frequent etiology for adult colo-colonic intussusception is malignancy.

FINAL DIAGNOSIS

A multidisciplinary team decided on surgery to reduce the intussusception and treat the malignancy. Before the operation, a colonoscopy was done to target the unrevealed malignancy, as there was no definite necrosis around the colonic region with intussusception. During colonoscopic procedures, An approximately 3.0 cm sized Anisakis body, which had penetrated the colonic wall was seen in the transverse colon. The final diagnosis for patient was colo-colonic intussusception caused by colonic anisakiasis.

TREATMENT

During colonoscopy, an approximately 3.0 cm sized Anisakis body, which had penetrated the colonic wall was seen in the transverse colon (Figure 2). The Anisakis body was removed with biopsy forceps and carried to the pathology department. The final tentative diagnosis was colonic Anisakis (Figure 3).

OUTCOME AND FOLLOW-UP

After removing the Anisakis body by colonoscopy, the patient's symptoms and lower abdominal pain completely resolved and did not require further intervention. A subsequent APCT showed successful reduction of the endoscopic intussusception (Figure 4). Without any further treatment, the patient was discharged 5 days after the endoscopy. After 6month follow up, all of the patient symptom and signs have been alleviated.

DISCUSSION

In this study, we report an extremely rare case of colo-colonic intussusception in an adult that occurred due to colonic Anisakis and was cured by endoscopic removal of Anisakis larvae.

Adult intestinal intussusception is a rare disease, which accounts for only 5% of all cases of intussusception[12]. Furthermore, colo-colonic intussusception is rarer than small bowel intussusception, and accounts for < 30% of cases[12]. The most common site for colo-colonic intussusception is the proximal colon, and colo-colonic intussusception in the transverse colon is particularly rare [11].

Cases of intestinal intussusception in adults and children differ in a number of aspects, including incidence, etiology, and treatment[12]. While child intussusception includes almost 95% of all intussusception cases, adult intussusception accounts for < 5% of all cases. It is the most common cause of obstruction in infants but is extremely rare in adult and accounts for < 1% of cases. While child intussusception is usually of the primary type, adult intussusception is always secondary to a benign or malignant intestinal neoplasm, stricture, or diverticulum[11]. Intussusception in children is usually treated with supportive care or a contrast enema, whereas 70–90% of adult intussusceptions often require definitive treatment and surgical resection as adult intussusception is generally secondary to a benign or malignant neoplasm, diverticulum, or stricture. In this case, a rare colo-colonic intussusception occurred caused by colonic anisakiasis[13].

Intestinal anisakiasis is a parasitic disease of the gastrointestinal tract. Nematodes in the Anisakidae family cause anisakiasis[14]. Humans are the incidental host in the life cycle after eating raw or uncooked fish containing Anisakis larvae[14]. In this regard, intestinal anisakiasis is prevalent in Asian countries where sushi or raw fish is

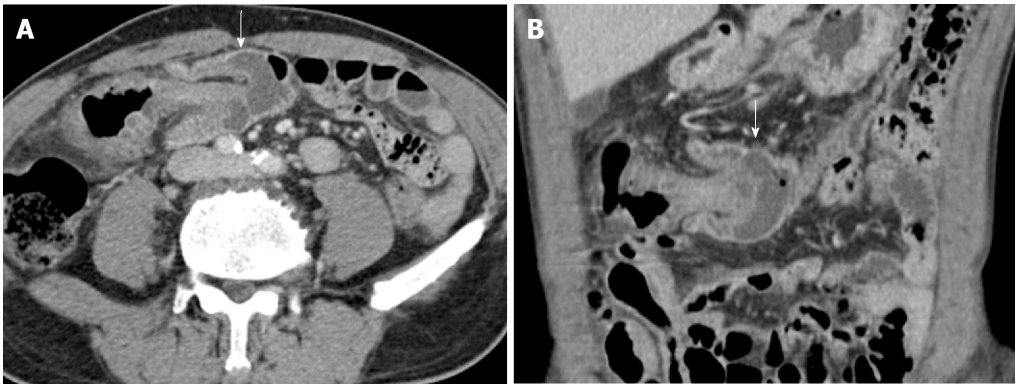

Figure 1 Pre-treatment abdominopelvic computed tomography. A and B: Axial and coronal reformatted images of contrast-enhanced computed tomography show a colo-colonic intussusception with subepithelial edema in mid transverse colon (white arrows). There is no evidence of visible tumor at intussusception in computed tomography.

popular.

The mechanism that precipitates intestinal intussusception is unclear. It has generally been accepted that an injury or irritation of the intestinal wall can alter normal peristalsis of the intestine related with the process of invagination[13]. Colonic Anisakis is a cause of wall injury, particularly when the Anisakis larva penetrates the colon wall; therefore, colonic Anisakis is a cause of colo-colonic intussusception even though colonic Anisakis is extremely rare. In this case, colonic Anisakis may have been the cause of the colo-colonic intussusception, as the patient's symptoms were relieved and the colonic intussusception was reduced after removing the larva[7,13].

In contrast to previously reported cases, colo-colonic intussusception in this case was successfully resolved by endoscopic reduction in an acute setting (< 24 h), and the cause of the intussusception was promptly diagnosed. Surgical management has been the treatment of choice for intestinal intussusception in adults, because most frequent causes for adult intussusception are malignant in origin. However, a preoperative colonoscopy should be carefully considered especially for cases with no evidence of necrosis of colon in initial imaging study to detect the cause which may be amenable to endoscopic intervention and to avoid an unnecessary surgical procedure. In this case, colo-colonic intussusception, without any evidence of colonic necrosis on the initial image studies including abdominal pelvic computed tomography, was successfully resolved by endoscopic reduction in an acute setting (< 24 h). Further studies comparing endoscopic (or preoperative diagnostic endoscopy) and surgical procedures on long-term outcomes are needed.

The treatment of choice for anisakiasis is endoscopic removal of the nematode, and the clinical symptoms usually stop[15]. In this case, the patient's symptoms were relieved after endoscopic removal of the Anisakis larva[15]. However, chronic cases with the evidence of the infected lesions on intestine should be considered surgical resection, and administration of tribendazole even though it is ineffective[16].

CONCLUSION

In conclusion, when colo-colonic intussusception occurs in adult patients, and without definite evidence of necrosis in the intestinal tract, a colonoscopy should be considered to exclude the cause that could be cured by endoscopy and to avoid an unnecessary surgical procedure. Further studies comparing endoscopic (or preoperative diagnostic endoscopy) and surgical procedures on long-term outcomes are needed.

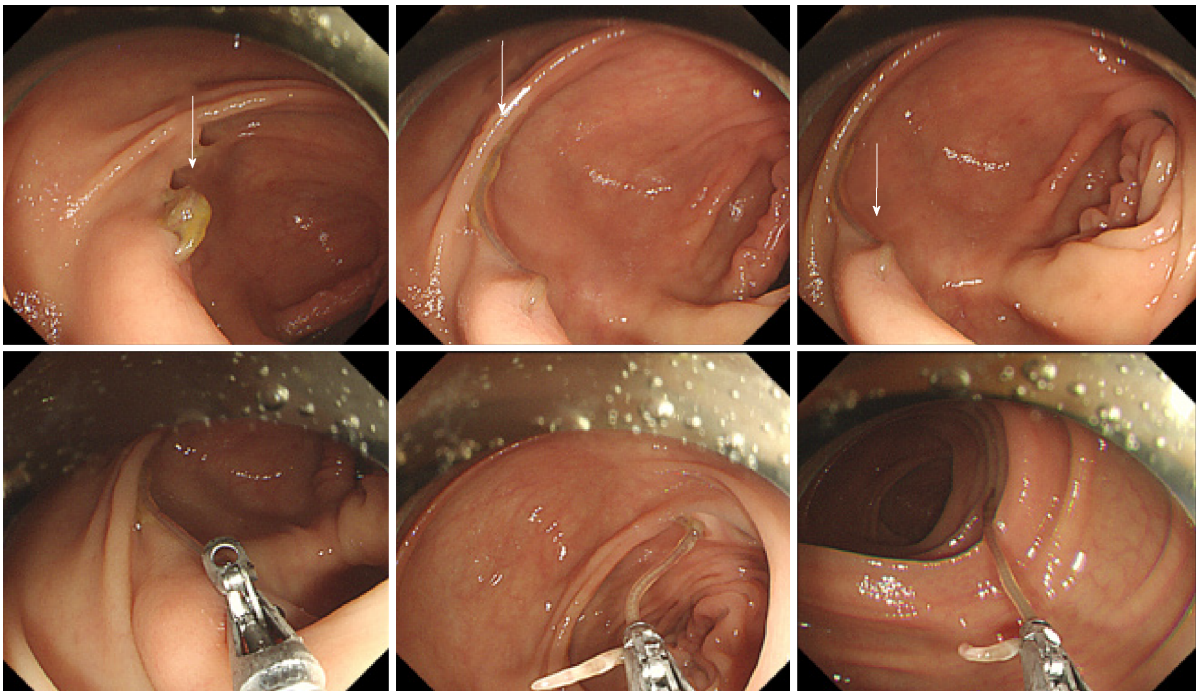

Figure 2 Series of endoscopic image of descending colon demonstrating biopsy forceps removing Anisakis simplex (arrow).

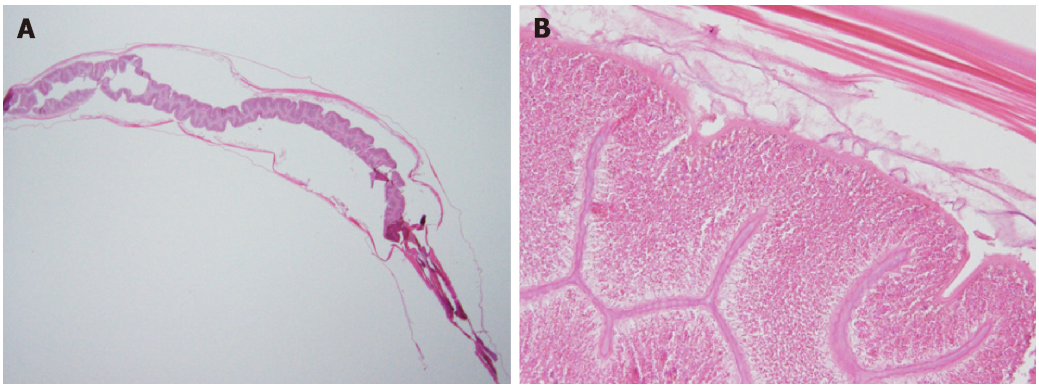

Figure 3 Histopathologic images of the Anisakis body. Histopathological findings of the specimen. A: Longitudinal section of Anisakis larva. The nematode is 2.9 cm in length and 0.1 cm in width (hematoxylin and eosin stain; × 12.5); B: High magnification showing cuticle and intestine (× 200).

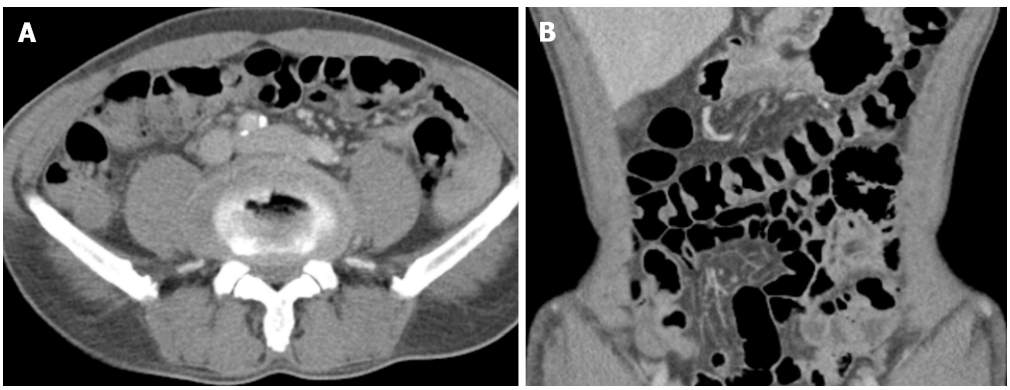

Figure 4 Post treatment abdominopelvic computed tomography. A and B: After removal state of parasite, repeated computed tomography images demonstrate the disappearance of colo-colonic intussusception.

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CASE REPORT

Robotic-assisted resection of ovarian tumors in children: A case report and review of literature

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Author contributions: Xie XX and Wang N contribute equally to this article and should be considered as co-first authors; Xie XX and Wang XQ performed the operation; Xie XX, and Wang N designed this case report; Wang ZH and Wang XQ wrote this paper; Zhu YY and Wang JR was responsible for sorting the data.

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CARE Checklist (2016) statement: The manuscript was prepared and revised according to the CARE Checklist (2016).

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Abstract

BACKGROUND

Ovarian tumors are common gynecological diseases in children, and the most commonly seen ovarian tumors are germ cell tumors. Robotic surgery is the new access for children ovarian tumors.

CASE SUMMARY

From June to October 2017, 4 children with ovarian tumors were admitted and treated in the Department of Pediatric Surgery of People's Liberation Army General Hospital. The mean age, height, and weight of these patients were 7.5 (1-13) years old, 123.75 (71-164) cm, and 36.8 (8.5-69.5) kg, respectively. Robotic-assisted resection of ovarian tumors was performed for all 4 patients. The 3-port approach was used for robotic manipulation. The surgical procedures were as follows. After creation of the pneumoperitoneum, the robotic scope was placed to explore and find the left ovarian tumor. The trocars for robotic arms 1 and 2 were placed at the sites to the lower right and left of the port of the scope. The tumor capsule in the fallopian tube was incised, and the tumor was completely stripped by an electric hook along the junction of the tumor and the capsule. The resected tumor was completely removed using an endobag. The average docking time of the robotic system was 18.5 min, the average operative time was 120 min, and the average blood loss was 20 mL. No drainage tube was placed except in one patient with a mucinous tumor of the ovary. No fever, pelvic fluid, or intestinal obstruction was reported after surgery. No antibiotics were used during the perioperative period, and the average length of hospital stay after surgery was 3

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d.

CONCLUSION
Robotic-assisted resection of ovarian tumors is a simple, safe, and effective surgical procedure for selected patients.

Key words: Children; Robotic surgery; Ovarian tumor resection; Case report

Core tip: Ovarian tumors are common gynecological diseases in children, and 4 children with ovarian tumors were treated using a robotic surgical system in the Department of Pediatric Surgery of People's Liberation Army General Hospital. There are no reports available on the use of robotic surgery systems to treat ovarian tumors in children in China. We think that robotic-assisted resection of ovarian tumors in children is feasible and promising.

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INTRODUCTION

Ovarian tumors are common gynecological diseases in children, and the most commonly seen ovarian tumors are germ cell tumors[1]. Ovarian mature cystic teratomas, also known as dermoid cysts, are the most common germ cell tumor, and they are also the most common benign tumors of the ovary[2]. Malignant germ cell tumors are relatively rare, but these malignant tumors usually a have high degree of malignancy. The proportion of malignancy is negatively associated with the age of the child (younger patients often have a greater likelihood of having malignant tumors)[3].

With the rapid development of minimally invasive surgery in recent years, robotic surgery systems have been widely used in many surgical procedures in adults[4-8]. However, due to the large age differences between pediatric patients, robotic surgery for children remains in the exploratory stage.

No reports are available on the use of robotic surgery systems to treat ovarian tumors in children in China. However, foreign medical centers have reported their experience in this field[9]. From June to October 2017, 4 children with ovarian tumors were treated using a robotic surgical system in the Department of Pediatric Surgery of People's Liberation Army General Hospital. This study retrospectively analyzed the clinical data and surgical procedures of these patients and aimed to explore the feasibility and safety of robotic surgery systems in children with ovarian tumors, as well as to provide preliminary experience with its clinical application.

CASE PRESENTATION

Chief complaints

Four children were admitted to the hospital with mass in lower abdomen.

History of present illness

The mean age, height, and weight of these patients were 7.5 (1-13) years old, 123.75 (71-164) cm, and 36.8 (8.5-69.5) kg, respectively. The Basic data of patients see Table 1.

Physical examination

The patient exhibited mass in lower abdomen.

Imaging examination

Ultrasonography revealed cystic mass in the lower abdomen.

Table 1 Basic data of patients, size of tumor and perioperative pathology

Case	Age	Height cm	Weight kg	Tumor cm	Side	Pathology
1	8	120	22.3	13.4	Right	Ovarian mature cystic teratoma
2	1	71	8.5	5.4	Right	Ovarian mature cystic teratoma
3	13	164	69.5	21	Left	Mucinous tumor of the ovary
4	8	140	47	11.6	Right	Ovarian teratoma

FINAL DIAGNOSIS

Ovarian tumors.

Preoperative diagnosis and treatment plan

For the treatment of ovarian tumors, Robotic-assisted resection was performed under general anesthesia. All of the patients were indicated for robotic surgery without contraindications. And the patients were fully informed and signed an informed consent form.

TREATMENT

Anesthesia and body position

Routine bowel preparation was performed before surgery. Total intravenous anesthesia was administered with tracheal intubation. The end-tidal CO_2 concentration was conventionally monitored. The patient was placed in the supine position and was restrained with tape or bandages. The direct trocar entry technique was used to create the pneumoperitoneum. The conventional CO_2 pneumoperitoneum pressure was maintained at 8 mm-10 mm Hg, but the recommended pressure was 6 mm-8 mm Hg in the neonates. The upper limit of pneumoperitoneum pressure was used to create the pneumoperitoneum to fully expose the abdominal cavity. After introducing robotic instruments, the pressure was reduced to the lower limit, and excellent exposure was achieved.

Trocar placement

A 12 mm trocar was directly inserted into the abdominal cavity at a site 5 cm to 10 cm above the umbilicus to create a pneumoperitoneum with placement of the robotic scope. An 8 mm trocar was placed at a site 1 cm below the right costal margin in the anterior axillary line and was used for arm 1 (Figure 1). An 8 mm trocar was placed at a site 1 cm below the left costal margin in the anterior axillary line and used for arm 2 (Figure 1).

Preparation of the robotic surgical system: First, the surgical robotic arms of the robotic surgery system were placed on the patient's leg side, and the connection between the surgical robotic arms and the trocar is described as follows: (1) The robotic arm of the scope was connected to the 12 mm trocar above the umbilicus, and the robotic scope was inserted; (2) The two robotic arms were connected to the left and right 8 mm trocars, respectively. A monopolar electrocoagulation hook or a robotic ultrasonic knife was mounted on one side, and a bipolar electrocoagulation hook was mounted on the other side.

Basic steps of the procedure (on the right side in a patient)

After successful anesthesia, the anesthesiologist placed the radial artery catheter. The urinary catheter was placed. The patient was placed in the lithotomy position with the feet elevated above the head. The operative field was routinely disinfected with iodine and draped. The pneumoperitoneum needle was inserted above the umbilicus to create a pneumoperitoneum with pressure of 13 cm H_2O. A 12 mm trocar and the robotic scope were placed. The exploration showed that the diameter of the left ovarian tumor was approximately 10 cm, and the right ovary was unremarkable. No pelvic or abdominal metastasis or malignant ascites was observed. The trocars for robotic arms 1 and 2 were placed to the lower right and lower left to the port of the scope, respectively. The robotic scope and the instrument arm were inserted and connected from the foot side.

The tumor capsule on the fallopian tube was circularly incised at a site approximately 3 cm from the infundibulum of the fallopian tube, and the tumor was

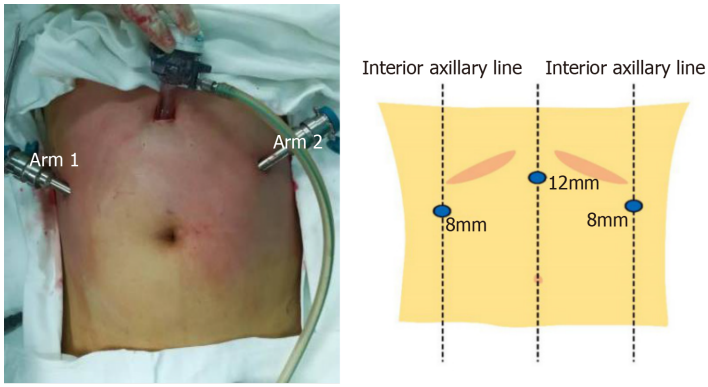

Figure 1 Trocar placement during surgery.

completely stripped with an electric hook along the junction of the tumor and the capsule. The examination was repeated to confirm no active bleeders in the fallopian tube stump and residual ovarian capsule. Robotic arms 1 and 2 were withdrawn. The incision for arm 1 was extended. The resected tumor of the left ovary was placed in an endobag, in which the tumor was punctured to rupture. Clear liquid flowed out, and hair and fat were visible inside. The resected tumor was completely removed using an endobag.

The procedure went well. The patient returned to the ward after surgery. No blood transfusion was needed.

Perioperative parameters

All 4 patients successfully underwent the robotic-assisted surgery, and there was no conversion to open surgery. The average docking time of the robotic system was 18.5 min, the average operative time was 120 min, and the average blood loss was 20 mL. No drainage tubes were placed except in a patient with a mucinous tumor of the ovary.

OUTCOME AND FOLLOW-UP

On the first day after surgery, the patients were allowed to ambulate and were provided with a liquid diet. On the second day, the patients were offered a semiliquid diet and were allowed to perform normal daily activities. No fever, pelvic fluid, or intestinal obstructions were reported after surgery. No antibiotics were used, and no complications (Clavien III or higher) occurred. The average length of hospital stay after surgery was 3 d.

No serious complications or recurrences were observed after the 6-mo follow-up.

DISCUSSION

In 2005, the United States Food and Drug Administration approved robotic surgery systems for gynecological surgery. Over the past 10 years, robotic surgery systems have been widely used in the surgical treatment of adult gynecologic tumors[10-12]. Robotic gynecological surgery in the treatment of benign and malignant gynecological tumors has been highly praised by gynecologists at home and abroad[13-16]. Robotic surgery in children was first used in urology[17], and since then, an increasing number of surgeons have reported the use of robotic surgery in various fields of pediatric surgery.

In this group of patients, the robotic arms were used to accurately complete exposure of the ovary, dissection of blood vessels, resection of the tumor, hemostasis of the wound, and removal of the specimen. During stripping of the cysts, the cysts were not ruptured in the 4 patients, and the blood loss was small. The morphology of the ovary was maintained, which is beneficial to the recovery of postoperative ovarian function.

In gynecological treatment, laparoscopic ovarian cystectomy is one of the most widely used procedures[18]. Laparoscopic ovarian cystectomy is a toilless procedure for separation of the tumor, and surgeons have sufficient understanding of the anatomy. Therefore, laparoscopic ovarian cystectomy is an ideal procedure for using

robotic surgery systems. In this study, the procedures were performed over a period of 4 months. In these 4 procedures, the docking time of the robotic system and the operative time of the robotic surgery decreased as the surgeons accumulated more experience. The procedure was prolonged in a few cases, but a prolonged operation time can be accepted, considering the benefits of minimally invasive surgery. Some studies have shown that[19-21], in the treatment of complex gynecological diseases, the learning curve with robotic surgery is shorter and easier than that with laparoscopic surgery, and the operator can complete the surgical task quickly and accurately.

We summarize the experience of using the Da Vinci system in pediatric gynecological surgery as follows. First, Chang *et al*[22] reported that the successful operation with robotic surgery requires four elements: A good understanding of the surgical procedure, superb surgical skills and frequent training, teamwork, and trocar placement. We agree with this statement and suggest that the most critical step is the placement of trocars, especially for children. In the early stage of this study, we noted that improper placement of the trocars would limit robotic manipulation in the abdominal cavity and increase the chances of instrument conflicts due to the small surface area of the abdominal wall of children and the relatively small space in the abdominal cavity. Therefore, the rational placement of the trocars is essential for a smooth operation. Second, unlike adult gynecological surgery, in which 4 robotic arms can be used, surgeons often only use 3 robotic arms in the majority of pediatric gynecological surgeries. Most pediatric gynecological surgeries can be completed using two operating arms. If the fourth arm is added, it will require more space and interfere with the operation of other arms in the pelvis, thereby increasing difficulty of the manipulation of the other arms. We suggest that, according to the experience of Finkelstein *et al*[23], the distance between the anterior superior iliac spine (> 13 cm) should first be evaluated before surgery to confirm that there is sufficient space to operate smoothly. Third, the standard operation of the robotic surgical system is to insert the trocar for the scope first and then insert the trocars for the robotic arms. The improvement that we made is to insert the trocars for the robotic arms on both sides first and then insert the trocar for the scope. This operation order is simple, safe, and consistent with the experience in previous reports. Fourth, children's abdominal walls are relatively thin and mobile. In the first few cases in this study, trocar detachment occurred and affected the operation of robotic surgery. The experience in some centers is to directly suture the trocar to the abdominal wall. We do not usually use this method. According to the position and degree of movement of the robotic arm, the position of the trocar's remote center is adjusted appropriately. The trocar should be placed in the abdominal cavity deeply or at least reach the remote center if the robotic arm needs to be moved in a large range, or it should reach the edge of the remote center if the robotic arm requires moving in a small range. Fifth, less pressure for the pneumoperitoneum was required for children's robotic surgery than with conventional laparoscopic surgery to achieve the same exposure effect. The main reason is that the abdominal wall can be retracted outward by the robotic arm to enlarge the space in the abdominal cavity. The principle of this method is to create a pneumoperitoneum with the abdominal wall hanging up. Therefore, the requirements of the body position are not as strict as those of conventional laparoscopic surgery[22].

There have been some controversies with robotic surgery in children. The population is relatively smaller in children than in adults. The number of accumulated procedures in children is difficult to compare with that in adults, which could lead to an imbalance between the efficiency and the cost. Cundy *et al*[24] suggested that robotic surgery in children is driven more by technology and industry than by clinical demand. Currently, there is no literature directly demonstrating the applicability of robotic surgery in children. As Peters[25] commented, "similar to children, new technologies, do not emerge in a mature form but, rather, require time for development and refinement".

Robotic surgery is undoubtedly a trend in minimally invasive surgery, and its emergence is not limited to itself. With the emergence of robotic surgery, a series of technological innovations will follow. Pediatric surgery-specific robotic techniques are on the rise, and the pediatric cardiac bioengineering laboratory led by Damian *et al*[26] is working on the invention of a small implantable robot; microrobots and nanorobots will be able to enter the human body to complete surgical tasks under wireless control without any awareness of patients[27].

CONCLUSION

Robotic-assisted resection of ovarian tumors is a simple, safe, and effective surgical procedure for selected pediatric patients. In centers where robotic surgery services are

newly available, robotic-assisted resection of ovarian tumors is a suitable entry-level procedure.

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CASE REPORT

Synovial sarcoma in the plantar region: A case report and literature review

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Author contributions: Gao J and Yuan YS contributed equally to this work and should be regarded as co-first authors; Gao J and Yuan YS treated the patient and wrote this paper; Liu T and Lv HR collected the information; Xu HL treated the patient and guided article writing.

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Abstract

BACKGROUND

Synovial sarcoma (SS), a rare malignant soft tissue tumor whose histological origin is still unknown, often occurs in limbs in young people and is easily misdiagnosed.

CASE SUMMARY

We report a 24-year-old man who sought treatment for plantar pain thought to be caused by a foot injury that occurred 4 years prior. Currently, he had been seen at another hospital for a 1-wk history of unexplained pain in the left plantar region and was treated with acupuncture, a kind of therapy of Chinese medicine, which partly relieved the pain. Because of this, the final diagnosis of biphasic SS was made after two subsequent treatments by pathological evaluation after the last operation. SS is rarely seen in the plantar area, and his history of a left plantar injury confused the original diagnosis.

CONCLUSION

This study shows that pathological and imaging examinations may play a vital role in the early diagnosis and treatment of SS.

Key words: Imaging examination; Pathological examination; Plantar; Synovial sarcoma; Case report

Core tip: A young male patient suffered from plantar pain for 1 wk. The symptoms were relieved after a kind of Chinese traditional invasive treatment. After that, the hemogram showed infection and magnetic resonance imaging showed that there was a soft tissue

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mass with a clear boundary in the plantar region. Rare location, complex medical history, invasive treatment, and auxiliary examination were easy to mislead doctors' judgments. Finally, the diagnosis was confirmed as synovial sarcoma by pathological examination. This case suggests that when soft tissue mass is encountered, biopsy is always the gold standard and must not be missed.

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INTRODUCTION

Synovial sarcoma (SS) was first reported by Knox in 1936, who believed that SS originated from synovial cells[1]. In 1938, Berger defined SS as a tumor that occurred in the synovium, bursa, and tendon sheath[2]. Later, in 2013, the World Health Organization classified SS as a tumor of indefinite origin[3] that could be divided into single phase, double phase, and poorly differentiated lesions based on its pathological characteristics. SS is the fourth most common soft tissue sarcoma[4], accounting for 5%-10% of soft tissue sarcomas[5]. It often occurs in boys and men aged 15–35 years old[6,7], with a male/female ratio of about 1.2:1.0[8,9]. SS is commonly found in soft tissues around the large joints of limbs, especially in soft tissues near the knee joint [10]. A plantar SS is rare. The 5-year survival of SS patients is 61%-80%, and the 10-year survival is 10%–30%[11,12].

It has been found that SS correlates closely with translocation of chromosomes 18 and X, which generates the SYT-SSX fusion gene now existing in no other disease but SS. Therefore, the molecular cytogenetic examination of T (x; 18) (p11.2; q11.2) and SS18-SSX fusion gene transcripts has been considered the most important evidence for diagnosing SS[13]. According to reported research[14], the sensitivity of fluorescence *in situ* hybridization (FISH) and reverse transcription-polymerase chain reaction (RP-PCR) for identifying SS are, respectively, about 80.0% and 83.8%, and their combined sensitivity is about 92.9%.

At present, there is no effective cure for SS[15]. A timely, correct diagnosis and the proper surgical treatment at an early stage are essential for a good prognosis. Kartha and Bumpous[16] reported that performing an operation to remove the tumor with a diameter < 5 cm is the treatment of choice for SS. For an SS with a diameter > 5 cm, radiotherapy is needed prior to the surgery[16,17]. In addition, Eilber *et al*[18] reported a randomized controlled trial showing that radiotherapy after surgery for SS increased the survival rate.

In 2016, Vlenterie *et al*[10] analyzed 3711 SS patients, among whom 313 had advanced-stage SS. They found that about 56% of the SSs at an advanced stage originated from limbs, and pulmonary metastasis was commonly detected (80%). Compared with other soft tissue sarcomas, metastasis of SS begins at an earlier age (median age, 40 years), and men more often experience metastasis than women at the same age (male/female = 191:122).

SS is sensitive to chemotherapy and has a better prognosis than other sarcomas at the same stage[9]. Recent research showed that chemotherapy for metastatic SS tumor with ifosfamide or doxorubicin could protract patients' lives, whereas radiotherapy had no positive effect on patients' prognosis[19]. Trabectedin, a novel, targeted anti-tumor, cytotoxic drug, has been approved in Europe for treating advanced liposarcomas and leiomyosarcomas[20]. Japanese researchers have shown that trabectedin plays a prominent role in repressing the growth of SS cells and has potential for use clinically in the treatment of SS[21]. Surgery combined with chemotherapy or radiotherapy as comprehensive treatment for SS in current clinical practice may hopefully improve the survival rate of patients with SS.

We describe herein a case of SS in the plantar region of the foot misdiagnosed due to the patient's complicated history of plantar trauma and repeated treatment for this atypical manifestation. The patient was misdiagnosed in different hospitals as having plantar fasciitis, soft tissue infection, and inflammatory granuloma. We assess the reason for these misdiagnoses and finally conclude that when a patient's symptoms are not typical and evidence of the imaging examination is insufficient, a pathological examination is essential for a timely, correct diagnosis, which should be established as

early as possible.

CASE PRESENTATION

Chief complaints

A 24-year-old man had a 4-year history of a left plantar injury from which he recovered within several days without treatment and with no mobility obstacles.

History of present illness

Currently, the patient suffered unexplained pain during walking in his left plantar region for almost a week. He noted some swelling in the left plantar area but no fever, chills, or pain. He took some nonsteroidal anti-inflammatory drugs, which partly relieved his walking-induced pain. The pain recurred within 3 d, however, at which time he visited a hospital where he was treated with acupuncture. The pain was once again relieved, although 2 d later it returned, hampering his mobility. He was brought to our hospital in an armchair (Peking University People's Hospital).

History of past illness

Since the onset of his walking pain, the patient had experienced no problems with his mental state, diet, sleeping, or weight.

Personal and family history

The family history was unremarkable.

Physical examination upon admission

Physical examination showed some swelling in his left plantar region and ecchymosis (1.5 cm × 1.5 cm) with accompanying tenderness at that site. When he back-stretched his left foot, the fourth toe had sharp pain. No mass was found in his left plantar area.

Laboratory examinations

Routine blood examination showed a white blood cell count of 10.06×10^9/L and C-reactive protein level was 9.51 mg/L.

Imaging examination

Plain radiography of his left plantar was normal (Figure 1). Color Doppler ultrasonography showed an inhomogeneous mass in the plantar area of the left foot (Figure 2), and magnetic resonance imaging (MRI) suggested that it could be a benign tumor or tumor-like lesion, such as inflammatory granulation or a giant cell tumor in the tendon sheath (Figure 3).

FINAL DIAGNOSIS

Taking into account the patient's disease history, symptoms, and examination findings, however, his suspected diagnosis was a soft tissue infection in the left plantar area.

TREATMENT

He was treated with antibiotics (cefuroxime, 1500 mg, bid, *i.v.*) for 3 d, which relieved the walking-induced pain, and his laboratory values returned to normal, with a white blood cell count of 6.90×10^9/L and erythrocyte sedimentation rate of 7 mm/h. He was discharged from the hospital on postoperative day 7 and continued to take cefuroxime orally as directed.

On day 11 after his discharge, his pain recurred, and he was again admitted to our hospital, this time demanding that we remove the mass in his left plantar region. Physical examination showed a swelling in the left plantar area and ecchymosis (1.5 cm^2 × 1.5 cm^2) in the left plantar region with accompanying tenderness (Figure 4). The mass had no clear margins with its surroundings, and the blood supply and nerves of the left plantar area were normal. We removed the mass on day 2 after admission, then used cefuroxime infusion as his last hospital stay. The lesion measured 3.0 cm × 1.5 cm × 1.5 cm and was elliptical, lobulated, yellowish gray, and soft (like adipose tissue). It had been located between the foot plantar flexion tendons and metatarsal with clear boundaries.

Postoperative pathological examination showed a focal adenoid structure,

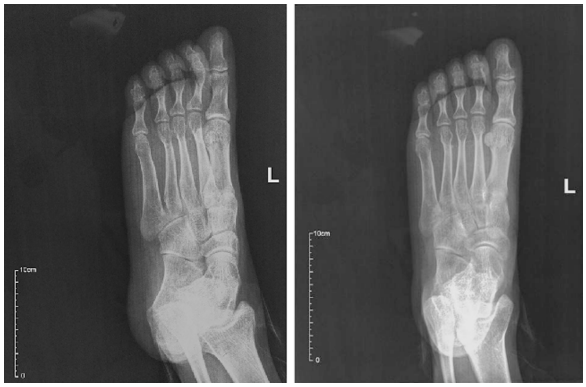

Figure 1 Plain radiography of the patient's left plantar. Both of the front view and foot oblique view show nothing abnormal in bones.

composed partly of interstitial fibrosis and multinucleated giant cells with scattered hemosiderin deposition. The HE staining showed a sign of tumor cell type (Figure 5). Immunohistochemical staining showed the following: CK (adenoid area) (+), CK7 (adenoid area) (+), desmin (−), CD34 (blood vessels) (+), TLE1 (+), S100 (−/+), P63 (−), KP-1 (coenocytes) (+), and KP-1 (+5%). The pathological diagnosis was SS (bipolar).

OUTCOME AND FOLLOW UP

This patient received postoperative chemotherapy with doxorubicin and cyclophosphamide for 2 mo, after which no metastasis was found.

DISCUSSION

This case of SS, with a 4-year history of plantar trauma, the inflammatory symptoms during the treatment, and the indication of a benign mass without a clear boundary on imaging, was easily misdiagnosed. Typical SSs are commonly found in deep soft tissue and manifest as a large mass with slow growth. In addition, they most often are accompanied by focal pain or tenderness. The average incubation of SS is 2-4 years, with some even reaching 20 years[22]. The patient discussed herein had an SS in his left plantar region after having experienced plantar trauma 4 years prior. In addition, his symptoms had not presented until about 2 wk before his first visit to the hospital complaining of plantar pain.

Walking-induced pain in the left plantar region in a patient with a history of plantar trauma 4 years prior is not commonly related to a malignant tumor, which caused the misdiagnosis at his first visit. When he was admitted to our hospital, the laboratory and imaging examinations suggested a benign mass due to infection that may have been caused by his prior acupuncture treatment. Thus, he was misdiagnosed as having a left plantar infection, which was relieved by the prescribed antibiotic treatment. When he returned a few days later, combined with the surgical findings, he was misdiagnosed a second time as having an inflammatory granuloma in the left plantar region. The patient was finally diagnosed correctly during the pathological examination as having SS. Without a pathological examination, SS of this kind could easily to be misdiagnosed, which could cause a great loss of the patient's quality of life.

The mechanism of SS is not fully understood. A few cases have been reported in which SS may have a correlation with the use of radiotherapy[23,24], and some believe that calcified SS may be related to trauma. Murphey *et al*[4], however, argued that trauma has nothing to do with SS and that SS causes some clinical symptoms that might increase the possibility of discovering it after trauma. Regretfully, in this case, the patient did not seek for medical help immediately, so no imaging details were available to study whether the plantar trauma that occurred 4 years prior was related to the development of the SS.

To better understand SS, we searched PubMed for articles about SS published from 1953 to 2017. We found that, except liposarcoma, almost all other soft tissue sarcomas lack peculiar manifestations during imaging examinations, and the diagnostic rate for SS is just 25%[25]. The images of SS have no apparent specificity, although there are

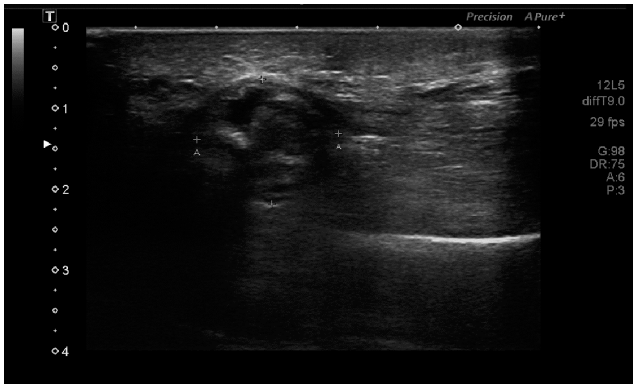

Figure 2 Doppler ultrasonography showed an inhomogeneous mass in the plantar area of the left foot.

some peculiar manifestations[26,27]. SS commonly manifests on computed tomography (CT) as a heterogeneous mass with low density and inapparent boundaries compared with the normal surrounding tissues. These characteristics may be intensified by different degrees with enhanced CT. On MRI, SS manifests as having clear boundaries and swelling around the mass, mainly equivalent signals on T1-weighted images (mixed with some higher signals) and compound signals in T2-weighted images[4,28], and this is one of the reasons for misdiagnosing SS as a benign tumor. Therefore, whether there is a clear boundary cannot be regarded as proof for distinguishing whether a mass is benign or malignant or the degree of histological differentiation[29,30].

CONCLUSION

The MRI results in this case conform to the characteristics reported above (*i.e.*, a round mass with a clear boundary and compound signals on T2-weighted images), ensuring its easy diagnosis as a benign tumor. Under such a circumstance, CT should be performed to further determine if it might be SS. If the results do not clearly indicate that it is SS, a pathological examination for the correct diagnosis is needed.

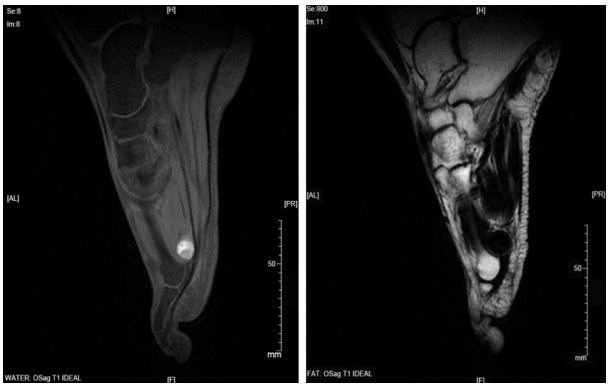

Figure 3 Magnetic resonance imaging suggested that the lesion could be a benign tumor or tumor-like lesion, such as inflammatory granulation or a giant cell tumor in a tendon sheath.

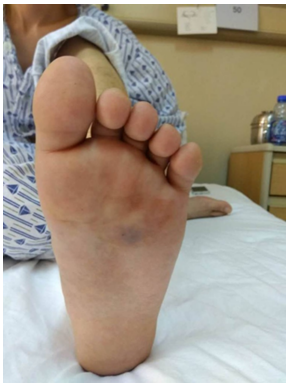

Figure 4 Physical examination showed a swelling in the left plantar area and ecchymosis (1.5 cm^2 × 1.5 cm^2) in the left plantar region with accompanying tenderness.

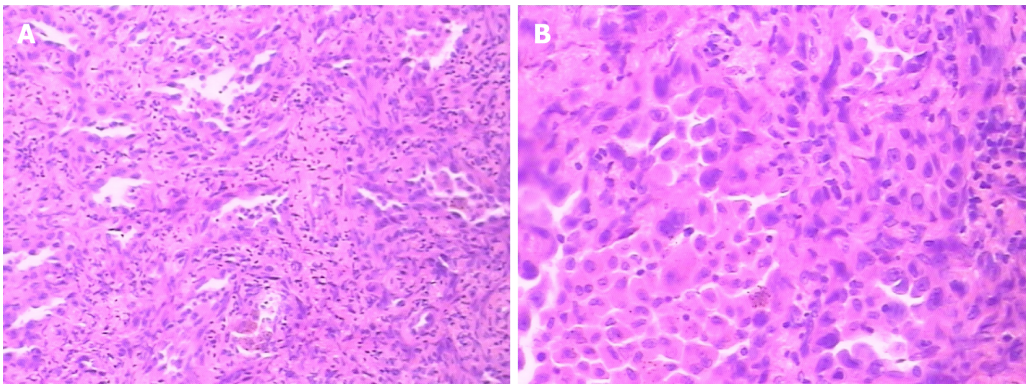

Figure 5 Hematoxylin-eosin staining showed a sign of tumor cell type. A: Magnification is 100 times; B: Magnification is 200 times.

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CASE REPORT

Severe serous cavity bleeding caused by acquired factor V deficiency associated with lymphatic leakage in a hemodialysis patient: A case report

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Author contributions: Zhao WB was the patient's renal physician, reviewed the literature and contributed to manuscript drafting; Chen YR reviewed the literature and contributed to manuscript drafting; Luo D and Lin HC performed the interpretation and contributed to manuscript drafting; Wu ZY analyzed data and interpreted the findings of statistical analysis; Long B performed the blood diseases consultation, reviewed the literature and drafted the manuscript; Peng H was responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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Abstract

BACKGROUND

Acquired factor V deficiency is a rare secondary hemorrhagic disease, which can lead to a severe bleeding disorder.

CASE SUMMARY

We report a 47-year-old hemodialysis patient who presented with severe hemorrhagic pleural effusion and hemorrhagic pericardial effusion associated with lymphatic leakage. The laboratory examination revealed decreased factor V activity (2% of population average value). With decreased lymphatic leakage, factor V activity increased (to 46%). Lymph drainage correlated with prothrombin time and active partial thrombin time. The cause of the disease favored an acquired disease. The common causes which trigger factor V inhibitors were excluded. An inhibitor was not detected. It is possible that there was a clotting factor inhibitor leaking with the lymph in the drainage. Inhibitor production may be due to immune dysfunction caused by persistent lymphatic drainage, or that coagulation inhibitors were produced, drained with the lymph, and partly cleared by hemodialysis.

CONCLUSION

In this case, we have firstly reported factor V deficiency associated with lymphatic leakage in a hemodialysis patient.

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Core tip: Acquired factor V deficiency (AFVD) is a rare secondary hemorrhagic disease, which can lead to serious bleeding disorder. We report a new AVFD case of a hemodialysis patient with severe serous cavity hemorrhagic effusion, associated with potentially secondary to lymphatic leakage, and factor V inhibitor detection is negative. This is the first report regarding the association between coagulation factor V deficiency and lymphatic drainage in hemodialysis patient of chronic kidney disease patient. Careful follow-up of blood coagulation is needed in patients under the treatment of lymphatic drainage.

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INTRODUCTION

Acquired factor V deficiency (AFVD) is a rare secondary hemorrhagic disease that can lead to a severe bleeding disorder. Streiff *et al*[1] reported AVFD for the first time in 1955. A recent literature review cited approximately 200 cases of AFVD[2]. AFVD is primarily due to the development of factor V inhibitors, *i.e*. antibodies against factor V. Exposure to bovine thrombin, antibiotics, surgical procedures, tumors, autoimmune diseases, infections, transplantations, and disseminated intravascular coagulation (DIC) may trigger factor V inhibitors in previously healthy patients[3].

The clinical symptoms of AFVD have been reported as variable, and range from asymptomatic to a severe bleeding disorder and thrombosis[4]. We report here a case of AVFD in a hemodialysis patient with a severe serous cavity hemorrhagic effusion secondary to lymphatic leakage, and no factor V inhibitor was detected. Even though the case occurred several years ago, we are of the opinion that the case is clinically meaningful. A large volume of lymphatic drainage can lead to a coagulation disorder, which may not arouse suspicion.

CASE PRESENTATION

Chief complaints and history of illness

The patient was a 47-year-old man who was admitted to our hospital on 7 January 2011 with a 2-year history of recurrent edema of the eyelids and lower extremities and a 7-d history of shortness of breath and severe hypertension. He was hospitalized due to exacerbation of limb and scrotal edema, as well as decreased urine output. The patient had no previous medical history. There was no family history of hemorrhagic disease and chronic kidney disease (CKD).

Physical examination

Physical examination revealed mild pitting edema in both lower extremities.

Laboratory examinations

Laboratory testing revealed the following: blood urea nitrogen, 60.26 mmol/L; serum creatinine, 1026 μmol/L; prothrombin time (PT), 14.3 s; active partial thrombin time (APTT), 40 s; hemoglobin, 63 g/L; white blood cell (WBC) count, 6.12 × 10^9/L; neutrophilic granulocyte percentage (N%), 79.2%; and platelet count, 176 × 10^9/L. Chest X-ray: Lung was negative. On 8 January 2011, a right femoral venous catheterization was performed to facilitate hemodialysis treatment. In the absence of ultrasonic guidance, the puncture needled the right femoral artery and resulted in a right common femoral artery pseudo aneurysm with a size of 63 mm × 37 mm. The patient received non-heparin dialysis during dialysis treatment. On 28 January 2011,

after a right femoral artery pseudoaneurysm resection and rupture repair, the lump resolved. One week post-operatively, a gradually increasing 2 cm × 3 cm mass without swelling, tenderness, and a fluctuating sensation was not found in the medial aspect of the surgical incision with a light yellow clear liquid exudate on the surface. After a diagnostic puncture and catheterization, 500 mL of light red liquid was drained under negative pressure (Table 1). A lymphatic fistula was diagnosed and the lymph liquid consisted of the following: WBC count, 3.0 × 10^6/L; red blood cell (RBC) count, 44 × 10^6/L; glucose, 7.31 mmol/L; total protein, 5.3 g/L; and lactate dehydrogenase, 88 g/L.

Five days later, the coagulation time was significantly prolonged after lymphatic drainage on the right side; a vitamin K1 supplement proved ineffective. The hemoglobin level was significantly decreased and the patient had a small amount of nasal mucosa bleeding and large bloody pericardial and pleural effusions. Laboratory testing revealed the following: albumin, 35.7 g/L; PT, 52.8 s; APTT, 180.1 s; fibrinogen, 4.67 g/L; coagulation factor II, 72%; coagulation factor VII, 84%; and coagulation factor X, 64% (Table 2). Factor V was deficient (2% of population average) and no inhibitor was detected. A total of 1140 mL of fluid was drained by pericardial aspiration, with a red and turbid appearance. In addition, 2400 mL of fluid was drained *via* thoracic drainage and had a deep red appearance without clots. Fluid cultures were obtained and negative.

FINAL DIAGNOSIS

The final diagnosis is AFVD and chronic kidney disease stage 5D.

TREATMENT

The main treatment measures included maintenance hemodialysis, supplementing fresh frozen plasma, and reducing the lymphatic drainage.

Since 5 February 2011, the patient has received treatment with a daily infusion of 200-600 mL of fresh frozen plasma. After applying a pressure dressing, the lymphatic drainage decreased, the skin bleeding resolved, the pericardial and pleural effusions decreased, coagulation function improved, and PT and APTT decreased. On 3 March 2011, the coagulation factor V level was 8% (Table 2, Figure 1). On 20 April 2011, coagulation factor V level improved (to 46%). The amount of lymph drainage was correlated with the PT and APTT.

OUTCOME AND FOLLOW-UP

The patient improved clinically and coagulation factor V level (to 46%) after the follow-up for three months. On 13 March 2018, coagulation factor V level was 98.9%.

DISCUSSION

We report a patient with chronic kidney disease who exhibited mucosal hemorrhage and multiple hemorrhagic effusions in the serous cavity associated with lymphatic leakage due to acquired coagulation factor V deficiency (Figure 1).

The patient had no exposure to bovine thrombin and no manifestations of DIC. There was no history of antibiotic use and no evidence of antibiotics contributing to the coagulant function abnormality. AVFD occurred two weeks after surgery, but there was no direct evidence of an association with the surgical procedure. The patient had no autoimmune diseases previously reported which could have led to AVFD.

In this case, the lymphatic vessel injury caused lymphatic leakage. Negative pressure drainage has been reported to be a method to treat lymphatic leakage[5]. After constant lymphatic drainage, the patient exhibited significant malnutrition, weight loss of approximately 10 kg, and decreased serum albumin and immunoglobulin concentrations. Biochemical testing revealed the existence of clotting factor deficiency that may have been due to immune dysfunction caused by persistent lymphatic drainage, or coagulation inhibitor production and coagulation inhibitor partly cleared by hemodialysis, resulting in no detection of inhibitors[3,6]. The lymphmay also be due to lymphatic drainage of the clotting factors rather than immune factors with producing an inhibitor, but the composition of the lymphatic drainage was not tested.

Table 1 Laboratory test results for lymphatic fistula, pericardial and thoracic drainage fluids

	Lymphatic Fistula fluid	Pericardial fluid	Thoracic drainage fluid
WBC (10^6/L)	3	4960	3320
RBC (10^9/L)	44	4620	1380
N (%)	5	70	60
Protein (g/L)	5.3	56.7	45.7
GLU (mmol/L)	7.31	3.15	7.18
LDH (U/L)	88	539	261
TB-Ab	Negative	Negative	Negative/Positive
Bacterial growth smear	Negative	Negative	Negative
Acid-fast bacilli smear	Negative	Negative	Negative

WBC: White blood cell; RBC: Red blood cell; N%: Neutrophilic granulocyte percentage; GLU: Glucose; LDH: Lactate dehydrogenase; TB-Ab: Tuberculosis antibody

Coagulation function was improved after supplementation by fresh frozen plasma. Eight days after reduced drainage following the application of a pressure dressing, coagulation factor V concentration increased to 8%, the bleeding tendency and bloody effusions in the pericardial and pleural cavities were resolved, and after removal of the drainage tube, coagulation factor V concentration increased to 46%. It has been reported that high-dose immunoglobulin treatment rapidly improved coagulation factor V deficiency caused by immune disorder[6]. The patient in the current study was treated with human immunoglobulin (10 g/d for four consecutive days) from 25 February 2011, which was ineffective. Because no coagulation factor inhibitors were detected, hormone and immunosuppressive drugs were not used[7].The amount of lymph drainage was positively correlated with the PT and APTT values, indicating that there was a quantitative relationship between the amount of lymph drainage and coagulation function (coagulation factor V deficiency).

CONCLUSION

This is the first report regarding an association between coagulation factor V deficiency and lymphatic drainage in a chronic kidney disease patient for hemodialysis. Careful follow-up of blood coagulation is needed in patients under treatment with lymphatic drainage associated with various diseases and operation.

Table 2 Time course of levels of coagulation factors and function

	Normal range	February 23, 2011	March 3, 2011	March 24, 2011	April 20, 2011	March 13, 2018
PT (s)	11.0-15.0	52.8	29.2	18.9	16.2	
PT (%)	70-120	13	27	58.4	67	
PT-INR		6.15	2.82	1.85	1.29	
APTT (s)	31.5-43.5	180.1	86.8	49.2	49	
TT (s)	14-21	15.6				
Fib	2.00-4.00	4.67				
FII (%)	70-120	72				
FV (%)	70-120	2	8	15	46	98.9
FVII (%)	70-120	84				
FX (%)	70-120	64				
PC:AC	70-120	92				

PT: Prothrombin time; APTT: Active part thrombin time; TT: Thrombin time; Fib: Fibrinogen; FII: Coagulation factor II; FV: Coagulation factor V; FVII: Coagulation factor VII; FX: Coagulation factor X; PC: Protein C.

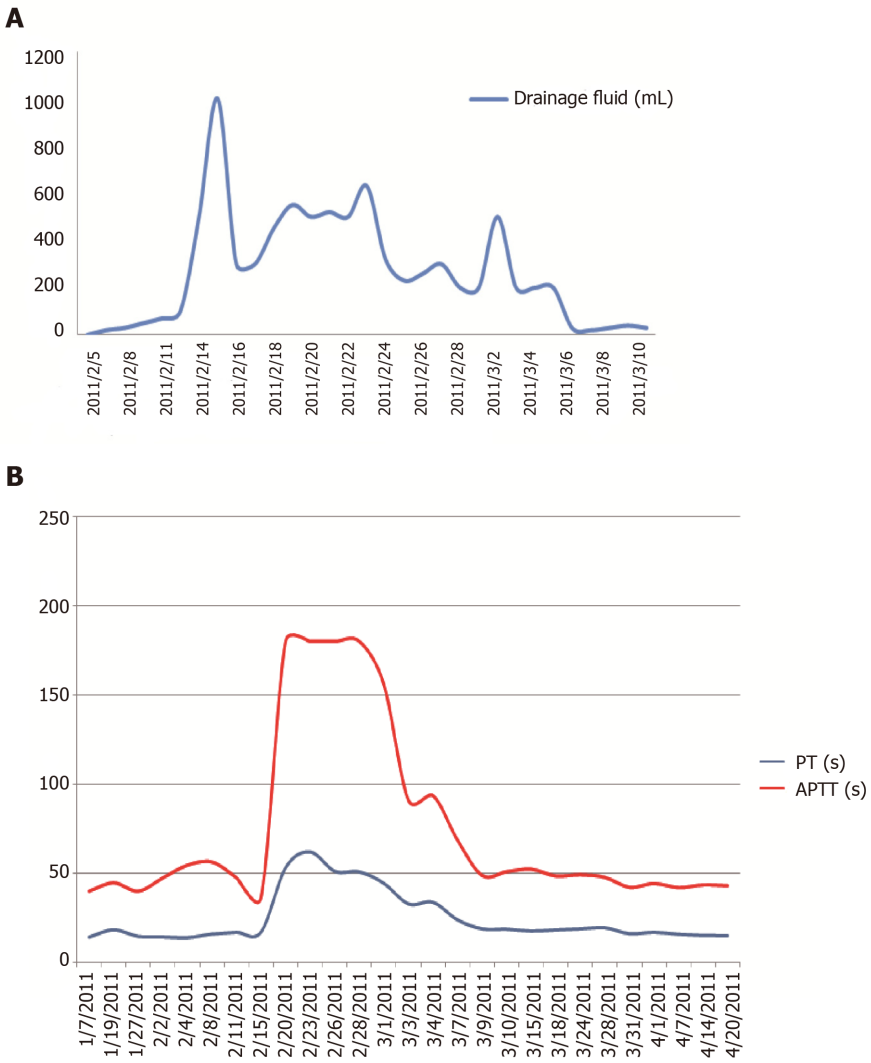

Figure 1 The amount of lymph drainage (A), the values of active partial thrombin time and prothrombin time (B) at the different time. APTT: Active partial thrombin time; PT: Prothrombin time.

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CASE REPORT

Supermicrosurgery in fingertip defects-split tibial flap of the second toe to reconstruct multiple fingertip defects: A case report

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Author contributions: Wang KL, Zhang ZQ and Yang Y were responsible for conception and design, acquisition of data and drafting the article and performed the surgery; Buckwalter JA revised the article.

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Abstract

BACKGROUND

Injuries to multiple fingertips pose a significant treatment dilemma. Numerous reconstructive options exist, all with the ultimate goal of restoring function and sensibility to the injured fingertips.

CASE SUMMARY

A 24-year-old male suffered injury to multiple fingertips of the right hand, resulting in exposed distal phalanges of the middle, ring, and small fingers. The amputated distal stumps were not possible for replantation. Free flap coverage was selected in order to achieve better functional outcome. The fingertip defects were covered by performing a right second toe split tibial flap using local anesthesia at the harvest site and brachial plexus nerve block for the right upper extremity. At 6-month follow-up, all three of the reconstructed fingertips had some preserved nail growth, Semmes-Weinstein Monofilaments testing was equal to the contralateral side and the Static Two-Point Discrimination were comparable to the contralateral side.

CONCLUSION

This report provides a novel reconstructive option for the management of multiple fingertip injuries and demonstrates the utility of supermicrosurgery in management of these injuries.

Key words: Supermicrosurgery; Fingertip defects; Split; Tibial flap; Second toe; Reconstruct; Case report

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Core tip: Injuries to multiple fingertips pose a significant treatment dilemma. Numerous reconstructive options exist, all with the ultimate goal of restoring function and sensibility to the injured fingertips. We present a case of a split tibial flap of the second toe utilized to treat multiple fingertip injuries, resulting in satisfactory restoration of function and sensation. This report provides a novel reconstructive option for the management of multiple fingertip injuries and demonstrates the utility of supermicrosurgery in management of these injuries.

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INTRODUCTION

The fingertips are the most frequently injured part of the hand[1,2]. The underlying finger pulps play a vital role in functions of daily life such as sensation, fine touch, and grip perception. It is imperative to manage fingertip injuries with the goal of obtaining a painless, functional finger with protective sensation[3].

Given the complexity of fingertip injuries, successful replantation of amputated finger pulp is not always possible. Therefore, numerous surgical options have been reported for finger pulp reconstruction with good functional and sensory outcomes, such as V-Y advancement, pedicle flaps, free flaps, and toe pulp transfer[1,2,4-15].

The purpose of this report is to describe a novel reconstructive method to restore function and sensation after injury to three finger pulps by using the split second toe tibial flap.

CASE PRESENTATION

Chief complaints

A 24-year-old male presented to our hospital, with a shearing, crush-type injury to multiple fingertips of the right hand, resulting in exposed distal phalanges of the middle, ring, and small fingers. The amputated distal stumps were retrieved, but due to the nature of the injury, replantation was not possible.

History of past illness

The patient was a healthy, non-smoker, without signs of tinea pedis or unguium. A variety of reconstruction strategies were presented to the patient and his family, including stump revision amputation, V-Y flap advancement, and pedicle or free flap coverage.

FINAL DIAGNOSIS

After consideration of the options, the patient elected for free flap coverage in order to potentially achieve better functional recovery.

TREATMENT

Initially, the patient underwent irrigation and debridement of the injured fingertips with vacuum-assisted closure (VAC) to cover the wounds. Three days later, we covered the fingertip defects by performing a right second toe split tibial flap using local anesthesia at the harvest site and brachial plexus nerve block for the right upper extremity. The defects of the right middle, ring, and small finger measured 1.8 cm^2 × 1.5 cm^2, 1.5 cm^2 × 1.2 cm^2, and 1.2 cm^2 × 1.0 cm^2, respectively (Figure 1A). A 1.6 cm^2 × 4.5 cm^2 tibial second toe flap was then harvested and accordingly split into three small

flaps as F1, F2, and F3 under the microscope with respective flap areas of 1.3 cm^2 × 1.0 cm^2, 1.6 cm^2 × 1.2 cm^2, and 1.8 cm^2 × 1.5 cm^2 (Figure 1B-D). The F3, F2, and F1 were transferred to middle, ring, and little fingertips with the one artery (the diameter for F3, F2, F1 was 0.8, 0.5, 0.4 mm, respectively), one vein (the diameter for F3, F2, F1 was 0.9, 0.8, 0.5 mm, respectively), and one nerve (the diameter for F3, F2, F1 was 1.0, 0.8, 0.6 mm, respectively) (Figure 2A-C). The anastomoses were completed to the recipient sites by using 11-0 Prolene suture under the microscope, and the donor site was closed with full thickness skin graft.

Post-operatively, Cefuroxime were administered for three days; Papaverine hydrochloride was administered intramuscularly (30 mg, q6h→qd, day1→day 7) for seven days; and Heparin was continually administered intravenously (12500 IU every 24 h) for seven days. Blood coagulation function was monitored every two days to ensure the activated partial thromboplastin time exceeded no more than 1.5 times of the normal level. The patient remained non-weight bearing for both the right upper extremity and right lower extremity, and was discharged from the hospital without any noted complications.

OUTCOME AND FOLLOW-UP

At 6-mo follow-up, the patient had no donor site or harvest site complications (Figure 3A and B), and reported no residual pain or cold intolerance. All three of the reconstructed fingertips had some preserved nail growth, measuring 17 mm, 13 mm, and 10 mm of the middle, ring, and small fingers, respectively. Semmes-Weinstein Monofilament testing was equal to the contralateral side with the 2.83 of the right middle, ring, and small fingertips. The Static Two-Point Discrimination (s2PD) measurements were 8 mm, 9 mm, and 8 mm in the right middle, ring, and small fingertips, while in the contralateral side the measurements were 6 mm, 5 mm and 4 mm, respectively.

DISCUSSION

The fingertips perform unique and significant functions of daily life such as sensation, fine handling, and gripping[1,2], and they are the most frequently injured part of the hand. For these reasons, it is of vital importance to treat fingertip injuries with careful strategy to achieve pain-free, quality functional and sensory outcomes. In cases where replantation of an amputated fingertip is not feasible, numerous reconstructive options exist[2-16]. When considering the appropriate surgical technique and reconstruction options, a surgeon should deliberate on the characteristics of the injury, the advantages and disadvantages of the reconstructive method, and the potential for recovering of function, especially for cases involving multiple fingertips injuries.

This case report offers a novel reconstructive option for the management of multiple fingertip injuries. In this case, the patient had no surgical or post-operative complications, and reported no pain, cold intolerance, or functional deficits. Although the patient reported no perceived functional or sensory deficits, the s2PD measurements were decreased compared to contralateral side. These s2PD measurements were all less than 10mm and Semmes-Weinstein Monofilaments testing was equal to the contralateral side, indicating a satisfactory sensory outcome.

CONCLUSION

The concept of supermicrosurgery has found increasing clinical applications in recent years[16]. With supermicrosurgery, the dissection and anastomosis of very small caliber structures with minimal donor-site morbidity had become a reasonable option. The split tibial second toe flap utilized for this patient is an advanced application of supermicrosurgery, in which the multiple defects were covered with one single split flap. This report is noteworthy for its originality and application of supermicrosurgery. Supermicrosurgery should continue to be explored and considered as a feasible option for fingertip defect reconstruction and other diseases treatment such as lymphedema, nerve repair, organ transplantation, and free flaps in the future.

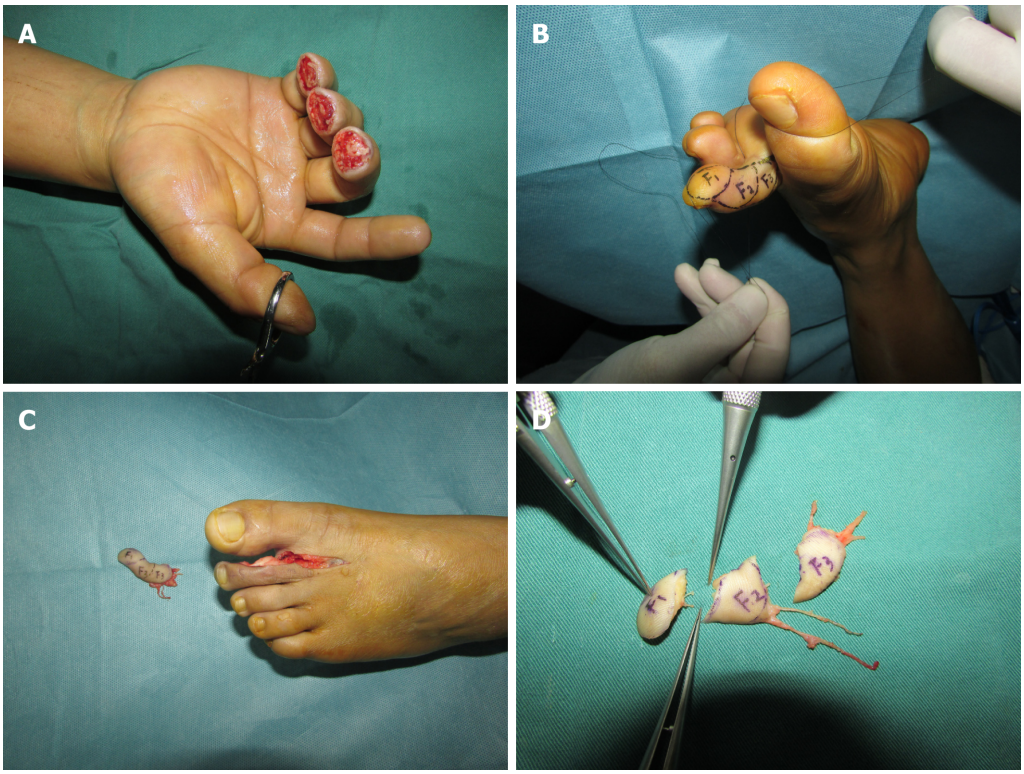

Figure 1 Split tibial second toe flap. A: Three days after the first stage surgery, the wounds were clean and ready for free flap transfer; B: A 1.6 cm^2 × 4.5 cm^2 tibial second toe flap designed before operation; C: Harvested tibial second toe flap; D: Flap was split into three small flaps as F1, F2, and F3 under a microscope.

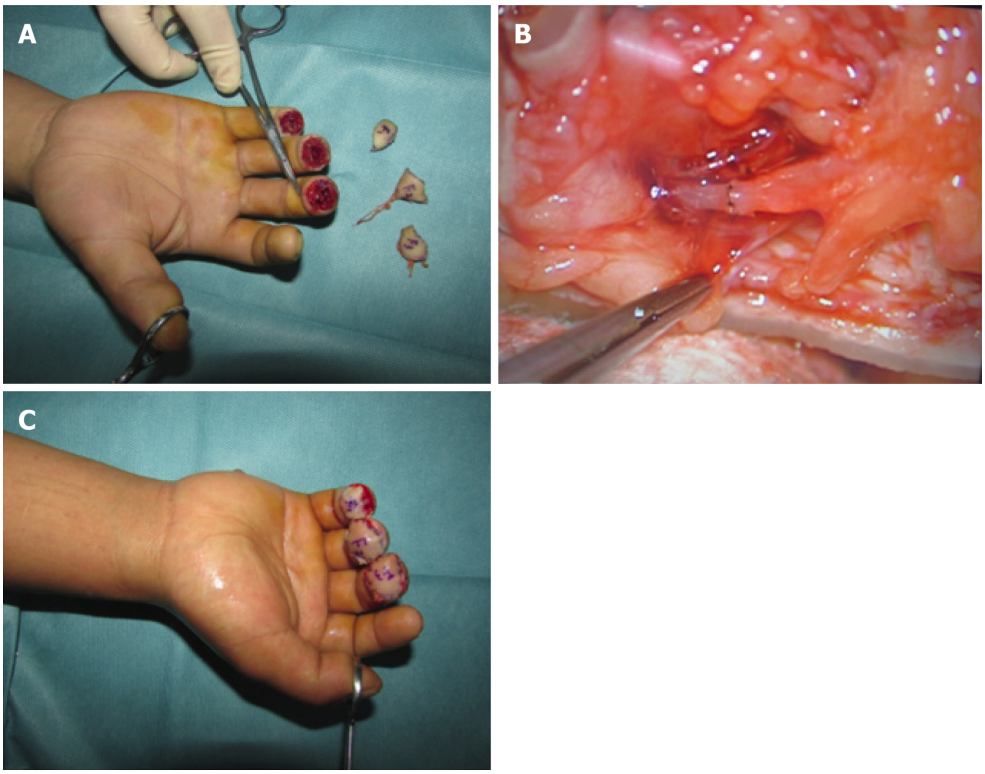

Figure 2 F3, F2, and F1 were transferred to middle, ring, and little fingertips with the one artery. A: F1, F2, and F3 flaps before transfer to recipient sites; B: Representative anastomosis of the vessels and nerve; C: F1, F2, and F3 flaps transferred to recipient sites.

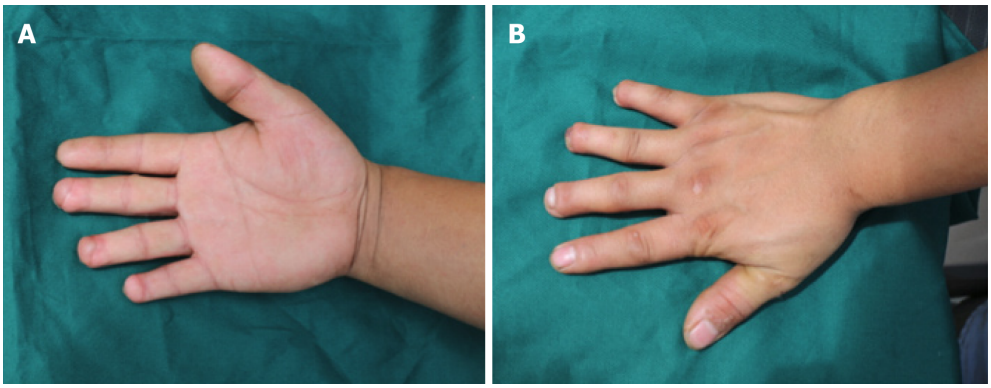

Figure 3 Six months after the surgery. A: Palmar view; B: Dorsal view.

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CASE REPORT

Ultrasound-guided fascia iliaca compartment block combined with general anesthesia for amputation in an acute myocardial infarction patient after percutaneous coronary intervention: A case report

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Author contributions: Ling C, Liu XQ and Li YQ contributed equally to this work. Ling C collected the case data and administered the anesthesia; Li YQ formulated the surgery regimen and administered the surgery; Liu XQ collected the case data and administered the anesthesia; Wen XJ formulated the anesthesia regimen, guided the anesthesia, and wrote the manuscript; Hu XD and Yang K administered the anesthesia.

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Abstract

BACKGROUND

Fascia iliaca compartment block is a technique that blocks three nerves, similar to a 3-in-1 nerve block. This block provides analgesia for patients undergoing lower limb surgery, and is a simple technique that is easy to implement. Here, we report a case of fascia iliaca compartment block in a patient with myocardial infarction who underwent emergency middle thigh amputation.

CASE SUMMARY

A 78-year-old female patient weighing 38 kg with gangrene and occlusive peripheral atherosclerosis of the right leg underwent an emergency middle thigh amputation. The patient had a history of hypertension, coronary heart disease, cerebral infarction, anterior wall myocardial infarction, and had recently undergone percutaneous coronary intervention consisting of coronary angiography and right coronary artery stent implantation. Considering the patient's condition, an ultrasound-guided fascia iliaca compartment block combined with general anesthesia was implemented for amputation. The fascia iliaca compartment block provided analgesia for the operation, and reduced the dosage of general anesthetics. It also alleviated adverse cardiovascular effects caused by pain stress, and ensured the safety of the patient during the perioperative period. This block also provided postoperative analgesia. The patient had a good prognosis, and was subsequently discharged from hospital.

CONCLUSION

Fascia iliaca compartment block provides surgical analgesia. It also alleviates adverse cardiovascular effects, and ensures patient safety during the perioperative period.

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Key words: Ultrasound-guided; Fascia iliaca compartment block; Acute myocardial infarction; Case report; Percutaneous coronary intervention

Core tip: Ultrasound-guided fascia iliaca compartment block combined with general anesthesia can provide better intraoperative analgesia for thigh surgery, reduce the dosage of general anesthetics, and alleviate the adverse cardiovascular effects caused by pain stress. In this case report, we describe the effects of fascia iliaca compartment block in a patient with myocardial infarction who underwent an emergency middle thigh amputation. Use of this block ensured the safety of the patient during the perioperative period.

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INTRODUCTION

Thigh surgery presents a challenging clinical problem commonly encountered by medical staff. Traditional analgesia for thigh surgery involves opioids and regional nerve blockade, which have been demonstrated to be effective. Emergency surgery is often encountered in the elderly, and presents special demands for the anesthesiologist. Fascia iliaca compartment block is a technique that blocks three nerves similar to a 3-in-1 nerve block. The fascia iliaca space has the iliopsoas muscle behind, the fascia iliaca in front, and the fascia lata covering the superficial fascia of the fascia iliaca. The femoral nerve, the lateral femoral cutaneous nerve, and the obturator nerve are located below the fascia iliaca at the pelvic segment. The fascia iliaca compartment block is used to block these three nerves to meet the needs of lower limb analgesia and anesthesia. From references[1,2], we know that fascia iliaca compartment block can provide superior analgesia and decreased opioid consumption with minimal side effects. It can be deployed in a relatively quick fashion after a small amount of training, and can be executed with high success rates under ultrasound guidance. Compared with general anesthesia, fascia iliaca compartment block combined with general anesthesia reduces the dosage of general anesthetics required, stabilizes the hemodynamics, and improves postoperative analgesia. Here, we report a case of fascia iliaca compartment block in a patient with myocardial infarction who underwent emergency middle thigh amputation.

CASE PRESENTATION

Chief complaints

Shortness of breath and dyspnea for 10 d.

History of present illness

A 78-year-old female patient weighing 38 kg was diagnosed with acute non-ST segment elevation myocardial infarction 10 d previously in another hospital, which manifested as chest pain, shortness of breath and dyspnea, and was treated with tracheal intubation, ventilator-assisted ventilation and vasodilation. Serum troponin concentration was 0.7 ng/mL. The patient was transferred to the intensive care unit (ICU) at our hospital.

History of past illness

Hypertension and coronary heart disease for 15 years, cerebral infarction for 8 years, and anterior wall myocardial infarction for 5 years.

Physical examination

The patient had decreased blood pressure, increased heart rate and fever, characterized by septic shock, cardiogenic shock, and blood oxygen saturation (SpO_2) fluctuations above 97% when tracheal intubation was connected to the ventilator. The lungs demonstrated thick breath sounds, and the lower lungs showed slight moist rale. Her heart rate was 100 bpm, the heart sound was low and blunt, and there was no noise in each valve area. Dry necrosis of the right lower foot and visible scattered ecchymoses were observed.

Laboratory examinations

The serum creatine kinase-MB concentration was 25.8 ng/mL, and the white blood cell count was 24.25 × 10^9/L.

Imaging examinations

The bedside digital radiography chest X-ray showed double lung infection. Color Doppler ultrasound showed moderate mitral regurgitation and mild aortic regurgitation.

FINAL DIAGNOSIS

Non-ST segment elevation acute myocardial infarction, right leg gangrene, and right leg peripheral arterial occlusive disease.

TREATMENT

In the ICU, the patient had been given imipenem and cilastatin sodium for anti-infection, as well as dopamine and norepinephrine as anti-shock treatment. Three days previous, the patient had undergone percutaneous coronary intervention (PCI) consisting of coronary angiography and right coronary artery stent implantation by a cardiologist. The coronary angiography showed that there was no obvious stenosis in the left main coronary artery, 70%-80% stenosis in the middle part of the anterior descending artery, 80% stenosis in the opening of the circumflex artery, and 90% stenosis in the proximal part of the right coronary artery. The patient was diagnosed with right coronary artery dominant type and three-vessel coronary lesions. Considering the patient's condition, a stent was implanted in the right coronary artery, and the effect of vascular opening was good. Following PCI, the patient's body temperature further increased (38.5-39 °C), and the white blood cell count was 33.74 × 10^9/L. The right lower extremity showed dry skin necrosis and scattered ecchymoses. The right middle iliac artery showed occlusion. The patient had an endotracheal tube in place and presented with fever, and the SpO_2 was over 97% with medium flow oxygen inhalation. Following multi-disciplinary team consultation, the patient was scheduled for mid-thigh amputation.

The patient was conscious and entered the operating room with a tracheal catheter in place. Dopamine was pumped continuously at 5 μg/kg per min, and norepinephrine was pumped at 0.06 μg/kg per min into the right internal jugular vein. The patient's non-invasive blood pressure was 95/45 mmHg, heart rate was 98 bpm, and SpO_2 was 99%. A left radial artery puncture catheter was used to monitor arterial blood pressure. The anesthesia system was connected to the tracheal catheter to assist ventilation.

Ultrasound-guided right-side improved fascia iliaca compartment block was used for surgical analgesia. The procedures were as follows: The ultrasound probe was vertically placed on the outer third of the inguinal ligament to identify the hourglass sign in the obliquus internus abdominis, sartorius muscle and iliopsoas muscle[3] (Figure 1). The in-plane technique was used to implant the needle from the tail end to the head of the patient to reach the deep surface of the fascia iliaca. Local anesthetics (0.33% ropivacaine hydrochloride 30 mL) was injected into the space between the obliquus internus abdominis and iliopsoas muscle. The anesthetic plane was tested by acupuncture after 5 min and 10 min to ensure the block effect. After blocking, midazolam 2 mg, sufentanil 10 μg, cisatracurium 6 mg and etomidate 6 mg were intravenously injected to induce anesthesia, and 1% sevoflurane inhalation anesthesia-maintained anesthesia.

The operation duration was 65 min. The bispectral index was maintained between 45 and 60. Vasoactive drugs were used to regulate blood pressure and heart rate. Vital signs were stable during the perioperative period. The Critical Care Pain Observation Tool (CPOT) score can be used to assess pain in critically ill patients with no hypnotic, opioid-based analgo-sedation[4,5], the CPOT score was 2 at 6 h after surgery, and the

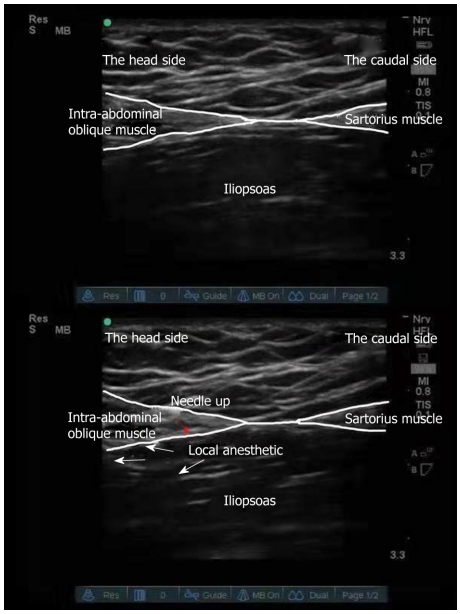

Figure 1 Procedure for ultrasound-guided fascia iliaca compartment block. The ultrasound probe was vertically placed on the outer third of the inguinal ligament to identify the hourglass sign of the obliquus internus abdominis, sartorius muscle and iliopsoas muscle.

Ramsay sedation score was 3. The effect of postoperative analgesia was satisfactory. Two days after the operation, inflammatory indicators improved, and tracheal intubation was removed.

OUTCOME AND FOLLOW-UP

No serious adverse cardiovascular events occurred during the perioperative period, and the patient was subsequently discharged.

DISCUSSION

The incremental risk of noncardiac surgery on adverse cardiac events among post-stent patients is highest in the initial 6 mo following stent implantation, and stabilizes at 1.0% after 6 mo[6,7]. From references[8], in the case of emergency surgery, it is particularly important for anesthesiologists to prevent, monitor and treat myocardial ischemia during surgery.

Our patient suffered from an acute myocardial infarction approximately 2 wk previous, and had undergone PCI. Due to vascular occlusion and necrosis of the right lower extremity, the patient presented with septic shock, and underwent both tracheal intubation and artificial ventilation. She also had multiple organ dysfunction. It was necessary to perform an urgent right lower extremity amputation to eliminate the source of infection. For amputation patients, intraspinal anesthesia is the preferred method of anesthesia. However, this patient was administered anticoagulation therapy after PCI, and coagulation function was abnormal; thus, intraspinal anesthesia was unsuitable.

As this patient had suffered from a recent acute myocardial infarction and her cardiac function was poor, it was crucial to maintain stable circulation, as well as a balance between oxygen supply and demand during surgery. If only general anesthesia was selected, deep anesthesia would be required. Anesthetic agents can depress myocardial contraction[9]. A large dosage of general anesthetics would aggravate myocardial depression and induce adverse cardiac events. Krych *et al*[10] reported that the quality of perioperative analgesia provided by the fascia iliaca blockade was excellent, and resulted in both low opioid consumption and a high quality of pain relief. Ultrasound-guided fascia iliaca compartment block provided the perfect analgesia, and decreased the consumption of general anesthetics, which avoided cardiac and circulatory function depression. This was caused by deep general anesthesia and the stress reaction caused by light anesthesia. Considering the patient's condition, ultrasound-guided fascia iliaca compartment block combined with general

anesthesia was employed for amputation.

The fascia iliaca space has the iliopsoas muscle behind, the fascia iliaca in front, and the fascia lata covering the superficial fascia of the fascia iliaca[11-13]. The femoral nerve, the lateral femoral cutaneous nerve, and the obturator nerve are located below the fascia iliaca at the pelvic segment[14]. Fascia iliaca compartment block is used to block these nerves to meet the needs of lower limb analgesia and anesthesia. It is used for anesthesia and analgesia of the hip, knee and thigh[15,16]. Ultrasound-guided fascia iliaca compartment block can be divided into parallel puncture of the inguinal ligament, and improved vertical puncture of the inguinal ligament. In a parallel puncture of the inguinal ligament, drugs spread to the lower part of the inguinal ligament, while the modified fascia iliaca compartment block technique under real-time ultrasound guidance and local anesthetics spread to the head[17,18]. As the distribution of the femoral nerve, lateral femoral cutaneous nerve and obturator nerve is concentrated above the inguinal ligaments, the number of local anesthetics needed in the improved vertical method is reduced. Due to infection, the patient required emergency amputation, and the improved vertical method of fascia iliaca compartment block combined with general anesthesia was adopted.

CONCLUSION

Ultrasound-guided fascia iliaca compartment block provided analgesia for surgery, and reduced the dosage of general anesthetics. It also alleviated adverse cardiovascular effects caused by pain stress, and ensured the safety of the patient during the perioperative period. The fascia iliaca compartment block also provided postoperative analgesia. The patient had a good prognosis and was subsequently discharged from the hospital.

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CASE REPORT

Rare spontaneous intrahepatic portosystemic shunt in hepatitis B-induced cirrhosis: A case report

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Author contributions: Tan YW, Sheng JH and Tan HY contributed equally to this work. Tan YW and Sheng JH designed the research; Tan HY, Sun L and Yin YM collected and analyzed the data, and drafted the manuscript; Tan YW and Tan HY wrote and revised the manuscript; all authors have read and approved the final version to be published.

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Abstract

BACKGROUND

The portosystemic shunt is the pathway between the portal vein (PV) and systemic circulation. A spontaneous intrahepatic portosystemic shunt (SPISS) is a rare portosystemic shunt type. Here we report an extremely rare type of SPISS, a spontaneous intrahepatic PV-inferior vena cava shunt (SPIVCS).

CASE SUMMARY

A 66-year-old woman was admitted to our hospital with the complaint of abdominal distention and a decreased appetite for 1 mo. The patient had a 20-year history of hepatitis B surface antigen positivity and a 5-year history of cirrhosis. She had been treated with Chinese herbal medicine for a long time. Liver function tests showed: alanine aminotransferase, 35 U/L; aspartate aminotransferase, 42 U/L; serum albumin (ALB) 32.2 g/L; and serum ascites ALB gradient, 25.2 g/L. Abdominal ultrasonography and enhanced computed tomography showed that the left branch of the PV was thin and occluded; the right branch of the PV was thick and showed a vermicular dilatation vein cluster in the upper pole of the right kidney that branched out and converged into the inferior vena cava from the bare area of the lower right posterior lobe of the liver. We diagnosed her with an extremely rare SPIVCS caused by portal hypertension and provided symptomatic treatment after admission. One week later, her symptoms disappeared and she was discharged.

CONCLUSION

SPIVCS is a rare portosystemic shunt with a clear history of cirrhosis and portal hypertension. Clarifying the type PV shunt has important clinical significance.

Key words: Spontaneous; Intrahepatic; Portosystemic shunt; Cirrhosis; Case report

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Core tip: Here we report a spontaneous intrahepatic portal vein (PV)-inferior vena cava shunt. A 66-year-old woman was admitted to our hospital with a 20-year history of HBsAg and a 5-year history of cirrhosis. Abdominal ultrasonography and enhanced computed tomography showed that the left branch of the PV was thin and occluded; the right branch of the PV was thick and showed a vermicular dilatation vein cluster in the upper pole of the right kidney that branched out and converged into the inferior vena cava from the bare area of the lower right posterior lobe of the liver.

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INTRODUCTION

Liver cirrhosis is often accompanied by portal hypertension, which often manifests as esophageal varices, ascites, splenomegaly, hypersplenism, upper gastrointestinal hemorrhage, portosystemic shunt encephalopathy, and spontaneous bacterial peritonitis[1]. Spontaneous portosystemic shunt (SPSS), a common but insufficient clinical manifestation, is a result of compensation of portal hypertension in cirrhosis[2]. The shunt can be congenital or acquired[3]. The incidence rate of SPSS in patients with cirrhosis is 38%-40%, and the incidence rate of splenorenal shunt (SRS) is 14%-21%[4]. The most common types of SPSS are SRS and umbilical vein recanalization[5]. Rare types include collateral veins in gastric varices, gallbladder varices, thrombotic portal vein (PV), intestinal-caval shunt, and right portal–renal vein shunt[6]. Spontaneous intrahepatic portosystemic shunt (SPISS), a rare SPSS type, includes PV branches that directly shunt to the intrahepatic vein and PV branches that shunt to the extrahepatic inferior vena cava (IVC).

We recently encountered a 66-year-old woman with a 20-year history of hepatitis B surface antigen (HBsAg) positivity. We found that she had an extremely rare SPISS, a spontaneous intrahepatic PV-IVC shunt (SPIVCS) caused by portal hypertension.

CASE PRESENTATION

Chief complaints

A 66-year-old woman was admitted to our hospital with the complaint of a 1-mo history of abdominal distention and decreased appetite.

History of present illness

She had no history of ascites, gastrointestinal bleeding, or hepatic encephalopathy. She had no history of alcohol abuse or hepatitis C.

History of past illness

The patient also had a 20-year history of HBsAg positivity and had been treated with Chinese herbal medicine for a long time. In the past 5 years, she had been diagnosed with cirrhosis induced by hepatitis B by a rural doctor.

Personal and family history

No alcohol abuse and no other drug and herbal used. No additional family history. While her daughter had history of HBsAg positivity but no history of hereditary diseases.

Physical examination upon admission

A physical examination revealed a blood pressure of 135/82 mmHg, heart rate of 78 beats/min, temperature of 36.8°C, and breathing rate of 18 times/min. Her skin was dark and gloomy; no yellowing of the skin and mucosa was evident; visible liver palms and spider angioma, an abdominal bulge, and visible abdominal wall vein exposure were evident, and splenomegaly (4 cm below the left midclavicular line–left ribs junction) were evident; no abdominal pain was reported; and the ascites buckle sign was positive.

Laboratory examinations

Routine bloodwork revealed the following: red blood cell count, 2.13 × 10^9/L; hemoglobin, 6.12 g/L; white blood cell count, 2.43 × 10^9/L; neutrophil count, 1.86 × 10^9/L; and platelet count, 5.25 × 10^{12}/L. Liver function test results were as follows: alanine aminotransferase, 35 U/L (10-40 U/L); aspartate aminotransferase, 42 U/L (10-40 U/L); serum total bilirubin, 17.2 μmol/L (1.71-17.1 μmol/L); direct bilirubin, 4.26 μmol/L (0-6.8 μmol/L); serum albumin (ALB), 32.2 g/L (35-53 g/L); serum globulin 28 g/L (20-40 g/L); alkaline phosphatase, 89 U/L (40-120 U/L); glutamide transphthalase, 63 U/L (10-40 U/L); and serum ammonia, 45 μmol/L (27-82 μmol/L). Hepatitis B virus (HBV) markers were as follows: HBsAg, 26 IU/mL (< 0.05 IU/mL); anti-HBs, 0.001 mIU/mL (< 10 mIU/mL); anti-hepatitis B e antigen, 2.143 Paul Ehrlich international units (PEIU)/mL (< 0.2 PEIU/mL); anti-hepatitis B core antigen, 3.221 PEIU/mL (< 0.9 PEIU/mL).

Other results were as follows: HBV DNA, not detected (< 20 IU/mL); alpha fetoprotein, 4.25 μg/L (< 20 ng/mL); ascites examination, clear; Li Fanta test, negative; nucleated cell count, 0.82 × 10^9/L; monocyte ratio, 55%; polymorphonuclear cell ratio, 45%; and serum ascites ALB gradient, 25.2 g/L.

Antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsome antibody type 1, anti-nuclear glycoprotein antibody, anti-soluble acid nucleoprotein antibody, soluble acidic nucleoprotein antibody, anti-hepatocyte cytoplasmic antigen type 1 antibody, anti-soluble liver antigen/hepatopancreatic antigen antibody, and other tests were negative. Other levels were: immunoglobulin G (IgG), 13.1 g/L (7.11-16 g/L); IgG4, 0.08 g/L (≤ 2.01 g/L); and ceruloplasmin, 0.33 g/L (0.2-0.6 g/L).

Imaging examinations

Abdominal ultrasonography revealed that echoes of the liver showed dense thickening and an uneven intrahepatic structure disorder; the liver capsule was unclear and irregular. The right branch of the PV showed obvious dilatation (local dilatation, up to 48 mm), was connected with the IVC, and showed a turbulent local spectrum, as shown in Figure 1.

Abdomen enhanced computed tomography (CT) revealed that the left branch of the PV was thin and occluded, while the right branch of the PV was thick, showed a vermicular dilatation vein cluster, branched out, and converged into the IVC from the bare area of the lower right posterior lobe of the liver, forming a venous dilatation vein cluster in the upper pole of the right kidney (Figure 2 and 3). In addition, a vermicular dilatation vein shadow was seen in the inner wall of the lower esophagus, perineural space, and hepatic-gastric space and the splenic vein diameter was increased to 1.7 cm. A portion of the liver lobe was disordered and the hepatic fissure was widened. The spleen was enlarged and numerous liquid shadows were visible in the abdominal cavity.

FINAL DIAGNOSIS

A rare SPISS in hepatitis B-induced cirrhosis.

TREATMENT

After admission, 3000 mL of ascites fluid was drained, 20 g of human ALB was intravenously infused, and 100 mg of spironolactone and 40 mg of furosemide were administered per day. One week later, the abdominal distension was relieved, her appetite improved, and she was discharged with maintenance therapy of propranolol 20 mg/d.

OUTCOME AND FOLLOW-UP

Follow-up of liver function and ultrasonography every 3 mo after discharge showed no further deterioration of liver function and ascites.

DISCCUSION

The portosystemic shunt is the pathway between the PV and the systemic circulation[7]. By etiology, it can be divided into congenital and spontaneous types[8] as

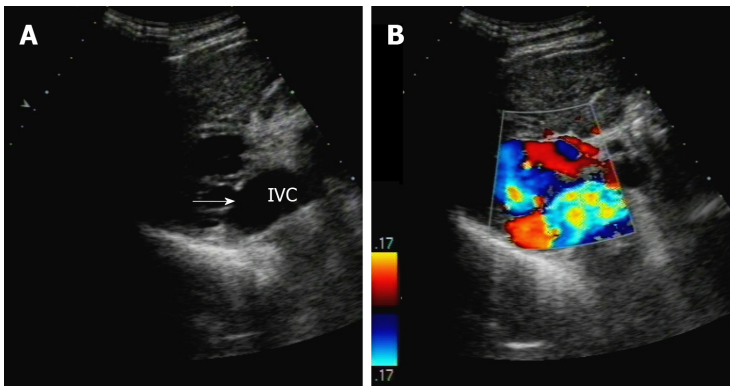

Figure 1 Ultrasonography revealed a spontaneous intrahepatic portosystemic shunt. A: The branch of the right portal vein connects to the inferior vena cava through (arrow); B: The extrahepatic venous plexus showed turbulent spectrum locally. IVC: Inferior vena cava.

well as intrahepatic and extrahepatic types according to anatomical location[9].

SPISS is a spontaneous venous pathway that extends from the intrahepatic venous system to the circular venous system[10]. It is mostly acquired, but a congenital type has not been identified[11]. Lalonde *et al*[12] reported a SPIVCS case which may be belong to the congenital type because the patient was only a 15-year-old adolescent with no evidence of liver cirrhosis or portal hypertension. There are still two types of SPISS: one in which the intrahepatic PV branch shunts to the intrahepatic vein, and another in which the intrahepatic PV shunts to the IVC through the lateral hepatic branch. The first type can occur in cases of tumors, liver trauma, or Budd-Chiari syndrome (BCS)[13,14]. The second type is very rarely discussed and refers to the right posterior branch of the PV connected with the IVC through the right posterior lobe of the liver in the right adrenal region. SPIVCS is common in cirrhosis patients with portal hypertension. Its possible anatomical basis is that the right branch of the PV communicates with the IVC through the accessory hepatic vein or the subcapsular venous plexus of the liver. Since there is no standard proper term to describe this type of shunt, we refer to it as SPIVCS.

Abernethy malformation is also a SPSS that requires differentiation from SPISS, a rare congenital extrahepatic portosystemic shunt malformation caused by abnormal development of the PV system[15]. Morgan and Supefina classified Abernethy malformations as follows[16]: type I, complete portosystemic shunt without PV perfusion in the liver; and type II, partial portosystemic shunt with partial portosystemic blood perfusion in the liver. Type I primarily affects children and women and is often accompanied by other congenital malformations such as biliary atresia, polysplenoma, heart defects, and liver tumors. Type II is rarer, primarily affects men, and features few other congenital malformations. Moreover, Abernethy malformation has no underlying diseases such as cirrhosis or portal hypertension and primarily affects children[17].

We retrieved the PubMed database using "intrahepatic portosystemic shunt," "intrahepatic portal cavity shunt," "spontaneous intrahepatic portosystemic shunt," and "portoinferior vena cava shunt" keywords and MeSH terms, respectively. By January 31, 2019, six articles describing intrahepatic SPSS similar to ours were found, as shown in Table 1.

During liver transplantation for severe hepatic encephalopathy, Vennarecci[18] found a very thick shunt between the right branch of the PV and IVC, which made the operation more difficult. The shunt vein was torn during the operation, causing a massive hemorrhage. After hemostasis was achieved, the surgical strategy was changed to hepatectomy from the left side to the right side. Therefore, the SPIVCS shunt will increase the liver transplantation difficulty. Another SPISS type, which involves the PV branches directly shunting to the intrahepatic vein, can be caused by intrahepatic tumors and trauma or occur spontaneously[19].

BCS characterized by obstructive lesions of the hepatic vein and the IVC is another cause of SPISS that is shunted to the vena cava system via the subcapsular or intrahepatic veins[14]. The use of a transjugular intrahepatic portosystemic shunt is an effective treatment for BCS-induced SPISS.

Kwon *et al*[10] reported a case of laparoscopic surgery used to circumcise the inflow of varicose veins. Their patient's hepatic encephalopathy improved postoperatively and liver function returned to normal. No shunt reappeared on a CT scan 8 mo later.

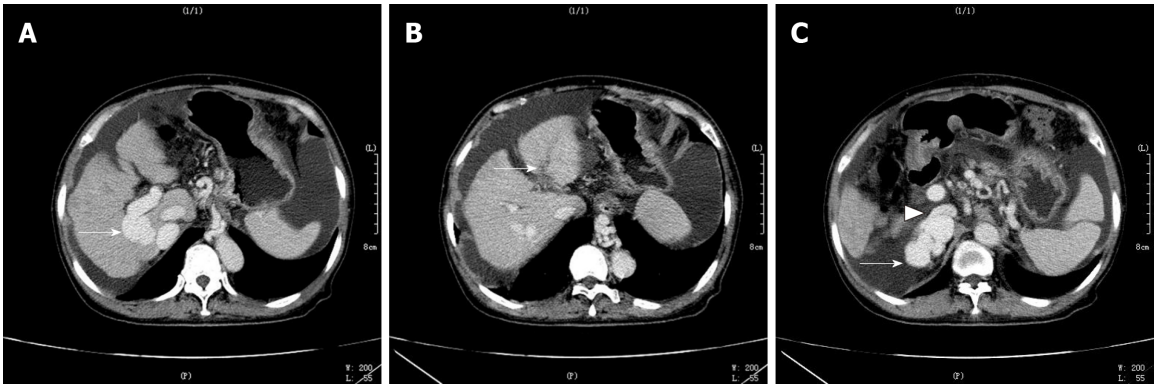

Figure 2 Abdomen enhanced computed tomography revealed a spontaneous intrahepatic portosystemic shunt. A: The right branch of portal vein (PV) was thick and showed vermicular dilatation vein cluster (arrow); B: The left branch of PV was thin and occluded (arrow); C: The right branch of PV connected with inferior vena cava (arrowhead), extrahepatic dilatation and distortion of blood vessels (arrow).

CONCLUSION

SPIVCS is a rare portosystemic shunt with a clear history of cirrhosis and portal hypertension. Clarifying the PV shunt has important clinical significance: (1) it aids the differential diagnosis of PV aneurysm and right adrenal lesion; (2) it guides clinical treatment because patients with PV shunt are more likely to suffer from hepatic encephalopathy induced by elevated blood ammonia; and (3) for patients who need surgical or other interventions such as abdominal puncture, the shunt helps the surgeon plan ahead of time.

Table 1 Clinical characteristics and treatment of spontaneous intrahepatic portosystemic shunt in literature reports

Reporters	Country	Sex	Old (yr)	History of liver disease	Encephalopathy	Serum ammonia	Liver function test	Splenomegaly	The maximum diameters of shunt
Kwon *et al*[10]	Korea	Woman	42	No	Yes	146 μg/dL	ALT, 152 U/L; AST, 112 U/L;	No	30.4 mm
Qi *et al*[20]	China	Man	58	Cirrhosis (HBV)	No	35 μmol/L	TBIL, 48.9 μmol/L, ALT, 66.04 U/L, AST, 93.11 U/L	Moderate	ND
Tsauo *et al*[21]	China	Woman	36	Cirrhosis (AIH)	ND	ND	ND	Yes	ND
Vennarecci *et al*[18]	Italy	ND	ND	ND	Yes	ND	ND	Yes	ND
Lalonde *et al*[12]	Belgium	Man	15	No	No	ND	Abnormal liver function	No	20 mm
Peng-Xu Ding *et al*[14]	China	Woman	42	Cirrhosis (HCV)		ND	ND	ND	ND

TBIL: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALB: Albumin; ND: No describe; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis.

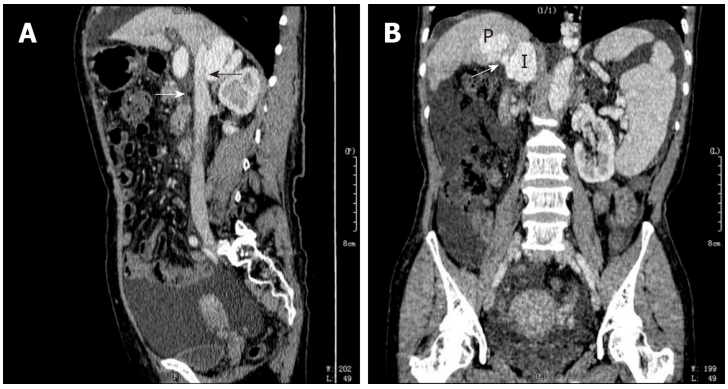

Figure 3 Abdomen enhanced computed tomography revealed a spontaneous intrahepatic portosystemic shunt at sagittal and coronal position. A: The right branch of portal vein (PV) shunt out of the liver to communicate with inferior vena cava (IVC) (arrow) at sagittal position (black arrow); B: The right branch of PV shunt out of the liver to communicate with IVC (arrow) at coronal position.

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CASE REPORT

Imaging of mixed epithelial and stromal tumor of the kidney: A case report and review of the literature

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Abstract

BACKGROUND

Mixed epithelial and stromal tumors of the kidney (MESTKs) are a rare entity (about a hundred cases reported). They occur almost exclusively in postmenopausal women, with only seven cases reported in men. As this entity is very rare, little is known on its imaging features, especially magnetic resonance imaging (MRI) findings. In women, at MRI, the cystic component shows T1 hypointensity and T2 hyperintensity, while the solid component shows T1 hyperintensity and T2 hypointensity.

CASE SUMMARY

We report the computed tomography (CT) and MRI findings of MESTK in a 19-year-old male adolescent. To our knowledge, this case report is the first report of MRI findings of MESTK in male adolescents. The patient was admitted to Subei People's Hospital (Jiangsu Province, China) in July 2017 after a renal mass on the left side was detected by ultrasound during a clinical examination. Blood tests were all normal. Non-enhanced CT showed a round, well-circumscribed complex mass, approximately 45 mm × 40 mm in size. MRI revealed a clear well-circumscribed mass with a mixed arrangement of solid and cystic components. On T2 weighted images, some hypointensities were found in the solid areas. After contrast enhancement, moderate or mild enhancement was found in the solid component, which increased with time. A radical left nephrectomy was performed. The pathology analysis revealed a mixed epithelial and stromal tumor. The patient had no imaging findings of recurrence or metastasis at 12 months following surgery.

CONCLUSION

The possibility of MESTK should be considered in male adolescents. MRI can provide useful information for the preoperative diagnosis.

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Key words: Mixed epithelial and stromal tumor of the kidney; Adolescent; Magnetic resonance imaging; Preoperative diagnosis; Case report

Core tip: Mixed epithelial and stromal tumors of the kidney (MESTKs) are rare benign tumors that occur predominantly in women. Little is known on its imaging features, especially magnetic resonance imaging (MRI) findings. We report the computed tomography and MRI findings of MESTK in a 19-year-old male adolescent. To our knowledge, this is the first report of MRI findings of MESTK in male adolescents. Although it occurs predominantly in menopausal women, the possibility of MESTK should be considered in male adolescents with a cystic solid mass in the kidney. MRI can provide useful information for the preoperative diagnosis.

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INTRODUCTION

Mixed epithelial and stromal tumor of the kidney (MESTK) is a rare type of tumor with about a hundred cases reported in the literature[1]. MESTKs are solid tumors that include both stromal and epithelial components, as well as spindle cells that look like ovarian stroma, especially since these cells also express the estrogen and progesterone receptors[2]. MESTKs are benign tumors and are often treated by surgery. Some cases of concomitant MESTK and sarcoma have been reported[3-8], but they are too rare to reach any conclusion about the natural history of the disease.

According to previous reports, the lesions occur almost exclusively in postmenopausal women[1,9-12]. Only seven cases have been reported in men[9,13-16]. Due to its rarity, accurate diagnosis before surgery is difficult since the ultrasound and magnetic resonance imaging (MRI) features are poorly known, but computed tomography (CT) usually shows a well-circumscribed, multiseptate cystic and solid mass with delayed enhancement[11-13]. On MRI, the cystic component shows T1 hypointensity and T2 hyperintensity, while the solid component shows T1 hyperintensity and T2 hypointensity, at least in women[12]. To our knowledge, there have only been three cases of MESTK in male adolescents reported in the English literature, and the MRI findings were not described[17-19].

In this report, we describe the CT and MRI findings in a 19-year-old man diagnosed with MESTK, focusing on MRI, and provide a review of the literature.

CASE PRESENTATION

Chief complaints

A 19-year-old man was found to have a renal mass on the left side during a clinical examination.

History of present illness

The patient was admitted to Subei People's Hospital (Jiangsu Province, China) in July 2017 after a renal mass on the left side was detected by ultrasound during a clinical examination. The initial diagnosis was renal tumor.

History of past illness

None.

Personal and family history

None.

Physical examination upon admission

The patient had no hematuria, urinary urgency, or cold fever. Physical examination showed no evidence of any abdominal mass.

Laboratory examinations

The blood test results for blood cell count, biochemistry, and tumor markers, including cancer antigen CA724 (4.57 kU/L; normal range, <6.00 kU/L) and carcinoembryonic antigen CEA (4.78 kU/L; normal range, <5.00 kU/L), were all normal.

Imaging examinations

A non-enhanced CT (Lightspeed VCT 64; GE Healthcare, Milwaukee, WI, United States) scan showed a round, well-circumscribed complex mass, approximately 45 mm × 40 mm in size. A contrast-enhanced CT scan showed delayed enhancement of the solid part of the mass and no enhancement of the cystic part of the mass (Figure 1). MRI (GE Signa EXCITE HD, Milwaukee, WI, United States) was performed using fast spin echo T2 weighted images (T2WI), as well as non-enhanced and contrast-enhanced T1 weighted images (T1WI), which revealed a clear well-circumscribed mass with a mixed arrangement of solid and cystic components. On T2WI, some hypointensities were found in the solid areas. After contrast enhancement, moderate or mild enhancement was found in the solid component, which increased with time (Figure 2).

FINAL DIAGNOSIS

The preoperative diagnosis was renal carcinoma. After surgery, the gross specimen showed a well-circumscribed mass with a white texture that looked like fish flesh (Figure 3). Microscopically, the tumor consisted of stroma and epithelium. The stroma consisted primarily of hypocellular fibrous cells with hyperplastic fibers and vessels, which constituted the largest proportion. Renal tubules with single-layer cubic cell lining were found in the epithelium (Figure 4). Immunohistochemistry revealed smooth muscle that was actin-positive, desmin-positive, H-caldesmon-positive, Gata-3-positive, and ki67-negative. The pathology analysis revealed a mixed epithelial and stromal tumor.

TREATMENT

A radical left nephrectomy was performed.

OUTCOME AND FOLLOW-UP

The patient recovered well and was discharged for rehabilitation after 13 d. He had no imaging findings of recurrence or metastasis at 12 mo following surgery.

DISCUSSION

MESTK is a rare, complex tumor composed of a mixture of cystic and solid areas that was first described in a case report by Michal *et al*[10] in 1998. At present, the pathogenetic mechanism of MESTK and its relationship to other renal neoplasms are still unclear. Most cases occur in menopausal woman (approximately 1:6 male-to-female ratio) and some cases had a long-term history of estrogen therapy[9,11,20-22]. Therefore, the hormonal milieu may play a critical role in the tumorigenesis of MESTK. Adsay *et al*[9] reported that the spindle cells of these lesions may arise from a periductal fetal mesenchyme which may have the capacity to interact with the epithelium. Hormone receptor positivity was detected in the mesenchyme of most MESTKs. A deranged hormonal milieu induces the proliferation of this mesenchyme, which in turn drives the growth of the epithelial component. In the case reported here, MESTK occurred in a 19-year-old man, and three cases of MESTK in male adolescents have also been described[17-19]. Therefore, we assume that hormone secretion disorder in male adolescents may lead to the growth of neoplastic cells. The rarity of the disease precludes investigation into the matter and the exact pathogenesis of MESTK needs further research.

Because hormonal factor is closely related to tumor development, hormone treatment could be a potential therapeutic approach in treatment of MESTK. But

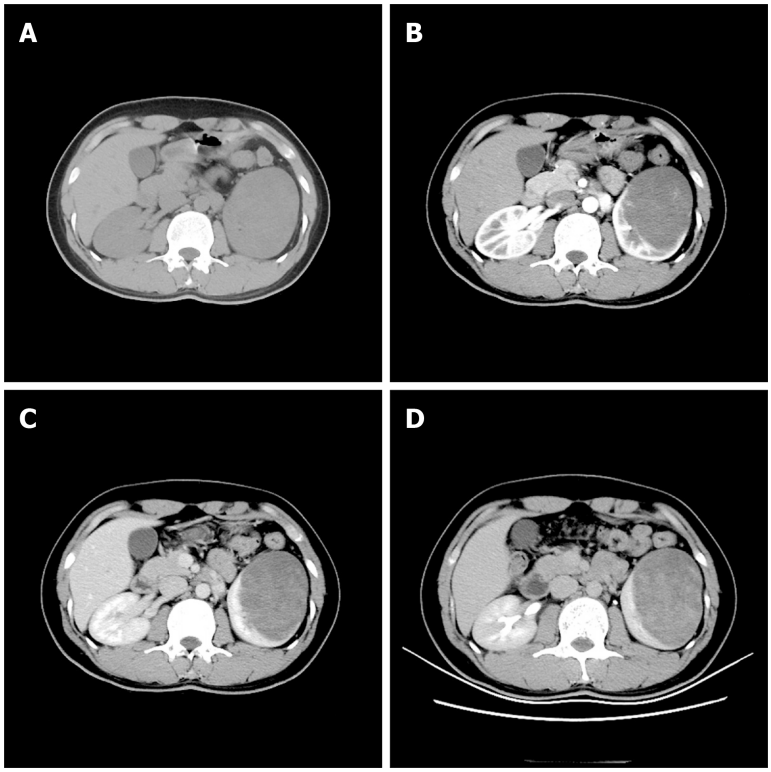

Figure 1 Computed tomography. A: Non-enhanced computed tomography image showing a round, well-defined, and mixed mass; B: Enhanced computed tomography image during the corticomedullary phase; C: Nephrographic phase; D: Delayed enhancement of the solid part and no enhancement of the cystic part.

preoperative radiologic diagnosis of MESTK is difficult, and its clinical treatment still follows the renal cell carcinoma protocol[22].

MESTK does not show any specific clinical manifestations. Most MESTK patients present with symptoms such as hematuria, abdominal pain, a palpable mass, or urinary tract infections[9,23,24]. Previous literature and this study reveal an increasing number of asymptomatic cases[11,25]. This could be because of advances in imaging modalities and the prevalence of routine medical examinations. In this case, the patient was asymptomatic and the tumor was detected incidentally.

The largest report on MESTK was conducted by Caliò *et al*[26], who described the clinicopathological features of MESTK in 53 patients. In their study, the MESTK generally appeared as a solitary, well-circumscribed, and solid or mixed mass. Morphologically, MESTK is typically a mixture of spindle cells and an epithelial component that lines a variable cystic architecture[20,27]. Recent studies have reported that hypocellular fibrous stroma and adipose tissue were more common in larger tumors, while cellular spindle cell stroma was more common in smaller tumors[26]. This finding is compatible with the present case, in which the tumor had the appearance of a large well-circumscribed mass with the stromal component consisting of paucicellular fibrosis cells and the epithelial component consisting of cysts or microcysts.

There have been some clinical and pathological studies of MESTK[5,9,10,20,23,24,28], but only a few radiological studies have been reported in adults[12,13]. MESTKs appear as well-defined, multi-septate cystic masses with a nodular component containing solid enhancing components after contrast enhancement. There have been few radiological reports of MESTK in adolescents. Lang *et al*[19] reported a 16-year-old male who had a large, well-defined mass protruding from the right kidney that was composed of solid parts on CT. This finding is similar to our case, but MRI was not described by Lang *et al*[19]. In the present case, MRI revealed a well-defined, expansive growth, and mixed mass that showed inconsistent delayed enhancement, which is similar to the MRI features found in women[12]. It has been shown that the degree of delayed enhancement may depend on the spindle cell components of these tumors, with minimal enhancement in paucicellular fibrosis and more intense enhancement in densely cellular areas[1,13,19]. The mass showed hypointensity on T2WI, suggesting that the mass contained a fibrotic component, which was supported by pathological findings.

Because of insufficient understanding, MESTK is easily misdiagnosed by both

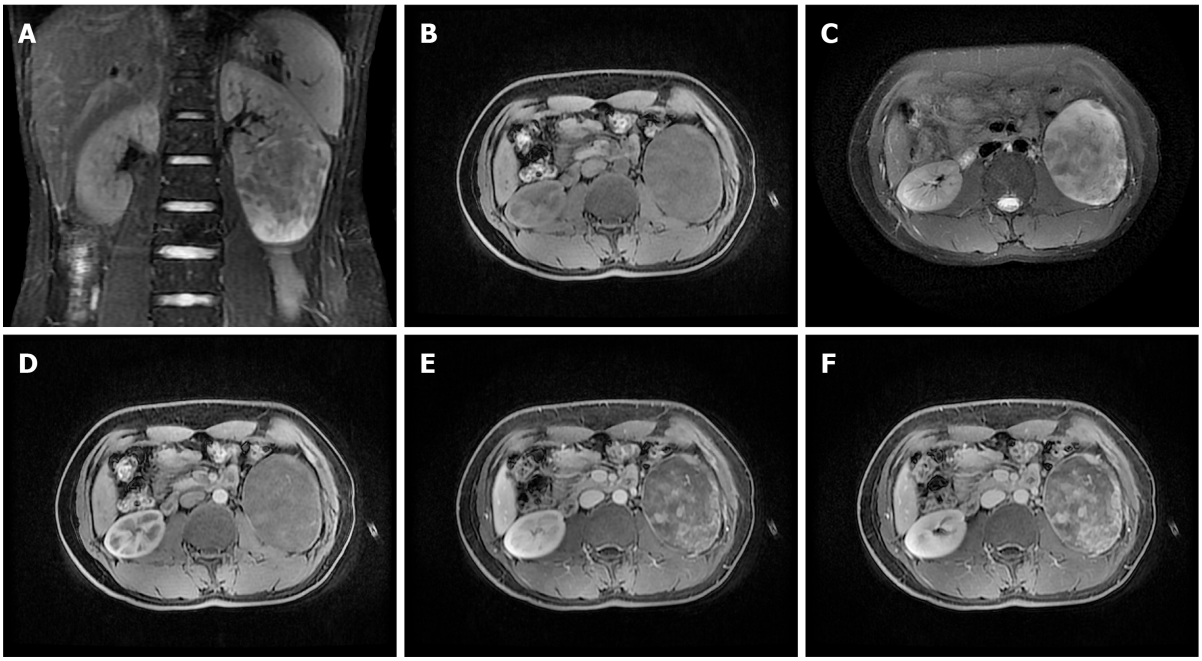

Figure 2 Moderate or mild enhancement in the solid component after contrast enhancement. A: Coronal T2-weighted image showing an exophytic cystic-solid mass in the lower pole of the left kidney; B: Cystic region shows T1 hypointensity and T2 hyperintensity; C: Solid region shows T1 hypointensity and T2 hyperintensity; D: Contrast-enhanced magnetic resonance imaging during the corticomedullary phase; E: Nephrographic phase; F: Excretory phase showing that the tumor's cystic parts were not enhanced and the tumor's solid parts were enhanced to a moderate or mild degree that increased with time.

clinicians and radiologists. The differential diagnosis of MESTK includes cystic renal cell carcinoma (CRCC), angiomyolipoma with epithelial cyst subtype (AMLEC), and cystic nephroma (CN). CRCC mainly consists of cystic components with thickened, irregular walls and rough septa, and shows intense contrast enhancement during the corticomedullary phase, which progressively decreases during the nephrographic phase[29]. An AMLEC should be considered if the solid component of the lesion is hyperattenuating on a non-enhanced CT scan and T2-hypointense with homogeneous enhancement[30,31]. CN is also a cystic renal tumor, with thinner walls and no solid component. The cysts vary in size and have thin walls[21]. Nevertheless, recent studies suggest that MESTK and CN may represent different parts of the morphologic spectrum of the same tumor entity[24,32].

CONCLUSION

In conclusion, this report describes the MRI features of MESTK in a male adolescent. MRI provides superior delineation of the histological layers of the tumor compared with CT, and substantially lower radiation exposure can be achieved using MRI. Because MESTK is generally considered to be a benign tumor with a good prognosis, nephron sparing surgery may be appropriate to preserve kidney function. Although it occurs predominantly in menopausal woman, the possibility of MESTK should be considered in male adolescents with a cystic solid mass in the kidney.

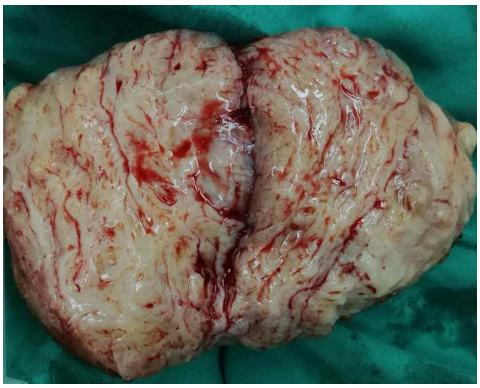

Figure 3 Gross specimen showing a well-defined mass with a white, fish-like texture.

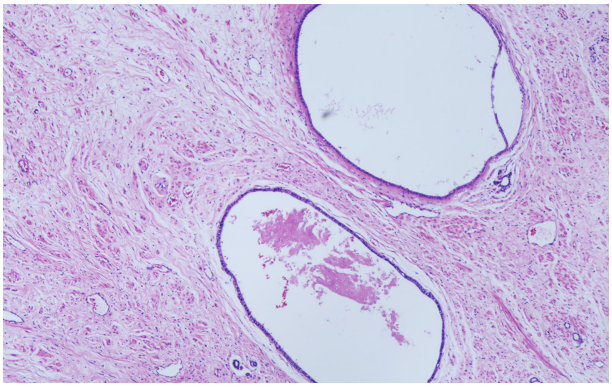

Figure 4 Histopathology. Microscopically, the tumor was composed of fibrous cells arranged in bundles. Fiber growth was observed in the lesion. Small tubular structures were observed within and around the tumor (magnification, ×100).

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CASE REPORT

Allogenic tooth transplantation using 3D printing: A case report and review of the literature

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Abstract

BACKGROUND

The history of allogenic tooth transplantation can be traced back to the 16th century. Although there have been many successful cases, much needs to be better understood and researched prior to the technique being translated to everyday clinical practice.

CASE SUMMARY

In the present report, we describe a case of allogenic tooth transplantation between a mother and her daughter. The first left maxillary molar of the mother was diagnosed with residual root resorption and needed to be extracted. The 3rd molar of the daughter was used as a donor tooth. Prior to transplantation, a 3D printing system was introduced to fabricate an individualized reamer drill specifically designed utilizing the donor's tooth as a template. The specific design of our 3D printed bur allowed for the recipient site to better match the donor tooth. With the ability to 3D print in layers, even the protuberance of the root can be matched and 3D printed, thereby minimizing unnecessary bone loss.

CONCLUSION

Our study is a pioneering case combining 3D printing with allogenic tooth transplantation, which could be able to minimize unnecessary bone loss and improve the implant stability. This article aims to enhance our understanding of allogenic tooth transplantation and 3D printing, and may potentially lead to tooth transplantation being utilized more frequently - especially since transplantations are so commonly utilized in many other fields of medicine with high success

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Core tip: The history of allogenic tooth transplantation can be traced back to the 16th century. Although there have been many successful cases, much needs to be better understood and researched prior to the technique being translated to everyday clinical practice. Our study is a pioneering case combining 3D printing with allogenic tooth transplantation, which could be able to minimize unnecessary bone loss and improve the implant stability. What's more, a review of the previous relevant research and the potential future avenues of research related to the novel introduction of 3D printing for tooth transplantation cases was performed.

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INTRODUCTION

The history of allogenic tooth transplantation can be traced back to the 16th century, particularly during the last decades of the 20th century. While individual organs are often transplanted from one individual to the next, in the dental field, transplantation of teeth is much less frequently performed. Several innovations from basic and clinical translational research has improved patient matching tests and clinical techniques[1,2]. Allogenic tooth transplantation refers to tooth grafting between two individuals of the same species whereas autogenic tooth transplantation indicates tooth grafting from one site to another in the same individual[3]. Atkinson reported in the 1970s that an autograft can be orthotopic (when transplanted to the natural location) or heterotopic (when transplanted to a completely different site). Generally, allografts are rejected by immune cells, which may cause the most common histopathological symptoms including chronic inflammatory infiltration of the grafted tissue[4,5]. However, a few cases of allogenic tooth transplantation have been reported[6]. Little progress has been made owing to the high rate of potential immunological rejections and the increased use of titanium dental implants[7]. Nevertheless, allografts can still function normally and often symptomless for many years[8].

There are many successful cases of allo-transplantation. Ole Schwartz reported 73 allotransplanting cases which were carried out by three surgeons in humans from 1956 to 1980[8]. The mean functional (without symptoms) time of the grafted teeth was 6.8 years (maximum 28.5 years, which is also the maximum observation period)[4,6,9]. This study illustrates the potential long-term survival rates of allograft tooth transplants with rates influenced by a series of factors.

In previous cases, since differences in root shape and length exist, surgeons have had to reposition the donor tooth back to its original socket and remodel the recipient site with a round implant bur[10]. The remodeling of the recipient site adds additional time to the surgical procedure with the possibility of surgically removing more bone than needed, which could totally be improved by the utilization of 3D printing. Today, 3D printing has been used widely in many fields of organ engineering[11-17]. A typical 3D printing process involves data collection, model analysis, structure design, and final manufacture. Specifically, data initially can be collected by a variety of systems including computed tomography (CT), digital scanning, magnetic resonance imaging, and other image modality systems[18]. Computer-aided design (CAD) software was followed by a precisely conducted 3D printing process controlled by a computer-aided manufacturing printer. The advantages of 3D printing include accurate control of material distribution, fast speed, scalability, and cost-effectiveness, which render this technology highly suitable and relevant in many areas of medicine including dentistry[19,20]. One of the greatest advantages of 3D printing in tooth transplantation is that osteotomy drills can be customized to the three-dimensional

geometry of the tooth root of the individual donor[21]. Such drills allow an optimal integration of transplanted tooth without unnecessary compression of tissues that may occur with standard burs, minimize unnecessary bone loss, and improve the implant stability[22,23]. Furthermore, allogenic tooth transplantation could be an alternative solution for financially compromised patients that by-pass the need for additional costs including an implant, abutment, and final crown. This case report is the first published case combining 3D printing technology for tooth transplantation, which aims to inspire future research endeavors into this largely unstudied field.

CASE PRESENTATION

Chief complaints

A 47-year-old Chinese patient presented to the dental clinic at Wuhan University with a missing 1st molar for 2 mo. Her daughter (the donor) was a 21-year-old dental student with an impacted wisdom tooth.

History of present illness

The first left maxillary molar of the patient had been extracted in a private dental clinic 2 mo prior to the tooth transplantation. The root canal treatment for the 1st molar has failed, and tooth extraction was conducted after the roots fractured. The donor recently extracted two right third molars 2 wk prior to the donation (upper and lower).

History of past illness

No other health conditions are reported.

Medication history

The patient is allergic to penicillin.

Personal and family history

The mother has hypertension.

Physical examination upon admission

In the initial physical examination, the patient had a blood pressure of 128/84 mmHg with a pulse rate of 79 beats per minute (bpm). And the donor had a blood pressure of 92/62 mmHg with a pulse rate of 82 bpm. The extraction wound was well healed, and the anteroposterior gap of the defect was acceptable. The mandibular and maxillary distance had not been compromised, and the buccolingual width was about 7 mm. No obvious inclination of adjacent teeth was observed for the patient. The patient's oral hygiene was acceptable, with little microbial plaque accumulation or associated trauma (Figure 1).

Laboratory examinations

The patient has an O blood type. The donor presents with an A blood type. Routine blood count and coagulation profile for both the patient and donor were within normal limits.

Imaging examinations

Cone beam computed tomography (CBCT) of the donor revealed a tapered root shape different in morphology from the recipient's residual 1st maxillary molar root (3 roots), which eliminated the potential for an immediate transplantation. The lower 3rd mandibular molar (the donor tooth) was scanned, and the data of the morphology were collected and analyzed before an individualized implant drill was designed to match the contour of the donor tooth roots, with expectation that the shape of the recipient site could be identical to that of the original socket. A direct metal laser sintering 3D printing system was introduced to manufacture the drill (Figure 2).

FINAL DIAGNOSIS

Maxillary dentition defect.

TREATMENT

The individual drill was produced by Wuhan Tianyu Intelligent Manufacturing

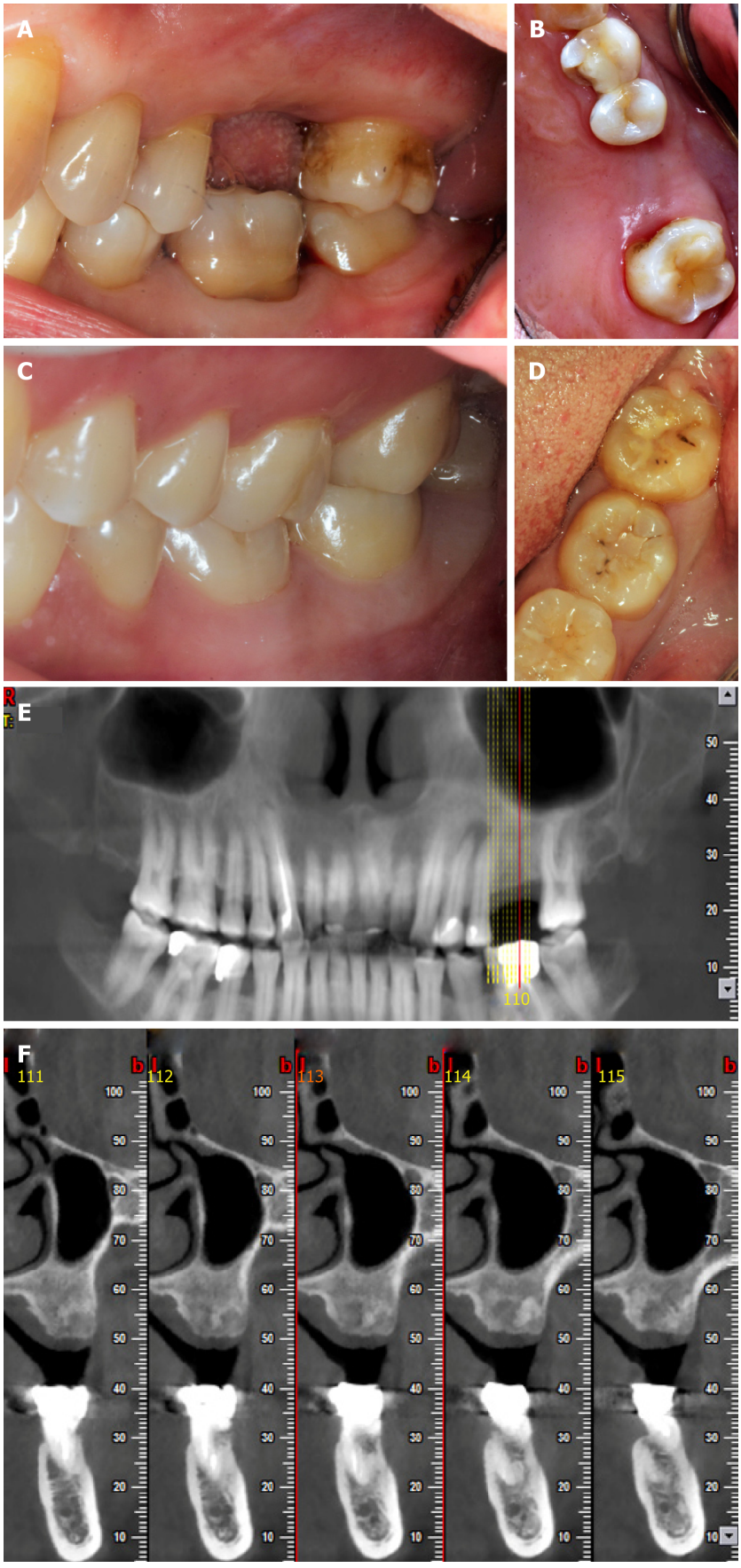

Figure 1 Preoperative photos and computed tomography scan of the donor and the recipient. A and B: Occlusal photos showing the recipient's missing #26; C and D: Occlusal photos showing the donor's #48; E: The recipient's orthopantomogram taken before the surgery; F: Computed tomography image showing the cross section of the bone at #26.

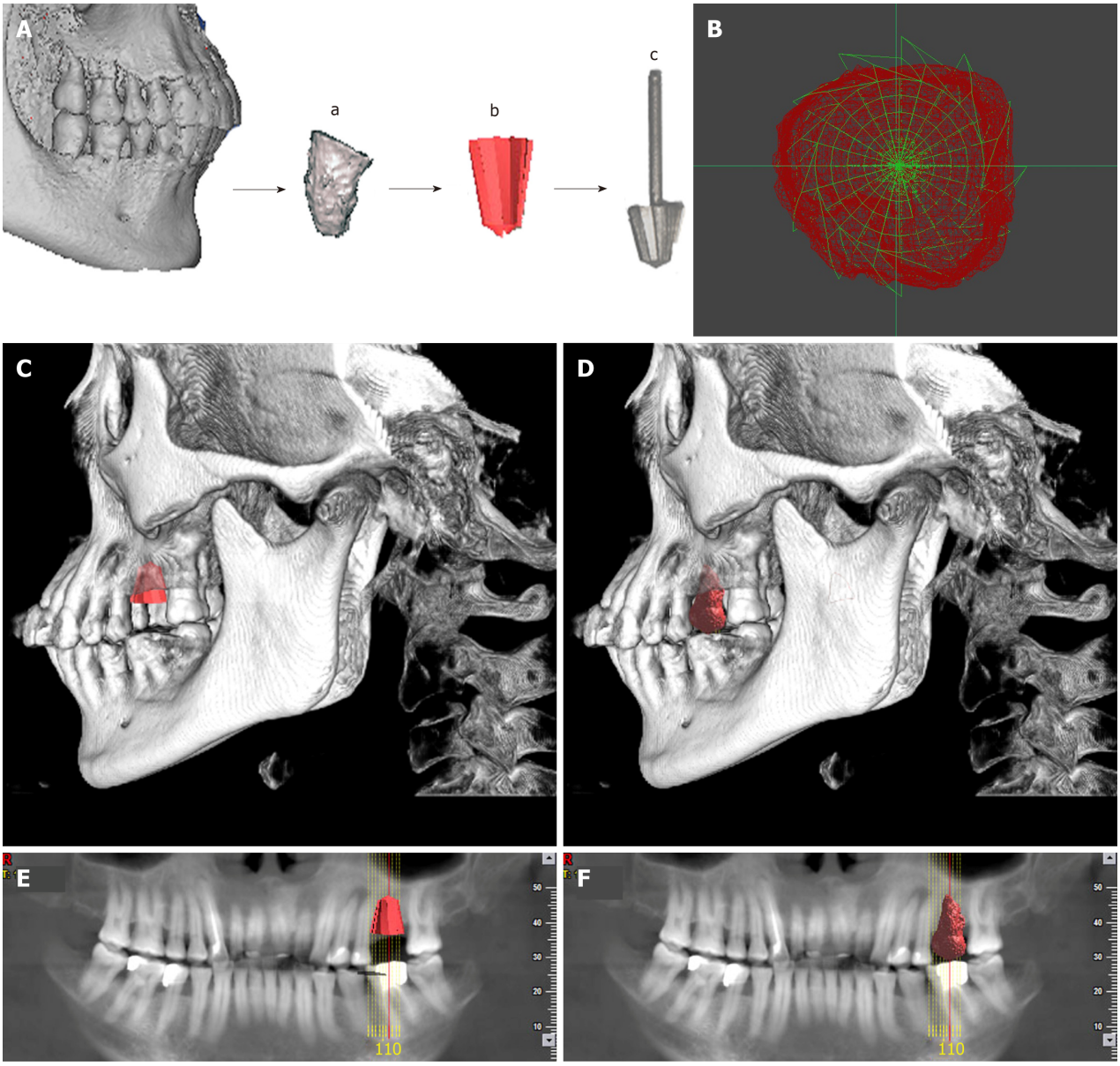

Figure 2 Individual drill compared with donor's tooth. A: The 3D image of the donor's tooth was extracted from the cone beam computed tomography, a computer-aided design model was built using measuring instrument to gather information for the shape and size, and an individual drill was manufactured by direct metal laser sintering; B: The cross section comparison of the individual drill and the donor's tooth; C and E: The model of the drill in the recipient's alveolar bone; D and F: The model of the donor's tooth in the recipient's alveolar bone.

Company using direct metal laser sintering as follows: (1) The 3d image of the donor's tooth was extracted from the CBCT; (2) The data of the donor's CBCT were imported into a STEP format CAD file using CAD software; (3) A CAD model was built using a measuring instrument to gather information regarding the shape and size of the tooth; (4) The shape of the drill was designed according to the donor's tooth, and the taper and the base of the drill were in accordance with the tooth's taper and the cervix, and then transferred into a CAD model; (5) The model was then sliced into discrete horizontal layers; and (6) A high-powered laser beam was focused onto a bed of powdered metal to fuse the model layer by layer. Each layer was printed followed by a subsequent layer of powder and printing to produce the next slice of the framework and fused with the first until all layers have been completely built. The laser was utilized to fuse the metal powder into metal solid particles and control their trajectory accurately.

In order to mitigate a potential immunological rejection, the tooth which was carefully extracted with minimal trauma was treated with solutions of 10 g/L cephalosporin, 75 g/L clindamycin hydrochloride, and 50 g/L aspirin in sequence. Then the pilot hole was expanded with progressively wider drills, and the preparation was completed using the 3D printed individual drill. The autogenous bone was collected during the entire drill preparation technique and utilized to fill the

compartment. After suture, the tooth was splinted with an acid-etch resin composite splint (Figure 3). The recipient was treated with antibiotics and a compound gargle solution of chlorhexidine gluconate was utilized for 2 wk. The follow-up radiographs and photos were taken after surgery (Figure 4).

OUTCOME AND FOLLOW-UP

Inflammation in the periodontal area was observed during healing 1 wk after transplantation. Resorption initiated after 2 wk, which was further increased after 4 and 8 wk. Replacement resorption on the external surface showed increasing appearance time, initiating at 4 wk. The periodontal ligament was no longer visible by X-ray after 4 wk. No pain or swelling was present; however, the height of the peri-implant papillae began to show some recession. The outcome was less than optimal or reported previously and further observations are needed. Other tooth treating methods such as sintering will be studied and carried out in the future.

DISCUSSION

The history of tooth transplantation

Allogenic tooth transplantation has been utilized for five decades with publications occurring in the literature at irregular intervals[3]. While studies regarding the immunological aspects of tooth transplantation were not published until 1963[24], more recently, a greater number of studies concerning these aspects have been performed, demonstrating that teeth can be antigenic and elicit an immune response from the host patient[4]. Today, an overgrowing research development is placed on whole tooth regeneration, yet research in this field remains wishful. Advances in molecular biology, experimental embryology, developmental biology, and bioengineering may one day overcome present limitations[25]. Nevertheless, tooth transplantation has received very little research in comparison owing largely to the developing field of dental implants. In general, the number of tooth transplantation cases have been decreasing and the utilization of new and modern bioengineering techniques and findings from immunological research have been seldom applied to transplantation research in the dental field. This makes this case report provide an insight into the potential development of future avenues of research and discovery in the field of tooth transplantation.

Complications

Root resorption is reported to be the most relevant complication in tooth transplantation and plays an important role in the long-term prognosis of allotransplanted teeth. However, it is also very common in the first few weeks following surgery. It has been suggested that the selection of autogenic tooth versus allogenic tooth is prominent to reduce the apoptosis of odontoblast-lineage cells, but this study also showed that the immunological rejection may have nothing to do with periodontal tissues[26,27].

Root resorption usually happens as replacement resorption and inflammatory resorption[28]. In previous cases, a surgeon had to remodel the recipient site to the according donor root sizes, which would definitely increase the surgical time required to transplant the tooth, and therefore worsen the prognosis as well as potentially lead to greater bone loss without the precise bur size created from the donor tooth[10]. The replacement resorption is reported to be a response to the operative trauma, which can be lightened by the use of 3D printed burs. Alloimmune rejection also plays an important role during root resorption. Inflammatory resorption can be affected by the endodontic treatment and interestingly the age of recipient[8].

There is also a potential for loss of marginal periodontal attachment which can be caused by pre/preoperative loss of bone and/or inflammation as a result of donor tooth root fracture[8]. As a result, a number of cases end up being failed/lost. Accordingly, a previously study conducted by Schwartz *et al*[8] found that after 10 years, 76% of allograft tooth transplants were lost and after 15 years, only six grafts (8.2%) were still in function. The findings further concluded that the cause of graft loss was root resorption in 38 cases, inflammatory resorption in 11, replacement resorption in 27, marginal periodontal complication in 2, apical periodontitis in 1, prosthetic failure in 1, and an unknown etiology in 3[8].

In our case report, a similar failure caused by resorption is expected. Nevertheless, this case report is the first attempt at combining modern 3D imaging and printing with allogenic tooth transplantation, which demonstrated plenty of advantages such

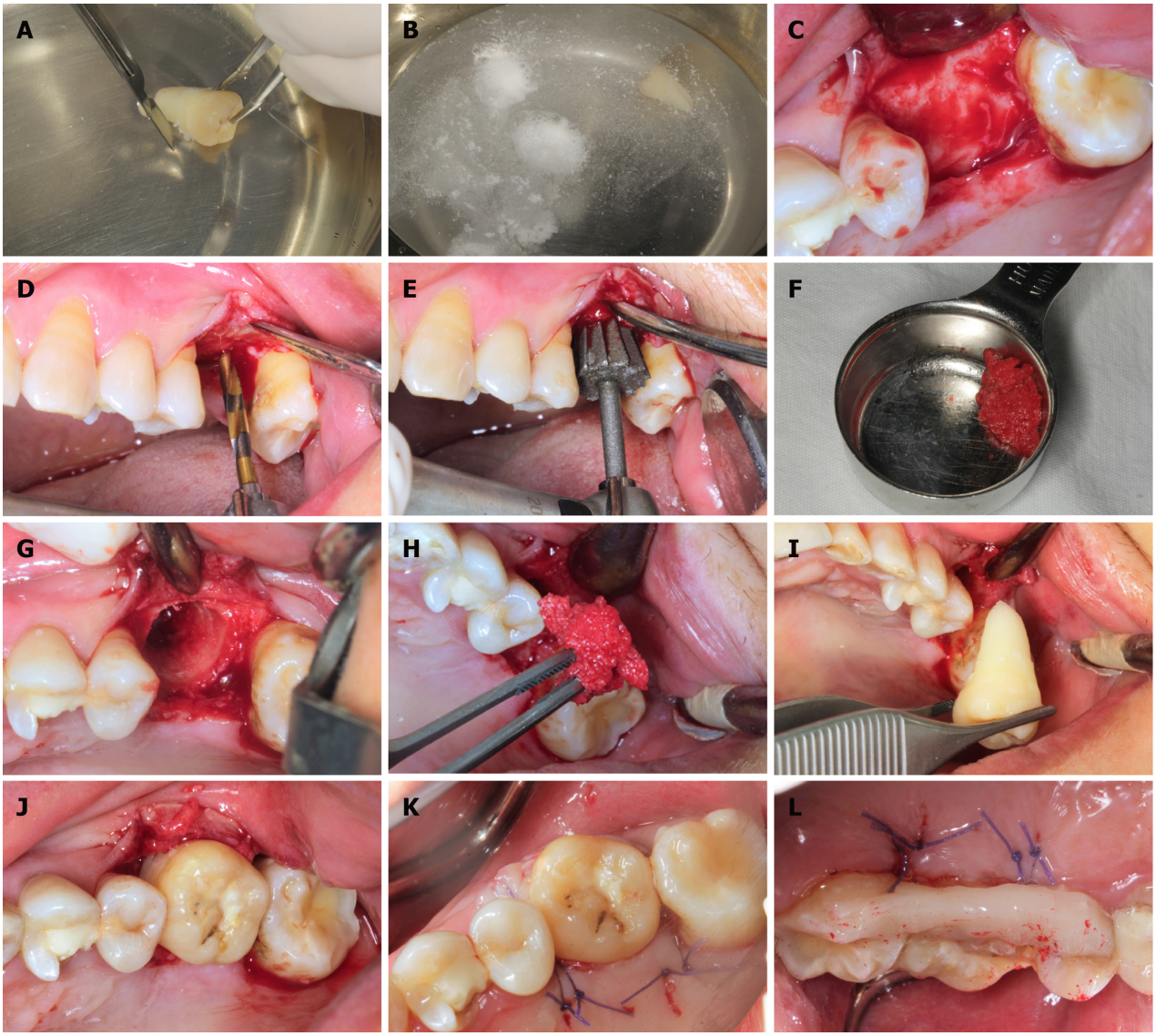

Figure 3 Surgical procedure. A: The donor's tooth was extracted, then the attached gingival was gently removed, but the periodontal ligament was kept; B: Treatment with solutions of 10 g/L cephalosporin, 75 g/L clindamycin hydrochloride, and 50 g/L aspirin in sequence; C: Soft tissue reflection; D: Expanding the pilot hole by using progressively wider drills; E: Finishing the preparation by using the individual drill; F: Collecting the autogenous bone during the hole preparation; G and H: Applying the autogenous bone to fill the compartment; I and J: Transplanting the tooth to the recipient's site; K: Suture; L: Splinting the tooth with an acid-etch resin composite splint.

as an accurate control of material distribution, lower surgical times required, better stability of the transplanted tooth owing to the 3D morphology of the bur, and cost-effectiveness[19,20,29]. With the utilization of 3D printing during tooth transplantation, it is expected that surgical trauma will be minimized with better final tooth stability. Based on previous publications, the use of aspirin was utilized as a means to minimize alloimmune rejection[30]. Aspirin has been shown to inhibit TNF-α and IFN-γ levels and reverse proinflammatory cytokines which may cause a higher immune response, leading to apoptosis of bone marrow mesenchymal stem cells[31].

Prevention and treatment of late effects after allogeneic tooth transplantation

To date there have been quite a few methods to inhibit alloimmune rejections, including donor and recipient's matching test, minimizing movement of the periodontal ligament of transplanted teeth, endodontic treatment prior to transplantation, repeated freezing treatment, irradiation of donor's teeth, and treatment with fluorinated fluid[32,33]. For instance, although Schwartz *et al*[34] used a monkey model to study the influence of endodontic treatment, and found that the teeth that were endodontically treated significantly decreased inflammatory resorption (almost totally eliminated, $P = 0.0003$), it had significantly increased replacement resorption ($P = 0.0004$)[34]. Over 40 years ago, Robinson and Rowlands demonstrated that repeat freezing and thawing and incubation with collagenase and

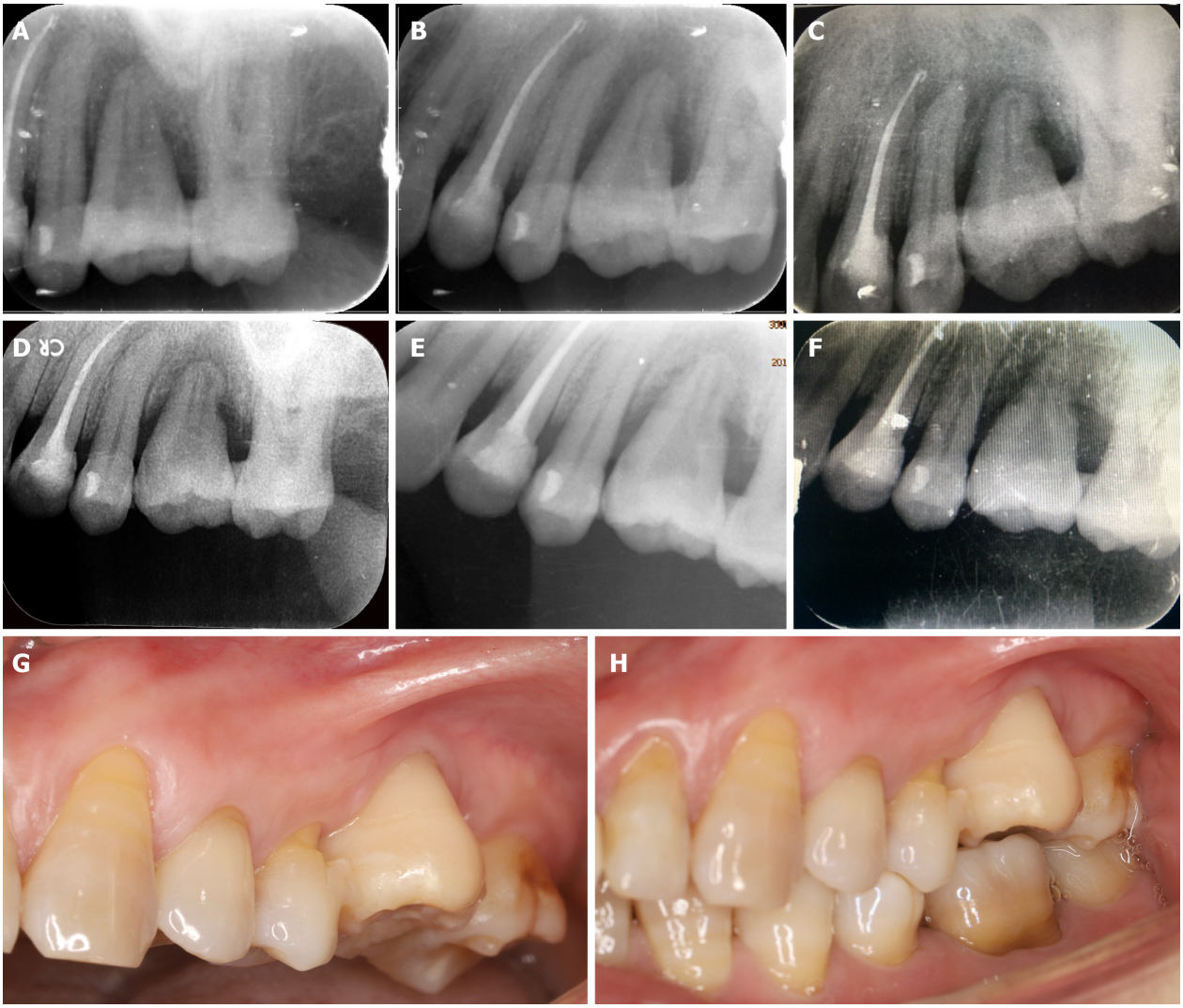

Figure 4 Periapical radiographs of the transplanted tooth after surgery. A: One day after transplantation; B: One week after transplantation; C: One month after transplantation, inflammatory resorption and replacement resorption were progressing; D: Two months after transplantation; E: Three months after transplantation; F: Four months after transplantation, inflammatory resorption and replacement resorption were stable, and there was no appearance of normal periodontal ligament up to this time; G and H: Photos showing the transplanted tooth four months after surgery.

hyaluronidase turned the tooth grafts non-immunogenic[35]. These reports are quite old, yet no recent attempts have been made to further investigate if tooth transplantation can become a routine clinical procedure.

The manufacturing process of the individual drill: Direct metal laser sintering

3D printing and bioprinting are modalities of additive manufacturing. Compared to other techniques used in tissue engineering, 3D printing has the advantages of accurate precision, resolution, efficiency, and accuracy[16,23]. Four main 3D printing techniques exist including inkjet, laser-assisted, extrusion, and stereolithography printing[36-39]. Although autogenic and allogenic tooth transplantation has a long history of use, several limitations still exist. In previous cases, since differences in root shape and length exist, surgeons have had to reposition the donor tooth back to its original socket and remodel the recipient site with a round implant bur[10]. The remodeling of the recipient site adds additional time to the surgical procedure with the possibility of surgically removing more bone than needed. In the present case report, the specific design of our 3D printed bur allowed for the recipient site to better match the donor tooth. With the ability to 3D print in layers, even the protuberance of the root can be matched and 3D printed, thereby minimizing unnecessary bone loss.

There are many factors that may affect the implanted tooth's primary stability including bone quality and quantity, surgical technique utilized, and the tooth geometry[40]. Since the shape of the donor's and recipient's roots are generally mismatching, implant stability is hard to predict and therefore the advantages of 3D printing may provide a better solution to the current standards. The advantages of 3D

printing include accurate control of material distribution and sizing, fast production, scalability, and cost-effectiveness, which have made this technology successful in many areas of medicine with positive outcomes[19,20]. It is therefore conceivable that since various allogenic transplantations are utilized in many areas of medicine including heart, lungs, kidneys, and other complex organs, the ability for dental clinicians to utilize this technique in the coming years should not be deemed unrealistic. With the advancements made in modern medicine and tissue engineering, future research endeavors should be geared towards utilizing this low-cost modality where 3D printing may help improve the predictability of such cases. In the present case, we report the first published attempt at utilizing 3D printing during a tooth transplantation procedure. Future research is necessary to further improve this technology, but this article offers a pioneering first attempt at such a therapy.

CONCLUSION

Our study presents a pioneering case combining 3D printing with allogenic tooth transplantation. A 3D printing system was introduced to print an individualized reamer drill for preparing the implant placement bed and the donor's tooth as a template for the drill. With the utilization of 3D printing, the surgical trauma was minimized and the tooth implant stability was more suitable. A detailed progress and prognosis of this cases were recorded, which makes the case very useful for reference purposes since it is the first study of its kind. Other tooth treating methods such as sintering will be studied and carried out in the future. This article hopes to enhance our understanding of allogenic tooth transplantation and 3D printing, and may potentially lead to tooth transplantation being utilized more frequently - especially since transplantations are so commonly utilized in many other fields of medicine with high success rates.

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CASE REPORT

Fecal microbiota transplantation as an effective initial therapy for pancreatitis complicated with severe *Clostridium difficile* infection: A case report

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Author contributions: Xiao HY and Hu Y searched for similar published cases, analyzed the data, and wrote the manuscript; Xiao HY collected the patient's clinical data; Zhu L designed the study; He C performed the fecal microbiota transplantation procedure; He C and Lv NH provided the materials for the study and participated in writing the paper; all authors issued final approval for the version to be submitted.

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Abstract

BACKGROUND

Moderately severe acute pancreatitis (MSAP) is a critical form of acute pancreatitis that is related with high morbidity and mortality. Severe *Clostridium difficile* infection (sCDI) is a serious and rare nosocomial diarrheal complication, especially in MSAP patients. Fecal microbiota transplantation (FMT) is a highly effective treatment for refractory and recurrent CDI (rCDI). However, knowledge regarding the initial use of FMT in patients suffering from sCDI is limited.

CASE SUMMARY

Here, we report an MSAP patient complicated with sCDI who was treated by FMT as a first-line therapy. The patient was a 51-year-old man who suffered from diarrhea in his course of acute pancreatitis. An enzyme immunoassay was performed to detect toxins, and the result was positive for toxin-producing *C. difficile* and toxin B and negative for *C. difficile* ribotype 027. The colonoscopy revealed pseudomembranous colitis. Due to these findings, sCDI was our primary consideration. Because the patient provided informed consent for FMT treatment, we initially treated the patient by FMT rather than metronidazole. Diarrhea resolved within 5 d after FMT. The patient remained asymptomatic, and the follow-up colonoscopy performed 40 d after discharge showed a complete recovery. Our case is the first reported in China.

CONCLUSION

This case explores the possibilities of initially using FMT to treat severe CDI. Moreover, FMT may become a critical component of the treatment for severe CDI in MSAP patients.

Key words: Acute pancreatitis; *Clostridium difficile* infection; Fecal microbiota

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Core tip: A rare complication of acute pancreatitis is *Clostridium difficile* infection (CDI). Certain antibiotics are used as the treatment of choice for CDI. However, in our case, fecal microbiota transplantation (FMT) was considered the best treatment and achieved good results. This case demonstrates that FMT can be considered a first-line treatment for primary severe CDI in moderately severe acute pancreatitis patients.

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INTRODUCTION

Clostridium difficile (*C. difficile*) infection (CDI) is the most common cause of diarrhea in resident patients, and its incidence, morbidity, mortality, and likelihood of recurrence are increasing[1]. CDI has become an important healthcare-associated infection with a considerable economic impact worldwide. CDI causes post-antibiotic associated diarrhea and colitis from dysbiosis due to the overgrowth of *C. difficile*. Certain antibiotic therapy remains the treatment of choice[2]. Moderately severe acute pancreatitis (MSAP) is characterized by transient organ failure or local or systemic complications without persistent organ failure[3]. However, in recent years, fecal microbiota transplantation (FMT) has emerged as a new treatment method that is highly effective for the treatment of recurrent and refractory CDI (rCDI)[4]. To date, limited data have been available demonstrating that FMT is more cost-effective than some antibiotics as a first-line treatment for the first episode of severe CDI, especially in the treatment of MSAP patients. Here, we report a patient suffering from MSAP with hospital-acquired CDI who was completely cured by FMT after the first CDI episode.

CASE PRESENTATION

Chief complaints

Persistent upper abdominal pain for 5 d.

History of present illness

A 51-year-old man was admitted to our Intensive Care Unit (ICU) after 5 d of persistent severe upper abdominal pain. On day 9 after admission to the hospital, diarrhea developed with a frequency of 4-10 times/d. We stopped all treatments (rhubarb, mirabilite, and mannitol, oral; glycerol enema) that could induce diarrhea and administered montmorillonite and probiotics (Medilac-s, Live Combined Bacillus Subtilis and Enterococcus Faecium Enteric-coated Capsules 500 mg, t.i.d). However, the amount and frequency of diarrhea remained unrelieved.

History of past illness

The patient had a history of chronic consumption of large amounts of alcohol (approximately 80 g/d), had no significant prior medical history, and denied any history of drug use or smoking.

Family history

The patient's family history was unremarkable.

Physical examination upon admission

Upon admission, the physical examination showed a pulse rate of 90 beats per minute, blood pressure of 120/70 mmHg , body temperature of 36.5 °C, and respiration rate of 23 breaths per minute. Pulse oxygen saturation was normal (96%). Moderate tenderness pain in the upper abdomen was observed without rebound

tenderness; the results of bilateral chest percussion revealed dullness, and the lower lung breathing sounds disappeared; and the bedside ultrasound showed bilateral pleural effusion. Heart auscultation did not find anything. No jaundice was observed in the skin and sclera. After diarrhea occurred, rectal palpation was negative. The macroscopic aspects of the stools were yellow water-like stool.

Imaging examinations

Contrast-enhanced computed tomography (CT) showed the following findings: Necrotizing pancreatitis, CT Severity Index (CTSI) level D, and a pancreatic necrotic area < 30% (Figure 1).

Laboratory examinations

The laboratory analysis of the blood tests showed that many inflammatory markers were elevated (Table 1). The stool cultures were negative, and the fecal occult blood test scored 3+. An enzyme immunoassay (EIA) (GeneXpert, Cepheid, America) was performed to detect toxins, and the results were positive for toxin-producing *C. difficile* and toxin B and negative for *C. difficile* ribotype 027.

FINAL DIAGNOSIS

The preliminary combined results indicated MSAP according to the revised Atlanta classification[3]. Colonoscopy revealed pseudomembranous colonitis with yellow pseudomembranes on the wall of the transverse colon and descending colon (Figure 2A). In addition, HE staining revealed the presence of a pseudomembrane composed of an exudate made of inflammatory debris and white blood cells; Gram staining revealed the presence of Gram-positive bacilli. These results combined with the pathological and endoscopic characteristics led to a final diagnosis of pseudomembranous colitis due to severe CDI.

TREATMENT

We administered the routine treatments of fasting, gastric decompression, fluid resuscitation, and early enteral nutrition (EN); moreover, thoracic puncture and drainage were performed. The drugs administered included omeprazole (20 mg iv qd), ulinastatin (10 WU, q8 h, iv), somatostatin (0.5 mg/h, iv), an analgesic (butorphanol tartrate 3 mg/h, iv) as needed, catharsis (rhubarb, mirabilite, and mannitol, oral; glycerol enema), and a subcutaneous insulin injection for hyperglycemia. After these treatments, the patient clearly improved and was moved from the ICU. Because there was no evidence of pancreatic infection, no antibiotics were administered during hospitalization.

After CDI was diagnosed, we performed FMT on hospitalization day 20. The following abnormal laboratory finding was revealed before performing FMT: hemoglobin 116 g/L.

Fresh stool (50 g) from a donor was collected on the day of infusion, diluted with 200 mL sterile saline, and stirred in a blender (NJM-9060; NUC Electronics, Daegu, South Korea). The homogenized solution was filtered twice through a re-sterilized metal sieve. The sample was centrifuged, and the precipitate was dissolved in 200 mL normal saline twice. The final filtrates (200 mL) were infused into the patient *via* a nasal-jejunal tube. Before applying FMT, the patient was provided relevant knowledge and was required to fast for 1 h before the operation and 1 h after the operation. The infusion of the donor feces was performed three times (once every two days).

The stool donor for the FMT was a graduate student, who had no familial relationship with the patient. The donor was negative for blood-borne communicable diseases, and the stool tests were also negative for HBsAg, HCV-Ab, VDRL, HEV-IgM, HIV, CMV, syphilis, *C. difficile* toxin, roundworm, pinworm, hookworm, amoeba, and duovirus. The donor had no history of antibiotic use or any chemotherapy within the past year.

OUTCOME AND FOLLOW-UP

By the day after the second FMT, the frequency of diarrhea had dropped to twice a day, and the diarrhea resolved 5 d after the completion of the FMT process. During the treatment, the patient did not report any adverse events. The patient left the

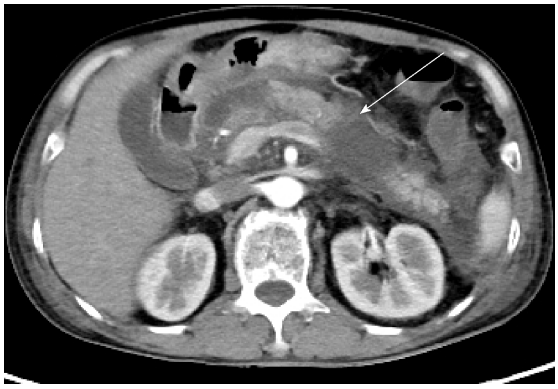

Figure 1 Contrast-enhanced computed tomography revealed necrotizing pancreatitis (as shown by the arrow).

hospital on day 25. After 40 d, a follow-up EIA for toxins did not detect toxin-producing *C. difficile*, toxin B, or *C. difficile* ribotype 027. Meanwhile, the follow-up colonoscopy showed that the bowel was normal (Figure 2B).

DISCUSSION

Our case shows that FMT can be a potential treatment option as a first-line treatment for severe CDI.

The Unites States data showed that the incidence of CDI had gradually increased from 30 per 100000 in 1996 to 84 per 100000 in 2005[5]. A cohort study showed that the prevalence of this epidemic in AP patients significantly increased from 386 per 100000 in 1998 to 576 per 100000 in 2012, and CDI increases the mortality of and economic burden on patients with AP[6]. However, to date, only a few reports of the treatment of CDI in patients with AP have been published.

We speculate that the causes of dysbacteriosis in our patient were as follows: (1) History of excessive alcohol consumption; (2) A hospital stay longer than 7 d for MSAP; (3) Gut barrier dysfunction; and (4) A high carbohydrate intake. We did not perform a confirmation test, which might have revealed a toxigenic culture, because the patient had a very particular diarrhea symptom, endoscopic findings, and positive toxin detection. According to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)[7], a two-stage test [glutamate dehydrogenase (GDH) or nucleic acid amplification tests (NAATs) for toxin genes, followed by a highly sensitive toxin test or GDH in combination with a toxin test] is recommended for the diagnosis of CDI. We performed the NAATs (Xpert) and toxin B EIA test, and both tests were positive; thus, we believe that CDI was most likely present. However, we used enteroscopy as another diagnostic tool in this patient because we thought that he might have other causes for the severe diarrhea, which is consistent with the indications for enteroscopy in patients with CDI[8]. According to the ESCMID guidelines[9], pseudomembranous colitis can support the diagnosis of severe CDI in our case.

There was no evidence of infection in our AP patient, and antibiotics may result in adverse events, affecting the patient's prognosis and prolonging the hospitalization time. Additionally, FMT is still in the preliminary stage of research at our center and is free of charge. Therefore, FMT was our first choice of treatment for this patient. Various options were discussed in length with the patient and his family. We agree that choosing FMT management instead of antibiotics in primary CDI is controversial. In recent years, with the deepening understanding of the pathogenesis of CDI in the medical community, great changes have been implemented in the management of CDI. Initially, metronidazole was mainly used as a first-line management[10]. Data before 2000 demonstrated that the proportion of patients receiving metronidazole to achieve a clinical cure was similar to the group of receiving vancomycin. However, recent data show that vancomycin had a significant effect on both symptom relief and a lower recurrence rate[11]. While antibiotics have been the mainstay of CDI treatment for decades, the increase in CDI frequency, severity, and treatment failures has prompted investigations into the development of alternative therapies that are less disruptive to the colonic microbiota. This effect may be driven by the resistance patterns of the bacteria. FMT is currently an alternative recommended option in select guidelines[4] due to more and more evidence suggesting efficacy. Unfortunately,

Table 1 Laboratory findings of the patient

Testing item	Results	Reference range
WBC, count/mL	12360	3500-9500
HCT, %	46.9	43-58.0
Serum amylase, IU/L	156	20-110
c(Ca^{2+}), mmol/L	1.79	2.11-2.52
CRP, mg/L	141	<10
Alb, g/L	26.8	40.0-55.0
LDH, U/L	529	120-250
FBG, mmol/L	5.86	3.9-6.1
ESR, mm/h	69	<20
HIV	(-)	(-)
HBsAg	(-)	(-)
HCV-Ab	(-)	(-)

WBC: White blood cells; HCT: Haematocrit; CRP: C-reactive protein; Alb: Albumin; LDH: Lactic dehydrogenase; FBG: Fasting blood-glucose; ESR: erythrocyte sedimentation rate; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus.

because data regarding the use of FMT in initial CDI episodes are limited, FMT is currently recommended only for the treatment of recurrent CDI infections. Based on this background, we discussed the advantages and disadvantages with the patient and obtained written informed consent from the patient and his family. We may consider how to choose drugs if vancomycin gradually lost its current therapeutic effect as metronidazole did, as FMT has no drug resistance problem. The strategy that not all people at risk of or with CDI need enduring antibiotic treatment suggests why FMT is a potential and much needed additional treatment approach. Indeed, more relevant clinical studies are needed to conquer the epidemic.

From an evidence-based perspective, to date, there is insufficient evidence to recommend FMT as an initial treatment for the first episode of CDI[4]. We searched MEDLINE for articles published in English from 1980 to January 2019 involving human participants that described the use of FMT to treat primary CDI (Table 2). We did not restrict the search on the basis of the study design. We identified 10 patients treated with FMT during initial episodes of CDI, all of which were reported in case study series, and not enough data were published[12]. Nine patients were a part of a series involving 20 patients initially treated with FMT for primary CDI[13]; an overall response to treatment was achieved in seven patients in the transplantation group and five patients in the metronidazole group. In one case report, FMT achieved a good effect with no adverse events, although the approaches and methods differed from those used in our patients[14].

Our report supports the availability of FMT for the management of severe CDI as an initial therapy. In addition, some studies show that FMT is more cost-effective than antimicrobial therapy[15]. The dramatic effect of FMT shown here provides evidence of the important role of gut microbiota in maintaining homeostasis. There is evidence to support that healthy donors' bacteria can restore the structure and function of the recipients' intestinal microbial community[16]. FMT can not only eradicate *C. difficile* but also restore the potential defect of the fecal flora.

To the best of our knowledge, this article presents the first report of severe CDI complicating MSAP that was treated successfully *via* FMT in China; this article also presents a rare report of FMT used as a first-line treatment for new-onset severe CDI. As the risks of FMT are small and the potential benefits for severe ill patients are considerable, we advocate that the use of FMT in this patient population is reasonable. Furthermore, FMT may play a role in treating patients with SAP complicated with infections. However, fecal microbiota constitutes a highly complex material, and we do not precisely know which components are beneficial or potentially harmful. More trials assessing FMT as an initial treatment for sCDI are needed.

CONCLUSION

CDI occurs when normal intestinal flora is weakened and induces a severe clinical

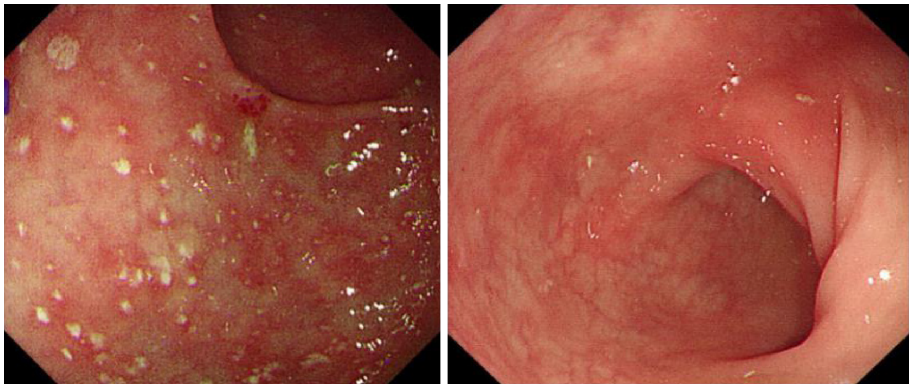

Figure 2 Colonoscopy results. A: Colonoscopy showing the appearance of "pseudomembranes" on the mucosa of the colon; B: Follow-up colonoscopy showing that the bowel was normal.

burden. Our case shows that the possibility of CDI should be considered when abnormal diarrhea occurs in a pancreatitis patient. Furthermore, FMT is equally effective in the initial CDI treatment and may become an alternative to antibiotic therapy in primary *C. difficile* infection, especially in AP patients.

Table 2 Published reports of fecal microbiota transplantation in patients with primary *Clostridium difficile* infection worldwide

Patient	Sex	Age(yr)	Complication	Antibiotics	EIA for toxins	Fecal material delivery	Adverseevents
1	M	51	MSAP	-	Positive for toxin-producing *C. difficile* and toxin B	Nasogastric tube	None
2[16]	F	64	Dental pain and infections	Clindamycin	Positive for *C. difficile* toxin and GDH	Colonoscopy	None
3[15]	F (4) M (5)	67 (34-88)	-	Yes		Retention enema	(1) A foul smell from the patient's stool; (2) No clinical symptoms but an increase in the CRP levels a few days after treatment

EIA: Enzyme immunoassay; MSAP: Moderately severe acute pancreatitis; GDH: Glutamate dehydrogenase; *C. difficile*: *Clostridium difficile*.

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CASE REPORT

Organ-associated pseudosarcomatous myofibroblastic proliferation with ossification in the lower pole of the kidney mimicking renal pelvic carcinoma: A case report

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Abstract

BACKGROUND

Organ-associated pseudosarcomatous myofibroblastic proliferation (PMP) is a very rare disorder. In the urogenital tract, PMP preferentially involves the urinary bladder; kidney involvement is rare. Here, we report a rare case of PMP with ossification in the lower pole of the kidney, which mimics urothelial carcinoma or an osteogenic tumor.

CASE SUMMARY

A Chinese man was admitted to our hospital due to intermittent hematuria for more than 1 mo. Enhanced renal computed tomography revealed a mass in the left renal pelvis and upper ureter. The preoperative clinical diagnosis was renal pelvic carcinoma, determined by imaging examination and biopsy. After a standard preparation for surgery, the patient underwent retroperitoneoscopic radical nephroureterectomy. The operative findings were an extensive renal tumor (6 cm × 4.5 cm × 4.5 cm) invading the lower pole of the kidney and upper ureter. The final pathological diagnosis was organ-associated PMP with ossification. After 6-mo follow-up, no recurrence or metastasis was found.

CONCLUSION

This case of PMP was unusual for its mimicking renal pelvic carcinoma in imaging examinations, making biopsy necessary.

Key words: Pseudosarcomatous myofibroblastic proliferation; Kidney; Renal pelvic; Carcinoma; Case report

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Core tip: Organ-associated pseudosarcomatous myofibroblastic proliferation (PMP) in the urinary bladder has been reported. However, it rarely occurs in the kidney and no previous case of renal PMP with ossification have been reported. In this case report, the preoperative clinical diagnosis of renal pelvic carcinoma was made by imaging examination and biopsy. Retroperitoneoscopic radical nephroureterectomy was performed, and the final pathological diagnosis was organ-associated PMP with ossification. This case may help us to better understand this disease with regards to the related clinical manifestations, laboratory examination, imaging and pathologic results.

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INTRODUCTION

Organ-associated pseudosarcomatous myofibroblastic proliferation (PMP), also known as inflammatory myofibroblastic tumor, pseudomalignant spindle cell proliferation and inflammatory pseudotumor, was first reported by Roth *et al*[1] in 1980. In general, the organ-associated PMP is a rare type of benign spindle cell tumor. The most commonly reported diagnoses involve the urinary bladder. Other potential sites where PMPs may occur include the head, neck, abdomen, pelvic cavity, retroperitoneum, and limbs[2]. Cases involving the kidney have been reported rarely, and no previous cases of renal PMP with ossification have been reported[3].

According to the 2016 World Health Organization classification of tumors of the urinary system and male genital organs, PMP is a benign mesenchymal bladder tumor with malignant potential derived from fibroblasts and myofibroblasts[4]. For the rare cases that have been reported in the kidney, either the renal parenchyma or the renal pelvis have been involved; furthermore, in these cases the tumor has presented in single, multiple or bilateral forms. Finally, the proportion of male-to-female patients in China is about 2:1, and the mean age is approximately 30 years old.

Herein, we report a rare case of PMP with ossification in the lower pole of the kidney, which mimicked urothelial carcinoma or an osteogenic tumor.

CASE PRESENTATION

Chief complaints

A 72-year-old man without prior contributory history presented with intermittent gross hematuria that had lasted for more than 1 mo. On the day before the hospital consultation, the symptoms had worsened remarkably and were accompanied by lower abdominal and back pain, which were relieved after urination.

History of past illness

The patient's past history was unremarkable.

Personal and family history

The patient's family history was unremarkable.

Physical examination upon admission

The preoperative physical examination provided findings that were unremarkable.

Laboratory examinations

Routine blood testing showed normal erythrocyte count (4.23×10^{12}/L; normal range: $4.3\text{-}5.8 \times 10^{12}$/L) and hemoglobin level (138 g/L; normal range: 130-175 g/L). Routine urine test showed occult blood of 3+, substantially elevated erythrocyte count (2512/μL; normal range: 0-7/μL) and high end of normal leucocyte count (12/μL; normal range: 0-12/μL). Urine culture was positive for *Enterococcus faecalis*.

Imaging examinations

Enhanced renal computed tomography (CT) showed a heterogeneous mass 6 cm in diameter at the left pyeloureteral junction, which indicated a benign lesion or hematoma (Figure 1A). Magnetic resonance imaging (MRI) showed that the left renal pelvis was occupied by a cystic and solid mass (approximately 6.0 cm × 4.5 cm × 4.5 cm in size) with calcification or ossification, which indicated a hamartoma or teratoma (Figure 1B). Emission CT showed that the left renal glomerular filtration rate was 15.4 mL/min and the right renal glomerular filtration rate was 58.9 mL/min (normal range: 80-120 mL/min).

FINAL DIAGNOSIS

According to the pathological examination, the final diagnosis was renal organ-associated PMP with ossification.

TREATMENT

In order to define the pathology of the lesion, a flexible ureteroscopic examination was performed and biopsy taken of the large mass (6 cm in diameter) in the left renal pelvis. Microscopic examination of the biopsy sample showed a highly proliferative area composed of spindle cells and irregular bone tissue. Heterotopic ossification was considered, and osteogenic tumor could not be excluded completely. To address the suspicion of renal pelvic carcinoma, a retroperitoneoscopic radical nephroureterectomy was performed.

The gross specimen presented as a gray-white and pink-grey mass with capsule, in the lower pole of the kidney (Figure 2A), with a negative surgical margin. Histopathologic features suggested it was an organ-associated PMP with ossification and chondrification of the left kidney (Figure 2B). Immunohistochemical staining showed positivity for calponin, SATB-2, and for Ki-67 (60%) (Figure 2C and 2D), and negativity for CK and P16.

OUTCOME AND FOLLOW-UP

After a 6-mo follow-up, the patient did not complain of obvious discomfort and no signs of recurrence were found.

DISCUSSION

The pathogenesis of PMP is unknown. In kidney, the tumor itself may represent a reactive hyperplasia related to chronic inflammation of the renal parenchyma. Many microorganisms, such as mycobacterium, corynebacterium, human herpes virus, Epstein-Barr virus and human papillomavirus, have been proposed as potential pathogenic factors[5-7]. In our case, the urine culture was positive for *Enterococcus faecalis*, supporting the possibility of such an association with chronic inflammation of the renal parenchyma.

Previous studies have indicated an association between PMP and expression of activin receptor-like kinase 1 and p80 expression or chromosomal rearrangements involving 2p23. It remains unknown, however, whether the tumor itself is reactive or neoplastic in nature. While renal clear cell carcinoma, chromophobe cell carcinoma and sarcoma with ossification have all been reported in the literature[8,9], no previous case of renal PMP with ossification has been reported. The mechanism of ossification is thus similarly unclear. We conjecture that it may be related to the transformation of immature fibroblasts into osteoblasts or chondrocytes in the mesenchymal tissue, due to the repair of tissue damage.

The clinical manifestations of renal PMP lack specificity and are mainly comprised of lumbago, fever, hematuria and renal percussion pain. As such, diagnosis of renal PMP depends on imaging and histopathological examination. The tumors appear as a solid mass of low density or slightly high density on CT scans, with contrast-enhanced CT images showing a low degree of enhancement. In MRI, the masses usually show low signal intensity with heterogeneous or homogeneous enhancement on T1- and T2-weighted images[10,11].

In our case, the CT showed a heterogeneous mass and MRI showed a cystic and solid mass with ossification in the left renal pelvis and upper ureter, which made it difficult to distinguish from renal pelvic carcinoma and osteogenic tumors. The

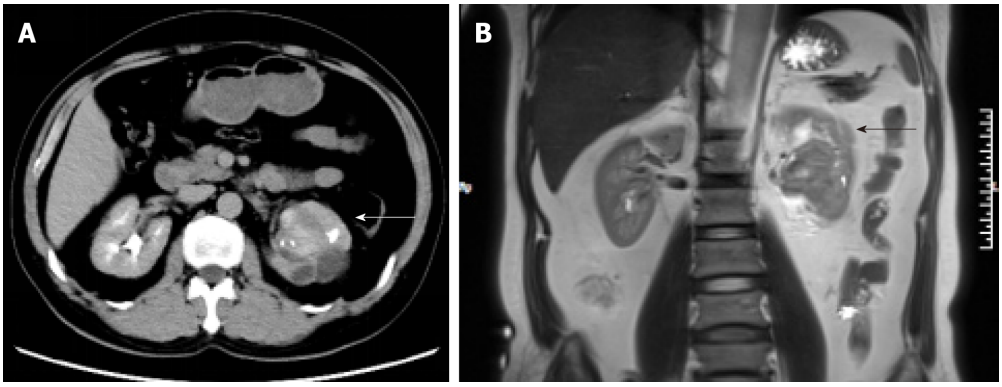

Figure 1 Imaging examination of our case of renal organ-associated pseudosarcomatous myofibroblastic proliferation. A: Computed tomography showed a heterogeneous mass (indicated with arrows) of 6 cm in diameter at the left pyeloureteral junction; B: Magnetic resonance imaging showed that the left renal pelvis was occupied by a cystic and solid mass (indicated with arrows) with calcification or ossification.

differential diagnosis of renal PMP includes renal cell carcinoma, renal sarcoma, teratoma, and renal pelvic carcinoma. However, renal PMPs are characterized by obscure edges, whereas the margins of renal cell carcinoma are clear. The CT-enhanced scans of our patient showed a gradual, slight enhancement in the renal PMP, different from the typical flow-type enhancement of renal cell carcinoma.

It was difficult to establish the diagnosis preoperatively. As such, the final diagnosis was dependent on findings from histopathologic and immunohistochemical examinations of the biopsied tissue. Microscopically, PMP lesions are mainly composed of proliferative fusiform myofibroblasts and inflammatory cells, lacking severe cytologic atypia and containing fewer mitoses than sarcomas[3]. Expression of p53 has been proposed as a marker to differentiate PMPs (usually negative on immunostain) from sarcomas (usually positive)[12]. In our case, the biopsied mass showed negativity for CK5/6, p53 and p16, along with positivity for calponin, smooth muscle actin and other smooth muscle-derived markers.

At present, there is no standard treatment regimen for renal PMP. Broad-spectrum antibiotics are recommended, accompanied by symptomatic treatment and traditional Chinese medicine. If conservative treatment is ineffective, simple tumor resection or partial nephrectomy would be feasible. It was recently reported that Myofibroblastic tumour patients had promising results with crizotinib treatment, so tyrosine kinase inhibitors (TKIs) can be used as an alternative to conservative treatment[13,14]. For tumors that are difficult to completely resect, TKIs can be also used as neoadjuvant therapy. However, since in most cases the prognosis of renal PMPs is good, TKIs adjuvant therapy after operation is not recommended routinely. According to our experience, It is recommended that CT examination be performed 3-mo or 6-mo in the first two years after operation, if nothing special found in the CT result,the re-examination time may extend to every 6-mo or 1 year afterwards. For patients undergoing partial nephrectomy, CT examination is also recommended 1-mo after operation. Most patients have a satisfactory prognosis, and for our case, the patient did not complain of any obvious discomfort at the 6-mo follow-up and no signs of recurrence were found.

CONCLUSION

Renal organ-associated PMP is a rare lesion that may mimic renal pelvic carcinoma, clinically and radiologically. Diagnosis of renal PMP depends on imaging and histopathological examination. Conservative treatment is recommended, and a satisfactory prognosis can be achieved.

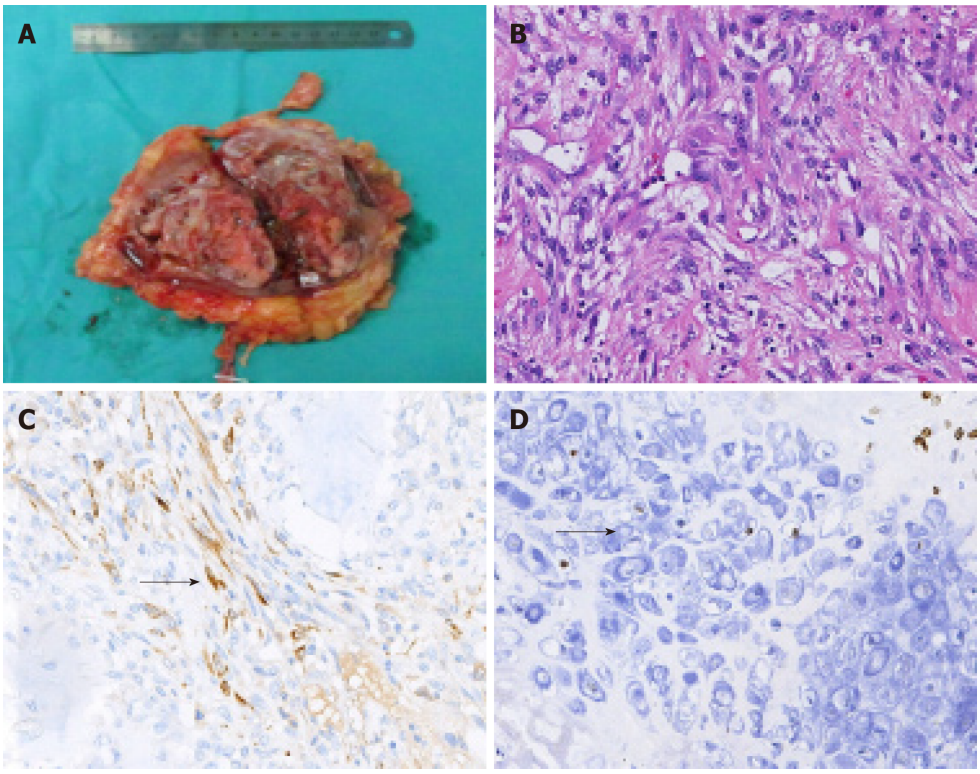

Figure 2 Gross specimen and histological examination of our case of renal organ-associated pseudosarcomatous myofibroblastic proliferation with ossification. A: Longitudinal section of our patient's kidney showing a gray-white and pink-grey mass, with capsule in the lower pole of the kidney; B: Microscopic view of the renal organ-associated pseudosarcomatous myofibroblastic proliferation staining with hematoxylin eosin (original magnification × 200). The lesions were found to be composed mainly of proliferative fusiform myofibroblasts and inflammatory cells; C, D: Immunohistochemical staining showed positivity for calponin (C) and SATB-2 (D) (Arrows indicate positive cells).

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CASE REPORT

Treating aplasia cutis congenita in a newborn with the combination of ionic silver dressing and moist exposed burn ointment: A case report

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Abstract

BACKGROUND

Aplasia cutis congenita (ACC) in newborns is a condition in which congenital defects or hypoplasia is present in part of the epidermis, dermis and even subcutaneous tissue (including muscle and bones). First reported by Cordon in 1767, ACC is a rare disease with a low incidence of 1/100000 to 3/10000. Currently, there are 500 cases reported worldwide. ACC can be accompanied by other malformations. The onset mechanism of the disease remains unknown but is thought to be correlated to factors such as genetics, narrow uterus, foetal skin and amniotic membrane adhesion, use of teratogenic drugs in early pregnancy and viral infection.

CASE SUMMARY

In August 2018, we treated a newborn with ACC on the left lower limbs using a combination of ionic silver dressing and moist exposed burn ointment (MEBO) and achieved a satisfactory treatment outcome. The skin defects were observed on the external genitals and on areas from the left foot to 3/4 of the upper left side. Subcutaneous tissue and blood vessels were observed in the regions with skin defects. The following treatments were provided. First, the wound was rinsed with 0.9% sodium chloride solution followed by disinfection with povidone-iodine twice. And then MEBO was applied to the wound at a thickness

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of approximately 1 mm. After applying ionic silver dressing, the wound was covered with sterile gauze. The wound dressing was replaced every 2-3 d. At the 4-mo follow-up, the treatment outcome was satisfactory. There was minimal scar tissue formation, and limb function was not impaired.

CONCLUSION
The combination of ionic silver dressing and MEBO to ACC is helpful.

Key words: Aplasia cutis congenita; Newborns; Ionic silver dressing; Moist exposed burn ointment

Core tip: Aplasia cutis congenita (ACC) is a rare disease in China and abroad. There is not yet a well-developed treatment for this disease. Combination of ionic silver dressing and moist exposed burn ointment in treating ACC is an useful and effective method. This treatment is worthy of being promoted in clinical practice.

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INTRODUCTION

Aplasia cutis congenita (ACC) is a rare disease in China and abroad. Patients with this disease often have other abnormalities or malformations. According to the literature, the incidence of ACC is approximately 1 in 100000, but the mortality rate is as high as 18%. Currently, there is not yet a well-developed treatment for this disease. A critical step in treating ACC is a prompt skin grafting to cover the wound[1]. Although skin grafting is important for patients with large areas of skin defect, this surgical process can aggravate the patient's pain and suffering. Recently, with more in-depth studies on the treatment of ACC in newborns, methods employed in treating burn wounds have yielded beneficial therapeutic effects for treating ACC[2]. Amongst the non-surgical methods, wound protection, infection prevention and nutrient supplementation are key to ensure treatment outcomes[2]. Herein, a case of ACC treated in our hospital is reported along with a retrospective analysis of the clinical data and discussion on lessons learned.

CASE PRESENTATION

Chief complaints
In August 2018, a female infant presented to our hospital with the skin defects on the external genitals and areas from the left foot to 3/4 of the upper left side.

History of present illness
Patient's symptoms were observed after birth

History of past illness
The patient was a female infant born at 37^{+6} wk *via* C-section. Intrauterine distress was not observed. However, premature rupture of foetal membranes and bloody amniotic fluid were present. The baby was found with the umbilical cord around her neck. There was no abnormality in the placenta, and no asphyxia was observed. The Apgar scores were 10 at 1-10 min after birth. The birth weight was 2800 g.

Personal and family history
The 28-year-old mother was in her second pregnancy but first birth. A miscarriage had previously occurred at age 25. The mother performed a urine pregnancy test 35 d

after menstruation and received a colour ultrasound 54 d after menstruation. The results suggested intrauterine pregnancy, and the foetal size was consistent with the gestational age. Foetal movement was sensed at week 16 and remained active until delivery. The thyroid function test at week 18 displayed no abnormalities. Foetal chromosome (T21, T18, T13) screening at week 22 indicated that the baby was at low risk of aneuploidy. A four-dimensional colour ultrasound examination at week 26 found no abnormalities. After admission for delivery, no abnormalities were observed by various examinations on the mother including a routine blood test, routine urine test, coagulation test, infectious disease tests, hepatitis B, liver and kidney functions and electrocardiogram. The family did not have a history of congenital conditions.

Physical examination upon admission

The results of the physical examination of the infant after birth are described next. The infant appeared to be born full term with normal appearance and responded well to stimulation. Skin defects were observed on the external genitals and on areas from the left foot to 3/4 of the upper left side. Subcutaneous tissue and blood vessels were observed in the regions with skin defects (Figure 1).

Laboratory examinations

Laboratory blood tests were normal.

Imaging examinations

The ultrasound, lower limbs computed tomography (CT) scan, high-resolution chest CT scan, and head magnetic resonance imaging were normal.

FINAL DIAGNOSIS

The baby was diagnosed with ACC and was transferred to the Division of Neonatology for further treatment.

TREATMENT

The following treatments were provided: (1) Wound treatment: The wound was rinsed with 0.9% sodium chloride solution followed by disinfection with povidone-iodine twice. Moist exposed burn ointment (MEBO) was applied to the wound at a thickness of approximately 1 mm. The surface covered by MEBO was extended beyond the edges of the wound. After applying ionic silver dressing, the wound was covered with sterile gauze. The wound dressing was replaced every 2-3 d; (2) Infection prevention: Intravenous injections of second-generation cephalosporin were provided for 7 d; and (3) Nutrition support: An intravenous infusion of 10% glucose was given along with premium powdered formulas. The condition of the infant was complicated by hypoproteinaemia, which was corrected by the infusion of albumin. With the above-described treatment, the skin on the lower limbs of the patient recovered after 26 d (Figure 2), and the patient was discharged. The patient was prescribed multi-sulfonic acid mucopolysaccharide cream to prevent scar tissue formation and soften existing scar tissue.

OUTCOME AND FOLLOW-UP

During treatment, the functions of the limbs were preserved; limb shortening was not observed. No blisters were observed on the skin. A histopathological examination was not performed. At the 4-mo follow-up, the treatment outcome was satisfactory. There was minimal scar tissue formation, and limb function was not impaired.

DISCUSSION

ACC is a rare neonatal disease with a low incidence rate. The incidences are typically sporadic. However, the condition may be genetic. The cause of ACC is not known. According to the literature, the most common factors of ACC include foetal chromosomal or genetic abnormalities (particularly *BMS1* and *UBA2* genetic abnormalities)[3], trauma[4], amniotic fluid or amniotic membrane abnormalities (*e.g.*, foetal skin and amniotic membrane adhesion)[5], intrauterine complications (*e.g.*, infection)[6], vascular lesions (*e.g.*, thrombus and vascular diseases)[7] and the use of

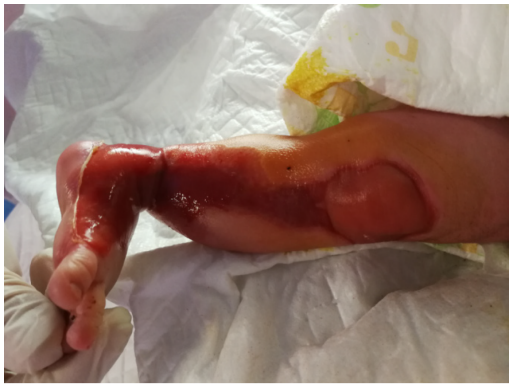

Figure 1 Aplasia cutis congenita in our patient.

teratogenic drugs during pregnancy (*e.g.*, cocaine, methotrexate, angiotensin inhibitor)[8]. ACC is diagnosed mainly based on clinical manifestations: Clear skin defects are observed on regions of the body at birth; the defects can be accompanied by defects or hypoplasia of subcutaneous tissues (including muscle and bones); the shape of the defected skin is irregular, which can be sheet-like, in patches, or irregular shapes; and the size and depth of the skin defects also vary. Pathophysiological examination often suggests defects in the epidermis and dermis. Total or partial defects can also be found in the lipids of the subcutaneous tissue. ACC can be accompanied by other diseases or complications such as epidermolysis bullosa (EB), cheilopalatognathus and polycystic kidney disease. In 1986, Frieden[9] classified ACC in newborns into 9 groups based on the location and features of the lesions and the accompanying conditions: Scalp ACC without multiple anomalies, scalp ACC with associated limb abnormalities, scalp ACC with associated epidermal and organoid nevi, ACC overlying embryologic malformations, ACC with associated foetus papyraceus or placental infarcts, ACC associated with EB, ACC localized to extremities without blistering, ACC caused by specific teratogens and ACC associated with malformation syndromes. Scalp lesions are the most common and comprise 70% of defects, followed by defects in limbs and the trunk. Some cases can be accompanied by defects in the oral mucosal membrane or perineal mucosal membrane and skeletal malformation in limbs[10].

Conservative and surgical methods can be employed as treatment for ACC. Conservative treatment includes the application of topical ointments such as silver sulfadiazine dressing, antibiotics, *etc*. Surgical treatments include split-thickness or full-thickness skin grafts, acellular dermal matrices, autologous epithelial transplantation, tissue expansion, cranioplasty, *etc*. The selection of the treatment method depends on the width, depth, location and involved subcutaneous tissues of the defects. Conservative treatments are recommended if the defect is only at the skin level without damage to the bones and if the area of the defect is less than 3 cm^2. Conversely, skin grafts are necessary when the defected area is large and involves critical organs or tissues such as the scalp while also accompanied by the exposure of large blood vessels or sagittal sinus. The skin defects in limbs often display clearly defined boundaries and typically involve the epidermis and dermis. Approximately 85% of ACC cases are simple defects without complications. However, the indications for selecting between conservative versus surgical treatment remain controversial. Bigliardi *et al*[11] reported a case of ACC in the right lower limb. The defect involved the thigh, knee and lower leg to the first and second toes. Ulcer-like defects were observed, and the blood vessels were clearly visible. The wounds recovered after 3 mo of silver sulfadiazine topical cream application. In a case reported by Pająk *et al*[12], a skin defect in the right lower limb was 4.0 cm × 1.5 cm in size. In addition to antibiotic ointment and ionic silver dressing, suturing was performed. Although the patient recovered after one month of treatment, a linear scar formed. These case reports suggest that for ACC that does not affect bone tissues, conservative treatment might provide a better outcome. However, surgical treatment is necessary when a large area of defect is present.

The major ingredients of MEBO include sesame oil, beeswax, berberine, phellodendron and baicalin. MEBO provides a moist environment to the wound tissue. An appropriate level of humidity is beneficial for tissue recovery. Linoleic acid, multiple amino acids, vitamins and trace elements are essential for the survival of cells. These ingredients can effectively activate the transformation of residual skin tissue to stem cells and allows in situ cultivation. The newly formed skin tissues can

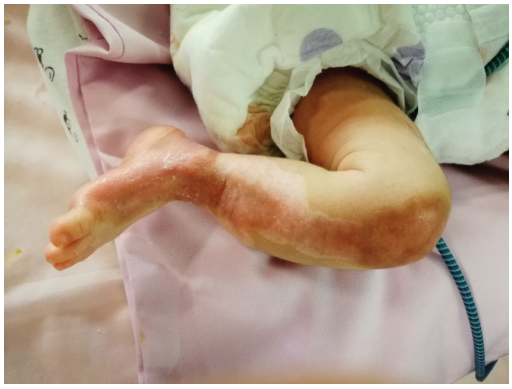

Figure 2 The same patient after 26 d.

then adhere to the adjacent hyperplasia tissues to promote natural recovery. Additionally, MEBO can relieve mild local and systemic inflammation, promote wound recovery and improve recovery quality.

Ionic silver dressing is a 3D foaming structure that allows the effective absorption of exudate and water vapor. This absorption can minimize impregnation of the wound, which then inhibits the growth of bacteria and lowers the risk of infection. Ionic silver dressing is a natural broad spectrum antimicrobicide that contains silver compound, which provides high bacterial inhibition with its slow-release abilities. In the process of treating the case reported herein, a high amount of exudate and the bleeding of the newly formed blood vessel were observed on days 4-7. The exudate and bleeding were greatly reduced with the application of ionic silver dressing.

CONCLUSION

The treatment of our case demonstrated that the combination of MEBO and ionic silver dressing can effectively promote skin growth and prevent infection. This treatment method does not involve surgical operation; thus, it reduces the pain and suffering of the patient while simultaneously reducing the financial burden. This treatment is worthy of being promoted in clinical practice.

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CASE REPORT

Cause of postprandial vomiting - a giant retroperitoneal ganglioneuroma enclosing large blood vessels: A case report

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Author contributions: Zheng X consulted literature, collected images and wrote this paper. Luo L collected clinical data and consulted literature. Han FG designed the research, reviewed and revised the paper.

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Abstract

BACKGROUND

Ganglioneuroma (GN) is a rare neurogenic tumor that accounts for about 0.1%-0.5% of all tumors of the nervous system. It originates from neural crest cells. GN has no specific clinical symptoms or laboratory findings, which leaves it easily overlooked and misdiagnosed as other tumors. Retroperitoneal GN with very large volume and vascular penetration is extremely rare.

CASE SUMMARY

We present the imaging and pathological findings of a giant retroperitoneal GN in a child. A 4-year-old boy had suffered from postprandial vomiting for more than 6 mo with no precipitating factors. Abdominal computerized tomographic examination showed a giant cystic mass in the retroperitoneal area. After injection of contrast agent, the mass showed heterogeneous enhancement. Surgery with local excision of the mass was performed to address the embedded abdominal blood vessels, and the histopathological and immunohistochemical diagnosis of the mass was GN. Postprandial vomiting was relieved, and no complications occurred after the operation.

CONCLUSION

In the diagnosis of giant retroperitoneal hypodense masses in children, GN should be considered if the mass presents delayed enhancement, punctate calcification, and vascular embedding but no invasion. Pathology is the golden standard for the diagnosis of GN, and surgical excision is the optimal treatment for GN.

Key words: Retroperitoneal; Ganglioneuroma; Postprandial vomiting; Case report

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Core tip: Ganglioneuroma (GN) is a rare benign neurogenic tumor originating from the sympathetic nerve chain. Although it often occurs in the retroperitoneum, we report a case of giant GN causing postprandial vomiting and enclosing all major abdominal vessels, which is clinically rare. Surgical resection is the optimal choice for the treatment of GN at present. Pathology is the gold standard for the diagnosis of GN, and the presence of mucous matrix and ganglion cells are pathological features of GN.

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INTRODUCTION

Ganglioneuroma (GN) is a benign neurogenic tumor that accounts for more than 0.1%-0.5% of all tumors of the nervous system[1]. It commonly occurs in the mediastinum (41.5%) and retroperitoneum (37.5%)[1-3]. Patients are usually asymptomatic, and GN is often found via physical examination. However, the tumor can press against the adjacent organs and cause complications if it reaches a great enough size. Here, we introduce a case of a 4-year-old boy with giant retroperitoneal GN associated with postprandial vomiting enclosing the main abdominal vessels. To our knowledge, existing reports mention only small arteries passing through GN, and there is no previous work reporting GN enclosing so many large arteries. The aim of our report is to present a rare case and discuss the related clinical, imaging, and pathological features.

CASE PRESENTATION

Chief complaints

A 4-year-old boy was admitted to our hospital with a history of postprandial vomiting for more than 6 mo without precipitating factors and abdominal pain, chill, fever, or anal cessation of exsufflation or defecation.

History of present illness

He had poor appetite but no weight loss during his illness.

History of past illness

The child was of full-term natural delivery with normal feeding and timely vaccination.

Personal and family history

He had no previous or family history of similar illnesses.

Physical examination upon admission

Physical examination showed abdominal bulge and intestinal type in the upper abdomen. The epigastrium showed a palpable mass with poor mobility; the lump was hard but was associated with no tenderness.

Laboratory examinations

The laboratory examinations (including blood and urine routine tests, coagulation function tests, liver and kidney function tests, and tumor markers) were normal.

Imaging examinations

The pre-contrast computerized tomographic (CT) scan presented a retroperitoneal giant hypodense mass with a size of 10.7 cm × 17.3 cm × 15.5 cm and a CT value of 33.8 HU. Spotted calcification with irregular distribution was noted in the mass. The tumor showed inhomogeneous flocculent enhancement in the venous phase and further enhancement in the delayed phase after intravenous injection of contrast agent (Figure 1). We observed that the stomach had been pushed forward and displaced, which was also considered the main cause of postprandial vomiting for the patient.

The tumor surrounded the celiac trunk, hepatic artery, splenic artery, superior mesenteric artery, bilateral renal artery, and portal vein. Nevertheless, the enclosed vascular lumen did not become narrowed or distorted (Figure 2 and 3). Of course, this created a difficult problem for the patient's surgical treatment, such that the surgeon was only able to remove the relatively non-vascular part of the tumor.

Histopathology revealed the spindle cell tumor with nerve fibers and ganglion cells. Immunohistochemical investigation showed the tumor cells expressed NSE (diffuse +), Syn (+), S100 (diffuse +), and NF (diffuse +) and were negative for GFAP, CR, P53, and SMA. The Ki-67 proliferation index was 5%.

FINAL DIAGNOSIS

Retroperitoneal GN.

TREATMENT

The patient underwent partial resection of two retroperitoneal tumors about 6.0 cm × 3.0 cm × 2.0 cm and 6.0 cm × 5.0 cm × 4.0 cm in size.

OUTCOME AND FOLLOW-UP

Postprandial vomiting was relieved, and no complications occurred. The patient was discharged 10 d after surgery. The patient's parents declined follow-up after discharge and did not disclose their reasons.

DISCUSSION

Retroperitoneal GNs account for 37.5% of all GNs and about 0.72%-1.6% of primary retroperitoneal tumors[1-3]. GNs can also occur in the vertebra, neck, and cerebellopontine angle region (trigeminal); all three of which are relatively rare[4-8]. GNs are found incidentally in most cases and manifest as asymptomatic masses[2,9,10]. The tumor could cause some complications if it becomes large enough to press against the adjacent organs. In our case, the stomach dilated after meals, peristalsis became limited after means due to the compression from the GN, and food could not easily enter the duodenum, causing postprandial vomiting. Occasionally, GNs occurring in the adrenal gland can secrete vasoactive intestinal peptides, dopamine, and cortisol, which lead to diarrhea, hypertensive crisis, and male-like metabolic disorders in women[11-13].

GNs are mainly composed of ganglion cells, mucus matrix, nerve fibers, and mature Schwann cells, and the first two of them are characteristic components in histopathology[14,15]. The pathological features of GN are closely related to its CT findings. The presence of mucus matrix in tumors determines the hypodensity on plain CT scans. The mucus matrix has been found to delay the absorption of contrast agents, which leads to the delayed enhancement of GNs[16,17]. This case was misdiagnosed as retroperitoneal cystic lymphangioma initially. Similar to this case, cystic lymphangioma tends to occur in children and presents as a large, well-defined low-density mass in the retroperitoneum[18], which can also wrap around blood vessels without distorting them, while a retroperitoneal GN of such a large size as this case is rare and it is predominant in adults. However, in this case, flocculent and strip delayed enhancement was observed, which was consistent with the enhancement of GN, while cystic lymphangioma was generally not enhanced, which was the most important distinguishing point between them. Calcifications have been noted in 20%-60% of GNs, and most of them are punctate, which is also one of the differences between GN and neuroblastoma[19,20]. Punctate calcification with scattered distribution was also noted on plain CT images in this case. Ko *et al*[14] and Duffy *et al*[21] suggested that the presence of fat components in GN may be one of the characteristics of GN, but their sample size was too small to verify this, and we did not notice any fat replacement in our case. Some scholars have proposed that the blood vessels are often surrounded or compressed by GNs instead of being invaded, although most of them are small vessels[16,22], and this finding further suggested that GNs are benign. In this case, GN enclosed all major abdominal vessels, including the celiac trunk, hepatic artery, splenic artery, bilateral renal artery, superior mesenteric artery, inferior vena cava, and portal vein. None of the enclosed vessels had a narrowed lumen or filling

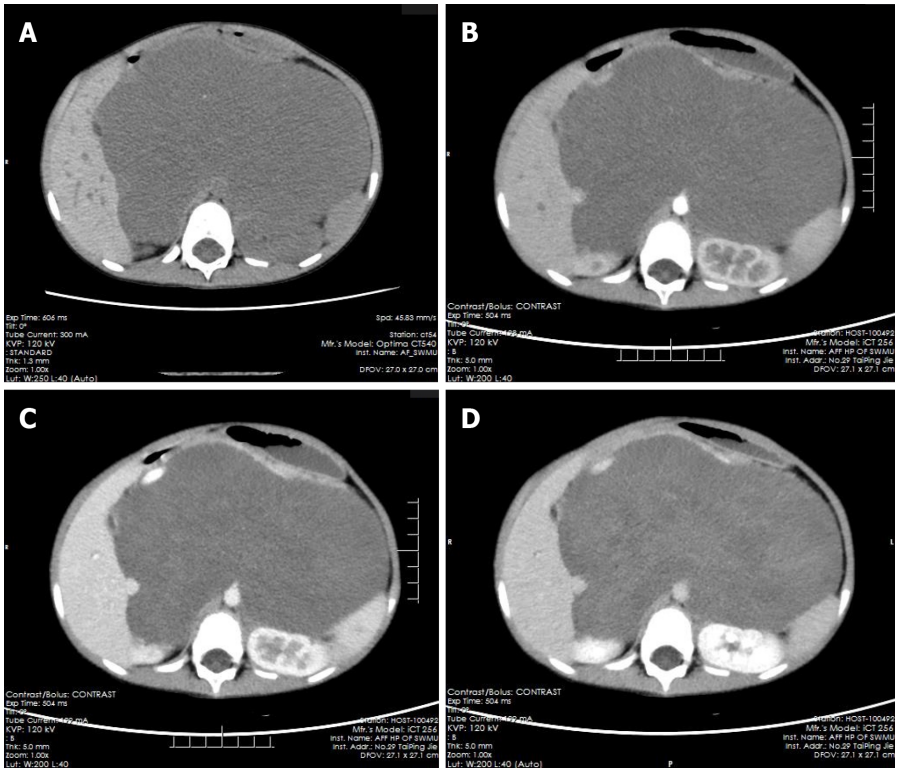

Figure 1 Multiphase enhanced computerized tomographic images of the patient. A: Giant retroperitoneal hypodense mass in pre-contrast and punctate calcification could be noted; B: The hypodense mass without enhancement in arterial and venous phase, and the stomach and kidneys were compressed and displaced; C: The mass presented mild enhancement in venous phase; D: The mass showed patchy and flocculent enhancement in delay phase, and the extent of enhancement was greater than that of the venous phase.

defect, which provided more reliable support for these scholars' views. However, there are some reports suggesting that GNs could behave aggressively, and recurrence or malignant transformation[2,23,24] and complete surgical excision are the most optimal choice for the treatment[8,25]. Therefore, patients with GN still need long-term radiological follow-up. In addition, some scholars have put forward a different view, arguing that incomplete resection of GN does not increase the risk of progression if residual tumors are less than 2 cm in diameter[10]. We believe that it is important to determine whether the tumor is invasive before surgery and assess pathology to select the most suitable surgical method, an area in which we believe the current research into GN is lacking.

In conclusion, GNs appear as hypodense masses on plain scans and present delayed and mild enhancement on contrast enhancement. Pathology is the gold standard for the diagnosis of GN, and mucous matrix and ganglion cells are their important features. Surgical excision is the best treatment for GN, and postoperative radiotherapy and chemotherapy are unnecessary. However, in cases where it is difficult to completely dissect the tumors and blood vessels, partial resection could still relieve the pressure symptoms created by the tumors. Long-term radiological follow-up after the operation is necessary, even though the biological behavior of GN is benign, because there is still a tendency to be malignant, especially in patients with GN who have undergone only local resection.

CONCLUSION

Retroperitoneal GN, which is huge and encloses a large number of blood vessels without invading, is rare in clinical settings. Although some previous studies maintain that complete resection of the tumor is not necessary, finding suitable ways of assessing the invasiveness of GN after pathology and radiology still needs further discussion and study.

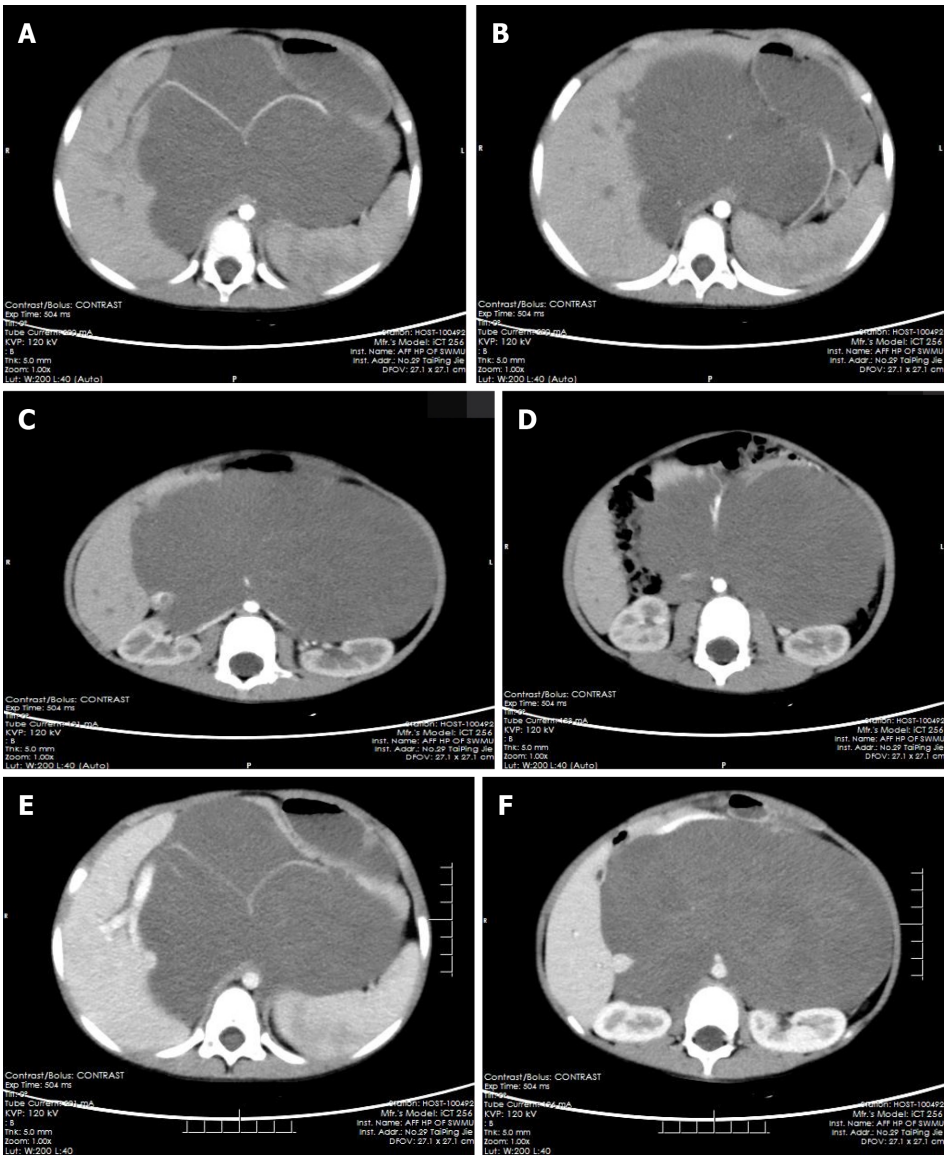

Figure 2 The computerized tomographic images of tumors surrounding blood vessels. A-D: Tumor-enclosed arteries: hepatic artery (A), splenic artery (A, B), bilateral renal artery (C), superior mesenteric artery (D); E, F: Tumor-enclosed veins: Portal vein (E) and inferior vena cava (F).

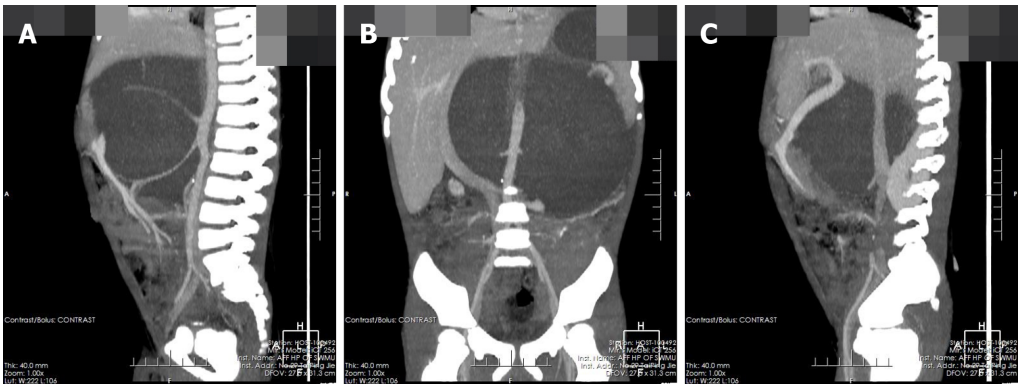

Figure 3 Coronal and sagittal of the computerized tomographic images. A, B: Tumor-enclosed arteries; C: Tumor-enclosed veins.

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CASE REPORT

Carcinoma ex pleomorphic adenoma of the trachea: A case report

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Abstract

BACKGROUND

Carcinoma ex pleomorphic adenoma (CXPA) is defined as a malignant salivary gland tumor arising from a primary or recurrent pleomorphic adenoma. Only three cases of CXPA of the trachea have been reported in the literature.

CASE SUMMARY

We report a case of tracheal CXPA in a 55-year-old woman, who presented with a more than 3-mo history of progressive dyspnea. Computed tomography of the neck and thorax revealed an inhomogeneous, broad-based lesion arising from the tracheal wall on the right side. Endoscopy revealed a subglottic neoplasm causing up to 90% luminal stenosis. The tumor was resected using a high-frequency electrosurgical snare combined with argon plasma coagulation. Histopathology and immunohistochemistry revealed that the tumor was a CXPA of the trachea.

CONCLUSION

We report the fourth case of tracheal CXPA, and present the first instance of resection of CXPA using high-frequency electrosurgical snare and laser ablation. We also discuss the pathogenesis, diagnosis, histopathology, and systemic therapy of this rare disease.

Key words: Case report; Carcinoma ex pleomorphic adenoma; Trachea; Pleomorphic adenoma

Core tip: After extensive search of literature in English, there are only 3 previous reports

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of primary Carcinoma ex pleomorphic adenoma of the trachea. In our case, there are many unique features. In imaging examination, there is no calcification can be seen in the primary tracheal CXPA of the previous cases, but ours can. Given the rare incidence of CXPA in trachea, no standard systemic therapy options have been established. We successfully performed endobronchial resection of the tumor with a high-frequency electrosurgical snare combined with argon plasma coagulation with less injury and quick recovery.

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INTRODUCTION

Pleomorphic adenoma is the most common benign tumor of the salivary glands. Approximately 6% of pleomorphic adenomas have the potential to transform into carcinoma ex pleomorphic adenoma (CXPA)[1]. The main histopathological finding in CXPA is the co-existence of the benign characteristics of pleomorphic adenoma with malignant changes in the epithelial components of the tumor. CXPA mainly involves the major salivary glands, of which the parotid gland is the most commonly involved, followed by the submandibular gland[2]. Tracheal CXPA is an exceedingly rare entity. Herein, we present a case of CXPA arising in the trachea, and a review all cases of tracheal mixed malignant tumors reported in the literature.

CASE PRESENTATION

Chief complaints

A 56-year-old woman was admitted to our hospital with a complaint of progressive dyspnea over the last 3 mo.

History of past illness

The patient had no history of disease in the head and neck region. Her past history was unremarkable.

Personal and family history

The family history was unremarkable.

Physical examination

The patient's inspiratory phase was prolonged and the inspiration was laborious. There were wheezing, laryngeal ringing, and three depressions sign can be seen. Her temperature was 36.8 °C, heart rate was 102 bpm, respiratory rate was 26 bpm, blood pressure was 133/86 mmHg and oxygen saturation in room air was 96%.

Laboratory examinations

Blood analysis revealed normal. The blood biochemistries, as well as urine analysis were normal.

Imaging examinations

A computed tomography scan of the neck and thorax revealed an inhomogeneous, broad-based lesion arising from the tracheal wall on the right side. The lesion measured 1.8 cm × 1.7 cm. Calcification was observed in the anterior part of the lesion (Figure 1). On bronchoscopic examination, a subglottic neoplasm was observed at approximately 5 cm from the carina. The tumor caused up to 90% luminal stenosis of the trachea (Figure 2).

FINAL DIAGNOSIS

Take together, a final diagnosis of primary CXPA of the trachea was established.

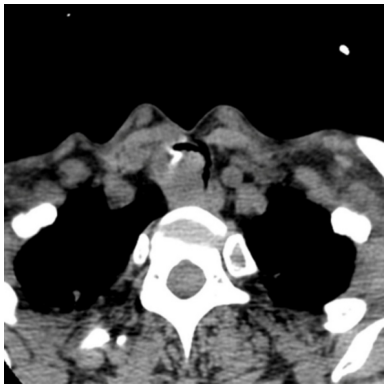

Figure 1 Computed tomography scan showing an inhomogeneous, broad-based lesion arising from the tracheal wall on the right side. Calcification can be seen in the anterior part of the tumor.

TREATMENT

The tumor was resected using a high-frequency electrosurgical snare combined with argon plasma coagulation (APC). At 30 min before the operation, the patient was anesthetized with 5 mL of 2% lidocaine (inhaled *via* oxygen-driven atomization) and an intranasal drip of lidocaine combined with 1% furosemide. Propofol 20 mg and fentanyl 100 mg were intravenously administered before surgery. During the surgery, intravenous propofol was administered through a micropump (2-4 mg/kg/h). Throughout the treatment, the patient's pulse, oxygen saturation, respiration, and blood pressure were dynamically monitored. Routine nasal insertion of a bronchoscope was performed to reach the lesion site. A high-frequency electrosurgical snare and an APC catheter were inserted into the airway through the bronchoscope. The power supply for electrocutting (35-40 W) and electrocoagulation (30-35 W) was turned on at the same time. To resect the tumor, we placed the snare near the base of the tumor and slowly closed it around the tumor pedicle while simultaneously applying electrocoagulation.

For the remaining tumor tissue in the basal part, we placed the electrocoagulation probe on the lesion and applied a current for 0.5-1.0 s. Electrocoagulation was performed multiple times to coagulate and vaporize the lesion. The necrotic tissues were removed using biopsy forceps or bronchoscopic suction. The surgical field was intermittently rinsed with a cold saline solution containing adrenaline (dilution, 1:10000) to maintain a clear view. The depth of electrocoagulation did not exceed 3 mm. After APC treatment, jelly-like cellulosic exudates and necrosis may form and lead to airway obstruction; these need to be cleaned regularly by using biopsy forceps or bronchoscopic suction.

Histopathological examination

On histopathological examination, benign pleomorphic adenoma-like areas and large malignant cells with pleomorphic and prominent nucleoli were recognized (Figure 3). The tumor was composed of glandular and tubular structures along with myoepithelial cells within stromal elements, which was suggestive of a pleomorphic adenoma. In the epithelial areas, solid nests and cords of polygonal tumor cells were observed. The adjacent areas showed chondromyxoid materials. The solid nests had a cribriform pattern, and were associated with dense hyalinized stroma, which was incorporated into the tumor islands and sheets. The cribriform pattern was suggestive of adenoid cystic carcinoma (Figure 4).

Immunohistochemistry revealed strong immunoreactivity with cytokeratins in both the ductal epithelial cells and myoepithelial cells. The tumor was negative for glial fibrillary acidic protein. The myoepithelial cells were positive for smooth muscle actin, the myoepithelial marker P63, vimentin, and CD43. Staining for s-100 protein and CD117 was positive in the ductal epithelial cells. Alcian blue staining was positive in the mucous-like substance that filled in the sieve-like structure of the tumor cells. Periodic acid-Schiff staining was positive in the luminal contents of the gland.

OUTCOME AND FOLLOW-UP

At 6 d after the tumor resection, the patient was well and was discharged.

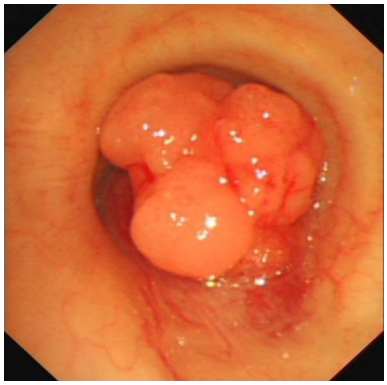

Figure 2 Bronchoscopic examination showing a subglottic neoplasm causing up to 90% luminal stenosis of the trachea.

Unfortunately, fiberoptic bronchoscopy revealed tumor recurrence after 11 mo. The patient again underwent treatment with a high-frequency electrosurgical snare combined with APC. Additionally, postoperative radiotherapy (60 Gy) was performed. The patient has been well for 10 mo until now after the second surgery.

DISCUSSION

CXPA is defined as an epithelial malignancy arising in or from a primary or recurrent benign pleomorphic adenoma[1,3-4]. This tumor most commonly affects the salivary glands. Primary CXPA of the tracheobronchial system has been reported only infrequently. The pathogenesis of CXPA is unknown. Chooback *et al*[5] proposed a role for the deficiency of some genes, such as those on chromosomal arms 8q, 12q, and 17p. Kim *et al*[6] suggested that the accumulation of genetic instabilities was the main cause of malignant transformation in pleomorphic carcinoma. The above hypotheses were based on salivary gland tumors, and it is unclear whether these apply to CXPA of the tracheobronchial system.

Malignant mixed tumors of the salivary glands classically encompass three distinct tumors: CXPA, carcinosarcoma, and metastasizing pleomorphic adenoma[7]. A review of the literature disclosed 11 previous cases of primary malignant mixed tumors of the trachea and bronchus[8-13]. Of these, only four cases (Ding *et al*[10], Demirağ *et al*[11], Hemmi *et al*[12], and Mori *et al*[13]) involved the trachea (Table 1); the others involved the hilum and/or bronchi. In the case reported by Hemmi *et al*[12], no foci of benign pleomorphic adenoma were found in the primary tumor. This indicates that the tumor was a malignant pleomorphic adenoma, and not a CXPA. Thus, only three cases of true primary CXPA of the trachea have been reported. The present case is the fourth report of a primary CXPA of the trachea.

A review of the four previous cases of tracheal malignant mixed tumors showed that the ages of the patients ranged from 56 to 69 years; there were two women and two men. Our patient was a 55-year-old woman. The common clinical symptoms were cough, asthma, and dyspnea; hoarseness was reported by Mori *et al*[13]. Thus, tracheal CXPA may not have distinct symptoms. On imaging examination, no calcification could be seen in the previous four cases, but calcification was present in our patient.

The diagnosis of CXPA requires the presence of both the pleomorphic adenoma component and the malignant component. The presence of cohesive clusters of ductal cells, a background of myoepithelial cells, dense fibrillary metachromatic matrix, atypical cells, an abnormal chromatin pattern, and necrosis are essential to make a diagnosis of CXPA. In our patient, benign pleomorphic adenoma-like areas and large malignant cells with pleomorphic and prominent nucleoli were recognized on histopathological examination, confirming the diagnosis. The most common malignant component in CXPA is adenocarcinoma. Other malignant components include adenoid cystic carcinoma, myoepithelial carcinoma, and salivary duct carcinoma, and rarely acinic cell carcinoma, epithelial–myoepithelial carcinoma, basal cell carcinoma, myoepithelial carcinoma, squamous cell carcinoma, and clear cell carcinoma[14]. In our patient, the malignant component was an adenoid cystic carcinoma. The malignant component in the case reported by Ding *et al*[10] was an adenocarcinoma, while the type of malignant component was not mentioned in the cases reported by Demirağ *et al*[11] and Mori *et al*[13].

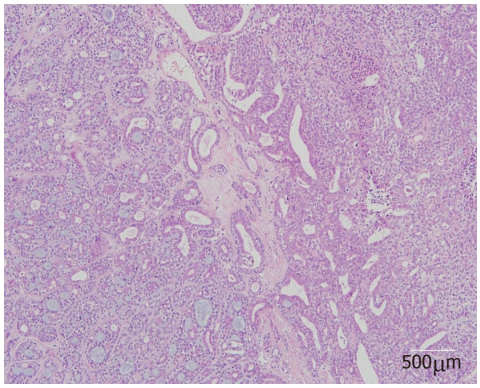

Figure 3 Microscopic examination of the resected specimen showing a biphasic composition with benign histological characteristics suggestive of pleomorphic adenoma and malignant changes in the epithelial components (hematoxylin and eosin).

Given the rarity of tracheal CXPA, no standard systemic therapy options have been established. Surgery appears to be the primary treatment modality, and postoperative radiotherapy may be used in patients with poor prognostic factors, such as stage III/IV disease, perineural invasion, and distant metastasis[15]. Endoscopic resection is simple, convenient, safe, and effective, and is associated with minimal injury and rapid recovery. It is widely applied in the diagnosis and treatment of benign airway stenosis, including that caused by tracheobronchial pleomorphic adenoma[16]. However, Gaissert *et al*[17] noted that bronchoscopic resection does not provide confirmation of the resection margins and can leave tumor behind, which leads to tumor recurrence. Studies on the endoscopic resection of tracheal tumors have not provided long-term follow-up data[18]. In the three previous reports of primary tracheal CXPA, all patients were treated conservatively with complete excision. For our patient, we successfully performed endobronchial resection of the tumor with a high-frequency electrosurgical snare and laser ablation. Demirağ *et al*[11] and Mori *et al*[13] performed postoperative radiotherapy for their patients. Postoperative radiotherapy was not performed by Ding *et al*[10] and in the present case. The necessity and benefits of postoperative radiotherapy remain unclear at present. If distant metastases are present, effective regional radiation in addition to resection may provide meaningful palliation. The three previous patients were free of disease for 3 mo[9], 16 mo[12], and 30 mo[10] after tumor resection. In our patient, the tumor recurred after 11 mo. However, whether bronchoscopic resection and the lack of postoperative radiotherapy led to tumor recurrence in our patient cannot be definitively stated at present.

CONCLUSION

In conclusion, given the rarity of CXPA in the trachea, no standard systemic therapy options have been established. Endoscopic resection is a simple, safe, minimally invasive, and effective method for treating CXPA patients.

Table 1 Clinical features of the four patients with carcinoma ex pleomorphic adenoma of the trachea

Study	Age (yr) / Sex	Tumor location	Size (cm)	Clinical features	Treatment	Follow-up
Ding *et al*[10]	65/M	Posterior tracheal wall	2.2	Chronic obstructive pulmonary disease	Surgical resection	3 mo
Demirağ *et al*[11]	56/M	Approximately 4 cm from the carina	2.5	Dyspnea	Surgical resection and radiotherapy	2.5 yr
Mori *et al*[13]	69/F	On the left side of the trachea	-	Husky voice, dyspnea	Surgical resection and radiotherapy	16 mo
Hemmi *et al*[12]	76/F	Trachea	1.3	Cough, dyspnea	Surgical resection	11 yr
Present study	56/F	Tracheal wall, on the right side	1.8	Progressive dyspnea	High-frequency electrosurgical snare combined with argon plasma coagulation and radiotherapy	10 mo

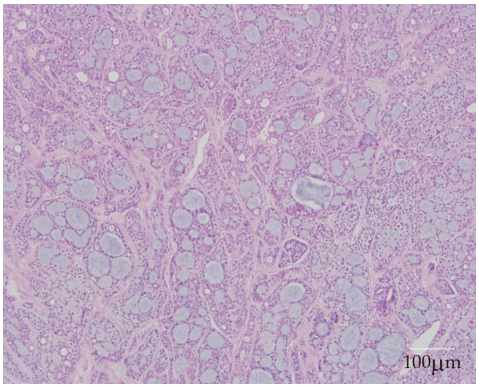

Figure 4 Microscopic examination of the resected specimen showing solid nests in a cribriform pattern associated with hyalinized stroma, which is incorporated into the tumor islands and sheets (hematoxylin and eosin).

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CASE REPORT

Wilson disease associated with immune thrombocytopenia: A case report and review of the literature

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Author contributions: Ma TJ was responsible for acquisition of the clinical information and writing the manuscript; Yao F assisted in developing the figures and table for the manuscript; Sun GL was responsible for acquisition of the clinical information and reviewing the manuscript; Yang ZL analyzed the data and wrote and reviewed the manuscript; all authors read and approved the final manuscript.

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Abstract

BACKGROUND

Wilson disease (WD) is a genetic disorder of hepatic copper excretion, leading to copper accumulation in various tissues. The manifestations are quite variable, and hemolytic anemia is the most common hematological presentation. WD associated with thrombocytopenia is very rare.

CASE SUMMARY

We report the case of an 11-year-old Chinese girl with WD that was associated with immune thrombocytopenia (ITP). Thrombocytopenia was the initial chief complaint for her to visit a hematologist, and ITP was diagnosed based on the results of a bone marrow biopsy and positive antiplatelet autoantibodies. About two weeks before the thrombocytopenia was found, the patient developed drooling. Tremors developed in her right hand about one week after being diagnosed with ITP, after which she was admitted to our hospital. Further evaluations were performed. Ceruloplasmin was decreased, with an increased level of copper in her 24-h urine excretion. Kayser Fleischer's ring (K-F ring) was positive. The ultrasound showed liver cirrhosis, and brain magnetic resonance imaging showed that the lenticular nucleus, caudate nucleus, and brainstem presented a low signal intensity in T1-weighted images and high signal intensity in T2-weighted images. WD was diagnosed and a genetic analysis was performed. A compound heterozygous mutation in *ATP7B* was detected; c.2333G>T (p.Arg778Leu) in exon 8 and c.3809A>G (p.Asn1270Ser) in exon 18. The former was inherited from her father and the latter from her mother. However, her parents showed normal liver function and negative K-F rings. Such a compound mutation in a case of WD associated with ITP in children has not been published previously.

CONCLUSION

WD can associate with thrombocytopenia but the mechanism is still unclear. We recommend that antiplatelet autoantibodies should be tested in WD patients with

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thrombocytopenia in future to verify the association.

Key words: Wilson disease; Immune thrombocytopenia; *ATP7B*; Case report

Core tip: Our findings indicate that Wilson disease (WD) can associate with thrombocytopenia. Some recessive heterozygous mutations can induce WD in combination with other recessive heterozygous mutations in *ATP7B*. Thrombocytopenia patients with neurological signs or abnormal liver function should be screened for WD because early detection and treatment of WD lead to a better outcome. We recommend that antiplatelet autoantibodies should be tested in WD patients with thrombocytopenia in future to verify the association.

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INTRODUCTION

Wilson Disease (WD), first described in 1912, is a hereditary genetic disorder induced by the dysfunction of copper metabolism in the liver. WD is fatal if untreated, but the prognosis can be good with timely and lifelong management[1-2]. The initial signs for WD are quite varied, and some rare presentations may lead to delays in diagnosis and treatment[3-5]. It is caused by mutations in *ATP7B*, which encodes a membrane-bound P1B-type ATPase involved in copper excretion from hepatocytes. The accumulation of copper in the body can lead to multiple organ damage. *ATP7B* was first identified as the responsible gene in 1993, and now over 500 mutations have been detected and most patients with WD are compound heterozygotes[6-8]. Some mutations in *ATP7B* show relatively higher frequencies in special populations, such as the mutation resulting in p.Arg778Leu in the Far East[9-15]. The identification of a mutation supports the diagnosis of WD, while a compound heterozygous status confirms the diagnosis. Recently, *Atox1* and *COMMD1* were also concerned in WD patients, but there was no evidence to show their contribution[16].

Coombs-negative hemolytic anemia is the hematological presentation reported for WD and is rare. Immune thrombocytopenia (ITP) is an acquired hemorrhagic disease caused by the accelerated clearance of platelets induced by antiplatelet autoantibodies such as antiglycoprotein (GP) IIb/IIIa[17-19]. WD has been associated with ITP in an adult[20], but such association has not been reported in children.

Here, we report a case of genetically-confirmed WD caused by a compound *ATP7B* mutation that was inherited from the proband's unaffected parents. The patient was diagnosed with ITP and revealed WD soon after the diagnosis of ITP, and we also discuss the association of WD with ITP.

CASE PRESENTATION

Chief complaints

The proband (Figure 1A) was an 11-year-old Chinese girl who was admitted to our hospital with chief complaints of thrombocytopenia for 15 d, and tremor in her right hand for 3 d.

History of present illness

About 15 d previously, she experienced coughing, drooling of saliva, and dysarthria without fever and was admitted to a local hospital with a diagnosis of epiglottitis. A routine blood test found a platelet count of 54 × 10^9/L, after which she visited a hematologist. A bone marrow examination and testing for antiplatelet antibodies were performed. HLA Class I antibody was negative, but antibodies against GP IIb/IIIa, GP Ib/Ix, and GP Ia/type IIa were positive. In bone marrow smears,

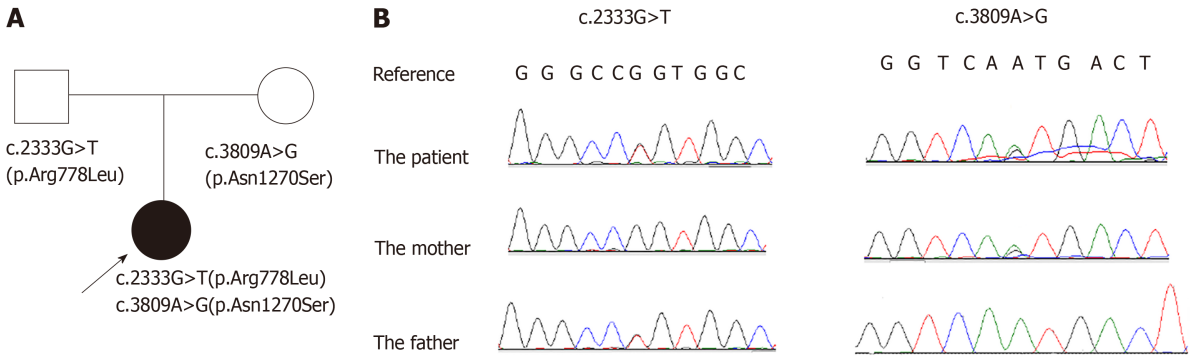

Figure 1 Wilson disease patient's family pedigree showing the mutations detected in *ATP7B*. A: The family pedigree. The arrow indicates the proband; her parents had no signs of Wilson disease; B: Non-synonymous mutations detected in the family. The proband had both mutations, while the c.3809A>G mutation was only detected in her mother and the c.2333G>T mutation was only detected in her father.

granulocytic and erythrocytic series were normal, while megakaryocytes appeared immature and platelet-producing megakaryocytes were not found. According to these results, ITP was diagnosed. The child was not treated for ITP because her platelet count was greater than 50 × 10^9/L and she had no signs of hemorrhagic tendency. About 3 days previously, she exhibited an involuntary tremor, with numbness in her right hand.

History of past illness
She was healthy in the past.

Personal and family history
Her medical and family histories were unremarkable, and she had not started menstruating. Her parents had no history of consanguinity.

Physical examination upon admission
On physical examination, she had dysarthria with normal orientation. She had no rashes, hemorrhagic signs, hepatomegaly, or splenomegaly. The pharyngeal reflex, abdominal reflexes, patellar tendon reflexes, finger-to-nose test, and Romberg's sign were normal. Barbinski signs were negative. Alternating movements with hands were slow, and her right hand trembled. Sensitivity to heat or pain stimulation was normal. Kayser Fleischer's (K-F) rings were found under a slit lamp.

Laboratory examinations
Laboratory investigations revealed serum platelet counts of 34-43 × 10^9/L (normal range, 100-300 × 10^9/L), and hemoglobin of 112-123 g/L (normal range, 120-140 g/L). Liver function tests revealed alanine aminotransferase (ALT) of 59 U/L (normal range, 7-40 U/L), aspartate aminotransferase (AST) of 65 U/L (normal range, 13-35 U/L), albumin (ALB) of 26 g/L (normal range, 40-55 g/L), total serum bilirubin of 45 μmol/L (normal range, 3.4-20.5 μmol/L), serum direct bilirubin (DBL) of 12.9 μmol/L (normal range, 0.3-8.5 μmol/L), and plasma ammonia of 35 μmol/L (normal range, 11-25 μmol/L). Her blood clotting profile showed a prothrombin time (PT) of 18.2 s (normal range, 11.0-14.3 s), prothrombin time activity (PTA) of 54% (normal range, 80-120 s), prothrombin time [international normalized ratio (INR)] of 1.53 (normal range, 08-1.15), activated partial thromboplastin time (APTT) of 55.5 s (normal range, 32.6-43.0 s), and fibrinogen of 1.27 g/L (normal range, 2.0-4.0 g/l). Plasma ceruloplasmin was 190 mmol/L (normal range, 220-330 mmol/L) and 24-h urine copper was 203 μg/24 h (normal value, <100 μg/24 h). Her lactic acid level and urinalysis were normal. Antibodies for viral hepatitis series (including hepatitis A, B, C, D, and E viruses) were negative. Tests of immunoglobin M for Coxsackie virus, herpes virus, cytomegalovirus, *Toxoplasmosis gondii*, rubella virus, adenovirus, respiratory syncytial virus, and *Mycoplasma pneumoniae* were negative. Antibodies for autoimmune hepatitis and connective tissue disease (including AMA-M2, LKM-1, LC-1, SLA/LP, Ro-52, PML, sp100, gp210, M2-3E, anti-nuclear antibodies, anti-ds-DNA, Sm, SS-A, SS-B, and ENA-Jo-1) were negative.

Liver biopsy was not recommended because of the patient's thrombocytopenia and disturbances in blood clotting functions. With written consent from her parents, genetic analysis for WD was performed. DNA was extracted from the peripheral blood samples, which were collected from the proband and her parents using the QIAamp Blood DNA Mini Kit (Qiagen, Germany). PCR was performed to amplify

each exon and its neighboring introns using an ABI9700 PCR amplifier (Life Technologies, United States). Direct sequencing was performed on the amplified DNA fragments using the ABI3500 sequencer (Life Technologies, USA) and the results were subjected to sequence analysis using Sequence Scanner v1.0 (Applied Biosystems, United States).

Genetic analysis showed that the proband had a compound heterozygous mutation in the *ATP7B* gene; c.2333G>T (p.Arg778Leu) in exon 8 and c.3809A>G (p.Asn1270Ser) in exon 18 (reference sequence: NM_000053.3). The former was inherited from her father and the latter was inherited from her mother (Figure 1B).

The detected mutations were interpreted according to the guidelines from the American College of Medical Genetics and Genomics and patient phenotype[21]. The PCR amplification and sequencing procedure were performed by Shenyang Kingmed for Clinical Laboratory (Shenyang, China), which provides third party inspection services. The hypothetical effects of the mutations on protein function were analyzed using the Polymorphism Phenotyping v2 (PolyPhen-2) prediction tool (http://genetics.bwh.harvard.edu/pph2/dbsearch.shtml), SIFT (http://sift.jcvi.org/www/SIFT_enst_submit.html), and MutationTaster (http://www.mutationtaster.org/index.html).

The c.2333G>T (p.Arg778Leu) mutation is known as a polymorphism (number rs28942074) and located in the transmembrane domain 4 (TM4). The p.Asn1270Ser mutation is located in the ATP hinge of ceruloplasmin. PolyPhen-2 and SIFT analyses suggested that the c.2333G>T mutation can negatively affect gene function, while MutationTaster suggested it is benign. PolyPhen-2, SIFT, and MutationTaster analyses suggested that the c.3809A>G mutation can be harmful (Table 1). A synonymous mutation, c.2310C>G (p.Leu770=) (rs398123136) in exon 8, was also detected in the proband and her father (data not shown).

Imaging examinations

The electroencephalogram (EEG) was normal. Brain magnetic resonance imaging scans showed a low signal intensity in T1-weighted images, and high signal intensity in T2-weighted images from the lenticular nucleus, caudate nucleus, and brainstem. Ultrasonography showed that the liver decreased in volume with an unsmooth surface and blunt edge, and the internal echogenicity was enhanced with tortuous hepatic veins. Splenomegaly was also observed.

FINAL DIAGNOSIS

WD was diagnosed.

TREATMENT

She was not treated for ITP because she had no hemorrhagic signs, but she was surveilled with the count of PLT. Liver protective therapy was begun when the patient's liver function was found to be abnormal. After the diagnosis of WD, oral penicillamine (from 125 mg to 1000 mg per day in one week, administered in four doses finally) and zinc sulfate (300 mg per day, administered in three doses) were administered, and intramuscular injections of dimercapto propanol (100 mg per day for two weeks then weaned off over two weeks) were also given after evaluating the benefits and possible side effects.

OUTCOME AND FOLLOW-UP

The 24-h urine copper was reexamined and was 261 μg/24 h after one month. The oral therapies were continued, and dimercaptopropanol was administered for another two weeks, weaned off over two weeks, repeated over three months, and then injected once weekly. At the 6-mo follow-up, the drooling of saliva had disappeared and the tremors in the patient's right hand and dysarthria had slightly improved, but the ultrasound results showed no marked changes. Platelet count increased and was sustained at about 60 × 10^9/L over the next month.

DISCUSSION

WD is an autosomal recessive disease. More than 500 mutations in *ATP7B* have been

Table 1 Functional evaluation of the *ATP7B* mutations detected

Base change	Exon number	Amino acid change	PolyPhen-2 analysis	SIFT analysis	MutationTaster analysis
c.2333G>T	8	p.Arg778Leu	Probably damaging	Damaging	Polymorphism
c.3809A>G	18	p.Asn1270Ser	Probably damaging	Damaging	Disease causing

identified in patients with WD and most patients are compound heterozygotes[6]. In the proband's family, c.2333G>T (p.Arg778Leu) and c.3809A>G (p.Asn1270Ser) were detected in the father and mother, respectively, and both mutations had been reported[13,15,22], in some cases as a compound heterozygote without thrombocytopenia[23,24]. The missense heterozygous mutations in the parents were autosomal recessives, even though the mutations induced abnormal protein function according to the bioinformatic analyses. It is possible that a normal allele produces sufficient protein to transport the copper in hepatocytes. But, when the patient inherited both mutations from her parents, the deleterious effects of the compound mutation could not be counteracted by a normal allele.

WD is characterized by the toxic accumulation of copper mainly in the liver and brain, but some other systems can be involved. Hemolysis has been reported as a presenting feature in 12% of 220 WD patients[25]. Thrombocytopenia with negative antiplatelet antibodies has been reported in children as a result of hypersplenism and/or a side effect of D-penicillamine therapy[26,27]. It is reported that the stability of biological membranes can be disturbed by an overload of copper which was accumulated on the membranes. If the membranes of erythrocytes are affected, hemolysis can be induced. We believe that platelets are more easily destroyed and cleared in patients with WD because the membranes of platelets can also be disturbed. It has been reported that the increased depolarization of the mitochondrial membranes can enhance the apoptosis of platelets in patients with chronic ITP[28]. The copper overload on membranes may also enhance apoptosis of platelets by disturbing mitochondrial membranes, but this will need to be investigated further. Serum copper is usually decreased in WD patients. Anemia and neutropenia were the most common hematologic abnormalities identified in copper deficiency patients[29,30]. It was considered that hypocupremia may be a reversible cause of bone marrow dysplasia that caused cytopenia[31]. Hypocupremia induced bone marrow dysplasia may be involved in thrombocytopenia.

In our case, autoimmune diseases and viral and *Mycoplasma pneumoniae* infections were excluded because of the absence of autoimmune, viral, and *M. pneumoniae* antibodies. Antibodies positive for GP IIb/IIIa, GP Ib/Ix, and GP Ia/type IIa and the bone marrow findings supported the diagnosis of ITP. Autoantibody-induced pathologies are quite complex[32]. In our case, platelets might initially have been destroyed because of the increased copper accumulation on the membranes. The GP was then released from platelet membranes and accumulated in blood. If the autoimmune response was triggered by GP, antibodies can be generated and the platelet count can decrease further. This is a reasonable explanation for the positive GP antibodies in our case, while these antibodies were negative in the other reported cases since the cases can be at different stages of the disease.

The ultimate therapy for WD is the clearance of copper, and the prognosis is better if therapy is started as early as possible. The first-line treatment for ITP is generally using corticosteroids, or intravenous immunoglobulin in severe cases[33,34]. But thrombocytopenia in WD cases has been reported to have a poor response to glucocorticoids[20,26,27]. After we evaluated the possible risks to the patient, glucocorticoids were not given. The observation that the patient's platelet counts ceased to decrease after copper clearance therapy also indicated the association of clearance of platelets with copper burden.

CONCLUSION

WD can associate with thrombocytopenia but the mechanism is still unclear. We recommend that anti-platelet autoantibodies should be tested in WD patients with thrombocytopenia in future to verify the association.

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CASE REPORT

Calcifying fibrous tumor of the mediastinum: A case report

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Abstract

BACKGROUND

Calcifying fibrous tumor (CFT) is a rare benign mesenchymal tumor that often occurs in deep soft tissue of children and young adults. CFT rarely occurs in the mediastinum.

CASE SUMMARY

In this paper, we describe a 31-year-old male patient with CFT in the mediastinum. The patient did not have any symptoms, and the posterior mediastinal lesion was unintentionally found during routine re-examination of thyroid cancer. The tumor had no adhesion to the surrounding tissue and was successfully and completely removed. Pathology showed a large amount of collagen-rich fibrous connective tissue. There was scattered dystrophic calcification and gravel in the fibrous tissue and a small amount of lymphocyte and plasma cell infiltration and lymphoid follicle formation in the interstitial fluid. In addition, findings showed 20 IgG4+ plasma cells per high-powered field of the diseased tissue, an IgG4+/IgG ratio of about 20%, and normal serum IgG4 levels. The final diagnosis was CFT of the mediastinum (CFTM). No evidence of tumor recurrence was observed by computed tomography at 3 mo after surgery.

CONCLUSION

IgG4+ plasma cell enlargement may occur in CFTM, but clinical manifestations and serological tests suggest that it is not IgG4-related disease. We speculate that it may be an independent tumor subtype.

Key words: Calcifying fibrous tumor; Mediastinum; IgG4-related diseases; Case report

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Core tip: Calcifying fibrous tumor of the mediastinum (CFTM) is a rare benign mesenchymal tumor that often occurs in children and young adults. Calcifying fibrous tumor rarely occurs in the mediastinum. Histological examination is the most important basis for diagnosis. Surgical resection is currently the primary means of treatment. There are no reports of recurrence of CFTM.

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INTRODUCTION

Calcifying fibrous tumor (CFT) is formerly called calcifying fibrous pseudotumor (CFP) and childhood fibrous tumor with psammoma bodies[1,2]. CFT often occurs in children and adolescents[2], with an average age of incidence of about 34 years[3]. It is slightly more predominant in female patients, with a male to female ratio of 1:1.27[3]. To the best of our knowledge, no deaths from CFT have been reported in the international literature, thus CFT *per se* is a benign mesenchymal tumors; nonetheless, 10% of cases recur after resection[3]. The etiology of CFT is unclear and may be related to myofibroblastic tumors, genetic and embryologic factors, and trauma[3]. The occurrence of CFT is rare, with only slightly more than 100 cases reported in the international literature as of 2018[2,3]. The most common locations of CFT include the stomach, small intestine, pleura, peritoneum, and mesentery, but it may occasionally be found in other places such as the heart and maxilla[3-5]; in particular, there are just nine reports of CFT in the mediastinum (CFTM)[6-13].

CASE PRESENTATION

Chief complaints and history of present illness

A 31-year-old male patient underwent thyroidectomy for thyroid cancer six months previously. A postoperative computed tomography (CT) examination revealed an oval mass in the posterior mediastinum. The patient had no symptoms such as cough, pain, or difficulty breathing.

History of past illness

Six months previously, the patient was diagnosed with thyroid cancer and underwent thyroidectomy.

Physical examination

No meaningful positive results were noted in the physical examination, except for the thyroid incision in the neck.

Laboratory examinations

Serum levels of tumor markers (α-fetoprotein, β-human chorionic gonadotrophin, and carcinoembryonic antigen) were normal. Serum IgG4 levels, erythrocyte sedimentation rate, rheumatoid factor, and anti-streptolysin and anti-nuclear antibodies were normal.

Imaging examinations

Chest CT examination revealed an oval tumor in the right posterior mediastinum, close to the spine; the tumor was of uniform density with a clear boundary and measured about 4.5 × 3.0 cm. The CT value was about 57 HU, and the enhanced CT value was about 113 HU (Figure 1). No tumor metastasis was detected on lung radiography, head CT, bone scan, or abdominal ultrasonography. The patient did not have a chest CT scan prior to the first surgery for thyroid cancer.

TREATMENT

Intraoperative exploration revealed that the oval mass was located in the right lower

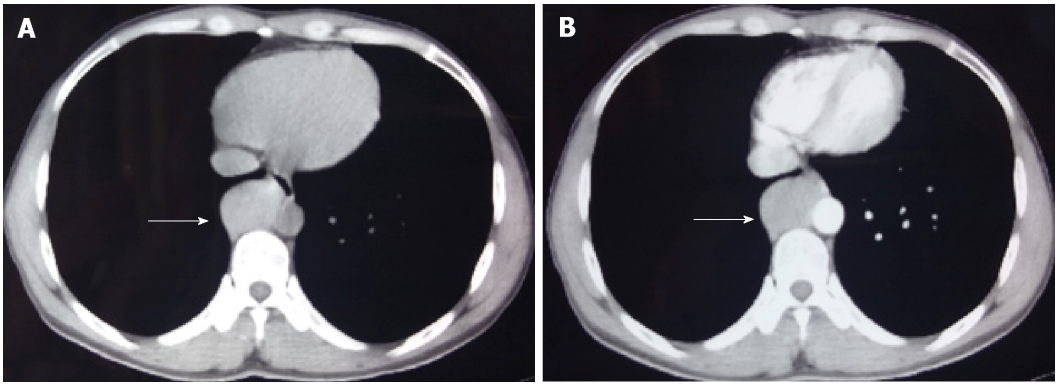

Figure 1 Chest computed tomography. The oval tumor (shown by the arrows) was located on the lateral wall of the abdominal aortic artery, with uniform density and a size of about 4.5 cm × 3.0 cm. The boundary with surrounding tissues is clear. The computed tomography (CT) value of the flat scan is about 57 HU (A), and the enhanced CT value is about 113 HU (B).

posterior mediastinum, was adjacent to T7–T9 and the descending aorta, and had no adhesion to the surrounding tissue. After the vessel was processed, the tumor was completely removed. The resected tumor was 5.5 cm × 3.5 cm × 2.5 cm in size and firm; the cut surface was grayish white.

Histological manifestations are as follows. Hematoxylin and eosin staining showed a large amount of collagenous fibrous connective tissue. There was scattered dystrophic calcification and boulder formation in the fibrous tissue. A small amount of lymphocytes and plasma cells had infiltrated the interstitial space, and lymphoid follicle formation was observed locally at 40× magnification (Figure 2A and Figure 2B).

Immunohistochemical examination showed that the tumor cells expressed CD99 and CD38, thus revealing the presence of plasma cells. The remaining immunohistochemical findings were EMA (−), SOX-10 (−), S100 (−), CD34 (−), SMA (−), ALK l (−), FXIIIa (−), and beta-catenin (−), and the Ki-67 proliferation index was about 5%. There were 20 IgG4+ plasma cells per high-powered field (HPF) and an IgG4+/IgG ratio of about 20%. The patient recovered smoothly after surgery and was discharged three days later. He did not receive radiotherapy or chemotherapy.

FINAL DIAGNOSIS

The final diagnosis of the presented case was CFTM.

OUTCOME AND FOLLOW-UP

The patient was followed 4 mo after surgery. The incision healed well, and there was no discomfort. Chest CT findings showed no tumor recurrence.

DISCUSSION

Including the present case, there are ten reported cases of CFTM, with a male to female ratio of 1.5 (six females and four males); this is slightly lower than the ratio of male to female in CFT (1:1.27)[3]. The age range for CFTM is 8–54 years, with an average of 31.3 years; this is slightly lower than the average age of CFT (about 34 years old)[3]. Six patients had no symptoms, and masses were found during a regular radiological examination or a review of a chest radiographic test[7,9,11,13]. Regarding symptoms, three patients had persistent cough[6,10,12], one patient had sternal discomfort[6], and one patient had hemoptysis and weight loss[10]. Regarding location, seven tumors occurred in the anterior mediastinum, and three occurred in the posterior mediastinum[6-13]. Most CFTMs were single tumors, and only one case exhibited multiple tumors[10]. Most CFTMs had clear boundaries with the surrounding tissues, and only two cases invaded the surrounding tissues, including the vein and thoracic duct[11,13]. Tumors were generally oval, and the longest diameter of a single tumor ranged from 4–11 cm[6,11]. The longest diameter of multiple tumors was less than 2 cm[10].

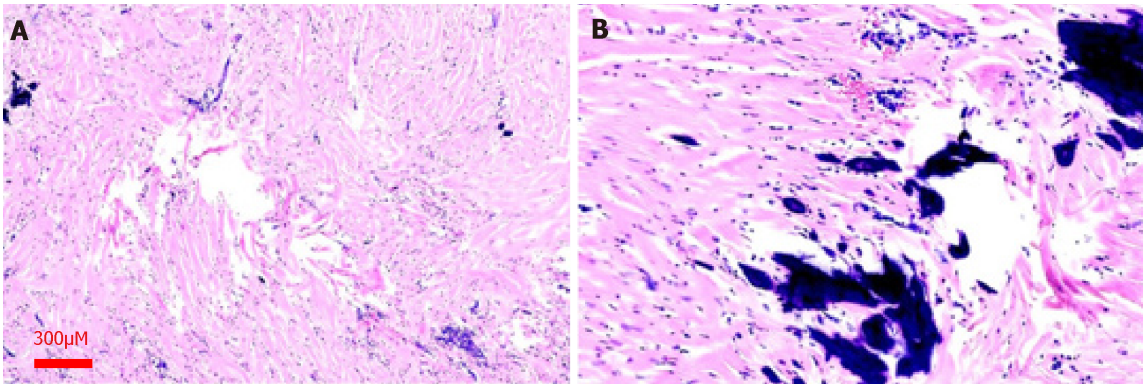

Figure 2 Hematoxylin and eosin staining. A: Tumor tissue consists of a large number of collagen fibrous connective tissue. The fibrous tissue can be seen to have scattered calcified foci. The interstitium is infiltrated by a small number of lymphocytes and plasma cells. The formation of lymphatic follicles is locally visible (magnification, ×40); B: Image shows dystrophic calcifications and gravel formation (magnification, ×100).

The diagnosis of CFTM has the following characteristics. First, CT shows isolated or multiple solid soft tissue tumors with a clear boundary[10], and the CT signal of the tumor is slightly enhanced after contrast injection. Some tumors show calcification on CT[13], whereas others have no significant calcification. Second, gross examination shows an oval tumor, with the longest diameter of 3-11 cm, a clear boundary, and an incomplete capsule. The cut surface is grayish-white, solid, and hard and could be accompanied by gritty and scattered yellowish lesion. Third, microscopic histological features include aberrant hyalinized collagen, fibrotic proliferation, lymphoplasmacytic infiltration, and psammomatous or dystrophic calcification[2,6]. Immunohistochemical spindle cells are positive for vimentin, CD10, FXIIIa, and occasionally CD34; they are negative for actin, desmin, S-100, NF, CK, CD31, and ALK1. To date, there are no specific immunohistochemical or genetic ectopic abnormalities that have been discovered in CFTM.

CFTM needs to be differentiated from other pleural intrapulmonary lesions such as solitary fibrous tumor (SFT), inflammatory myofibroblastic tumor (IMT), fibromatosis, and sclerosing thymoma. First, for SFT, there is a morphological feature that contains collagen fibers of varying thickness and shape; these can be keloid-like and resemble CFT. However, SFT can alternate between cell-poor and cell-rich regions. The spindle-shaped nuclei are vacuolated, are diffusely positive for CD34 and STAT6, and do not contain widely distributed gravel or dystrophic calcification. Second, for IMT, there is a late histologically visible scar-like structure, which is rich in plate-shaped collagen and exhibits low cell density and a small amount of plasma cell infiltration; however, IMT occasionally shows gravel and coarse calcification as well as proliferating myofibroblasts with hyaline-denaturing, cell-free collagen. Immunohistochemical staining of the proliferating fibroblasts shows diffusely actin-positive (50%) and ALKI-positive (50%) spindle cells; in contrast, CFT is actin-negative and diffusely FVIII-positive[8]. Third, regarding fibromatosis, characteristics include an unclear tumor mass, invasive growth, no capsule, frequent invasion of adjacent tissues, and presence in the muscle, aponeurosis, and deep fascia. Microscopic examination shows bundles of fibroblasts in the tumor. Calcification is rare, and β-catenin is positive. Fourth, in sclerosing thymoma, the interstitium has rich and transparent degeneration-like collagen similar to CFT, but contains epithelial cells and lymphocytes and is positive for epithelial markers.

The pathogenesis of CFT remains unclear. It was previously thought that part of the CFT was late stage sclerosis of IMT, but many scholars objected to it on the grounds that ALK-1 expression in the two lesions was different[8,9]. So far, there has been no molecular evidence that CFT is clonal[13] (Table 1), and there is no evidence of genetic dislocation in CFT. The pathological changes of CFT and IgG4-related diseases (IgG4-RD) are similar, and in recent years, some CFT cases have been found to have IgG4+ plasma cells and observable transparent vascular cavity calcification in the CFT lesion site[14,15]; accordingly, it has been considered that vascular lumen calcification in CFT results from occlusive vasculitis[16]. Therefore, it is speculated that CFT is related to IgG4-RD and that CFT may be a stage of development for IgG4-RD or an undiscovered IgG4-RD[17]. A study[17] reported one case of CFT in the ileum in which the lesion site showed 122 IgG+ plasma cells/HPF, of which 69 were IgG4+ pulp cells (56.56% of IgG+ plasma cells). Prochaska *et al*[18] reported one case of adrenal CFT, with an average of 183 IgG+ and 11 IgG4+ plasma cells in the lesion at high magnification. Zhang *et al*[15] reported one case of gastric CFT, with 62 IgG4+ plasma

cells in the lesion at high magnification; IgG4+ cells comprised 41% of IgG+ cells. Due to the current low number of cases and insufficient evidence, it is not clear whether the recurrence of cases is related to IgG4 levels and the effectiveness of the application of hormones or rituximab in treatment. As a result, the relationship between CFT and IgG4-RD needs further study. In addition, the report summarizes six other cases of IgG4-related CFT.

The present case was also been found to have about 20 IgG4+ plasma cells per HPF in the lesion tissue, with IgG4+ comprising 20% of IgG+ cells; however, we do not believe that the case can be diagnosed as IgG4-RD, mainly based on the following reasons. First, the patient was relatively young, and the site of the disease was not an immune-related organ. Second, the patient's serum was IgG4-negative, and there were no abnormalities in erythrocyte deposition rate, rheumatoid factor, anti-Streptococcus hemolysin, or anti-nuclear antibody. Third, the ratio of the total number of IgG4+ plasma cells to IgG+ plasma cells under the microscope was less than 40%. Fourth, no other physiological system was affected. This is consistent with CFT, which appears to be a benign tumor with a main treatment method of complete surgical resection [11]. Moreover, in a few cases, CFT can recur, and the recurrent lesion shows the same pathological morphology as the primary lesion[14]. In the ten published cases of CFTM, none exhibited recurrence, although this may be related to the small sample size and short follow-up time[19].

CONCLUSION

This article reports a case of CFTM. In some cases, CFT may have an increase in IgG4+ plasma cells and a cross-sectional histomorphology. However, it lacks the systematic clinical manifestations and serological manifestations of IgG4-RD. Clinicians should be vigilant not to misdiagnose it as IgG4-RD based on a clinical diagnosis.

Table 1 Characteristics of ten cases of calcifying fibrous tumor of mediastinum

Ref	Year	Age/sex	Symptoms duration	Localization	Gross examination	Treatment	Follow-up
Dumont *et al*[6]	1997	23/F	Cough with retrosternal discomfort	Anterior mediastinum	Firm, gray-white, homogeneous, and well circumscribed, non-encapsulated, 11 × 8 × 5 cm, 235 g	OP	Alive, NED after 18 mo follow-up
Jeong *et al*[7]	1997	54/F	-	Posterior mediastinum	8.5 × 6 × 5 cm, 320 g, clear boundary, grayish white, scattered in light, yellow specks	OP	Alive, NED after 49 mo follow-up
Sigel *et al*[8]	2001	37/F	NA	Anterior mediastinum	7.0 cm	NA	NA
Nascimento *et al*[9]	2002	27/M	-	Posterior mediastinum	7 cm	OP	NA
Nascimento *et al*[9]	2002	31/F	-	Anterior mediastinum	5.5 cm	OP	NA
Sleigh *et al*[10]	2010	22/F	Persistent cough, hemoptysis, weight loss	Anterior mediastinum and pleura	Circular mass, about 4.7 × 3.3 cm, clear boundary, uncoated film, gray-white; bilateral pleural nodules, 2–4.8 cm or smaller in diameter	OP (the anterior mediastinal and left pleural nodules were all removed, and the right side was not removed)	There was no recurrence in the left after 18 mo follow-up. No change in right lesion
Chang *et al*[11]	2011	51/M	-	Anterior mediastinum, involving vein	4.2 cm × 2.7 cm × 2.1 cm, clear boundary, uncoated film, gray to yellow	OP	NED after 11 mo follow-up
Chauhan *et al*[12]	2014	8/M	Chronic cough	Anterior mediastinum	7 cm × 5.5 cm × 3.6 cm, clear boundary, white, firm	OP	No recurrence (follow-up time not recorded)
Dissanayake *et al*[13]	2016	29/F	-	Anterior mediastinum, involving the thoracic duct	10 × 6 × 5.5 cm, 242 g, whitish tan, fleshy, homogeneous, surfaces with focal areas of yellowish tan, firm calcifications	OP (the thoracic duct was resected along with the mass)	NED after 3 mo follow-up
Present case	2019	31/M	-	Posterior mediastinum	5.5 cm × 3.5 cm × 2.5 cm, firm, grayish white	OP	Alive, NED after 4 mo follow-up

M: Male; F: Female; OP: Operation; NA: Not available; ND: Not done; NED: No evidence of disease; +: Yes; -: No.

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CASE REPORT

Brachiocephalic artery stenting through the carotid artery: A case report and review of the literature

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Abstract

BACKGROUND

As the population ages and people's living standards gradually improve, the incidence of cerebrovascular disease in China is increasing annually, posing a serious threat to people's health. The incidence of brachiocephalic artery stenosis in ischemic cerebrovascular disease is relatively low, accounting for 0.5% to 2% of patients, but its consequences are very serious. Herein, we report a case of brachiocephalic artery stenting through the carotid artery.

CASE SUMMARY

The patient was a 66-year-old man. He came to our hospital because of repeated dizziness and was diagnosed with ischemic cerebrovascular disease (stenosis at the beginning of the brachiocephalic artery). Cerebral angiography suggested that the stenosis of the brachiocephalic artery had almost occluded it. Contrast agent threaded a line through the stenosis, and there was reversed blood flow through the right vertebral artery to compensate for the subclavian steal syndrome in the right subclavian artery. To improve the symptoms, we placed an Express LD (8 mm × 37 mm) balloon expanding stent in the stenosis section. After the operation, the patient's dizziness significantly improved. However, after 6 mo, the patient was re-admitted to the hospital due to dizziness. A computed tomography scan of the head revealed multiple cerebral infarctions in bilateral basal ganglia and the right lateral ventricle. An auxiliary examination including computerized tomography angiography of the vessels of the head and cerebral angiography both showed severe stenosis in the brachiocephalic artery stent. During the operation, the guidewire and catheter were matched to reach the opening of the brachiocephalic artery. Therefore, we decided to use a right carotid artery approach to complete the operation. We sutured the neck puncture point with a vascular stapler and then ended the operation. After the operation, the patient recovered well, his symptoms related to dizziness disappeared, and his right radial artery pulsation could be detected.

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CONCLUSION
In patients with brachial artery stenosis, when the femoral artery approach is difficult, the carotid artery is an unconventional but safe and effective approach. At the same time, the use of vascular suturing devices to suture a carotid puncture point is also commendable. Although it is beyond the published scope of the application, when used cautiously, it can effectively avoid cerebral ischemia caused by prolonged artificial compression, and improper suturing can lead to stenosis of the puncture site and improper blood pressure, resulting in the formation of a hematoma. Finally, satisfactory hemostasis can be achieved.

Key words: Stenosis of the brachiocephalic artery; Trans-carotid approach; Vascular stapler; Case report

Core tip: Ischemic cerebrovascular disease is one of the diseases most harmful to the Chinese elderly population. Although the brachiocephalic artery stenosis is rare, it is very harmful. This article describes the possibility and safety of brachiocephalic arterioplasty through a carotid artery. It also illustrates the feasibility of suturing the carotid puncture site with a suturing device. We hope that it will inspire our peers.

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INTRODUCTION

As the population ages and people's living standards gradually improve, the incidence of cerebrovascular disease in China is increasing annually, posing a serious threat to people's health[1-4]. Ischemic cerebrovascular disease is the main type of cerebrovascular disease, accounting for more than 70% of cerebrovascular disease cases. It mainly includes vertebrobasilar insufficiency, cerebral insufficiency, transient ischemic attack, and cerebral infarction, and its main cause is atherosclerosis[5,6]. Regardless of the location, interventional therapy and open surgery are the standard methods of treatment. The stenosis or occlusion of the origin of the brachiocephalic artery has unique characteristics. If endarterectomy is used, making the incision in the neck makes it difficult to reach the target blood vessels and requires thoracotomy. These open surgeries are traumatic, risky, and difficult to perform. Interventional minimally invasive surgery has therefore become the main method to treat stenosis at the beginning of the brachiocephalic artery. The femoral artery approach is the most common approach used for endovascular exclusion of the aorta. However, in cases involving an abnormal aortic arch or obvious distortion of the arteries, the trans-femoral approach is difficult to use because of its low success rate and high incidence of complications during the perioperative period. In addition to avoiding the occurrence of this situation and achieving faster and more effective hemostasis, we used a Perclose Proglide vascular stapler to suture the carotid puncture point. Herein, we report a case sustaining the possibility and safety of brachiocephalic arterioplasty through a carotid artery. It also illustrates the feasibility of suturing the carotid puncture site with a suturing device.

CASE PRESENTATION

Chief complaints

A 66-year-old man presented with intermittent dizziness for two years and aggravation for 10 d.

History of present illness

The patient have been smoking for more than 30 years, with more than 20 cigarettes a day. He had drunk for more than 40 years and has stopped drinking now.

History of past illness

The patient had a more than 10-year history of type 2 diabetes and severe diabetic eye disease with blindness in the left eye. The patient self-injected long-acting insulin subcutaneously, 12 units per day. The patient denied having other diseases.

Personal and family history

His father died of heart disease at the age of 72 years. His mother and children are healthy.

Physical examination upon admission

First admission to hospital in March 2018: On physical examination, the patient's blood pressure in the left upper limb was 120/70 mmHg, and blood pressure was not detected in the right upper limb. The patient was conscious and able to answer questions fluently, no abnormalities were detected on a nervous system examination, and the right brachial artery and radial artery pulsations were not detected.

Second admission in October 2018: The pressures in the left and right upper limbs were 140/68 mm and 85/60 mmHg, respectively. The results of a nervous system examination were normal. The right radial artery pulsation could not be detected, but the left radial artery pulsation was accessible. The patient was conscious and could carry on a normal conversation but had slightly slurred speech.

Imaging examinations

Imaging studies including a computed tomography (CT) scan of the head, computerized tomography angiography (CTA) of the vessels of the head and neck, and cerebral angiography. Upon the first admission to hospital in March 2018, CTA of the vessels of the head and neck showed severe stenosis at the beginning of the brachiocephalic artery. A CT scan of the head showed no obvious abnormalities. Cerebral angiography showed that the stenosis of brachiocephalic artery had almost occluded it (Figure 1A). Upon the second admission in October 2018, a CT scan of the head revealed multiple cerebral infarctions in bilateral basal ganglia and the right lateral ventricle. CTA of the vessels of the head and cerebral angiography both showed severe stenosis in the brachiocephalic artery stent. Reverse blood flow through the right vertebral artery compensated for the right subclavian artery, and the left internal carotid artery was occluded.

Laboratory examinations

Laboratory examinations included routine blood tests, liver function, kidney function, electrolytes, coagulation function, routine stool, and urine tests and relevant immune factor tests, and no obvious abnormalities were found. Only blood lipid examination was abnormal (Table 1).

FINAL DIAGNOSIS

After a series of imaging examinations and laboratory tests, the patient was diagnosed with cerebral vascular stenosis caused by atherosclerosis (stenosis of the brachiocephalic artery).

TREATMENT

First admission to hospital in March 2018

In order to clarify the situation of vascular stenosis, we first performed cerebrovascular angiography. Cerebral angiography showed severe stenosis at the beginning of the brachiocephalic artery (Figure 1A). To improve the symptoms, including cerebral ischemia, and prevent cerebral stroke, interventional surgery was performed on March 19, 2018. We placed an Express LD (8 mm × 37 mm) balloon expanding stent (Boston, United States) in the stenosis section (Figure 1B). After the operation, the patient's dizziness significantly improved. His upper left arm blood pressure was 130/85 mmHg, his right upper arm blood pressure was 122/73 mmHg, and his right radial artery pulsation was detectable.

The patient continued oral aspirin (100 mg) and clopidogrel antiplatelet therapy (75 mg) after discharge.

Second admission in October 2018

In order to clarify the situation of vascular stenosis, we first performed

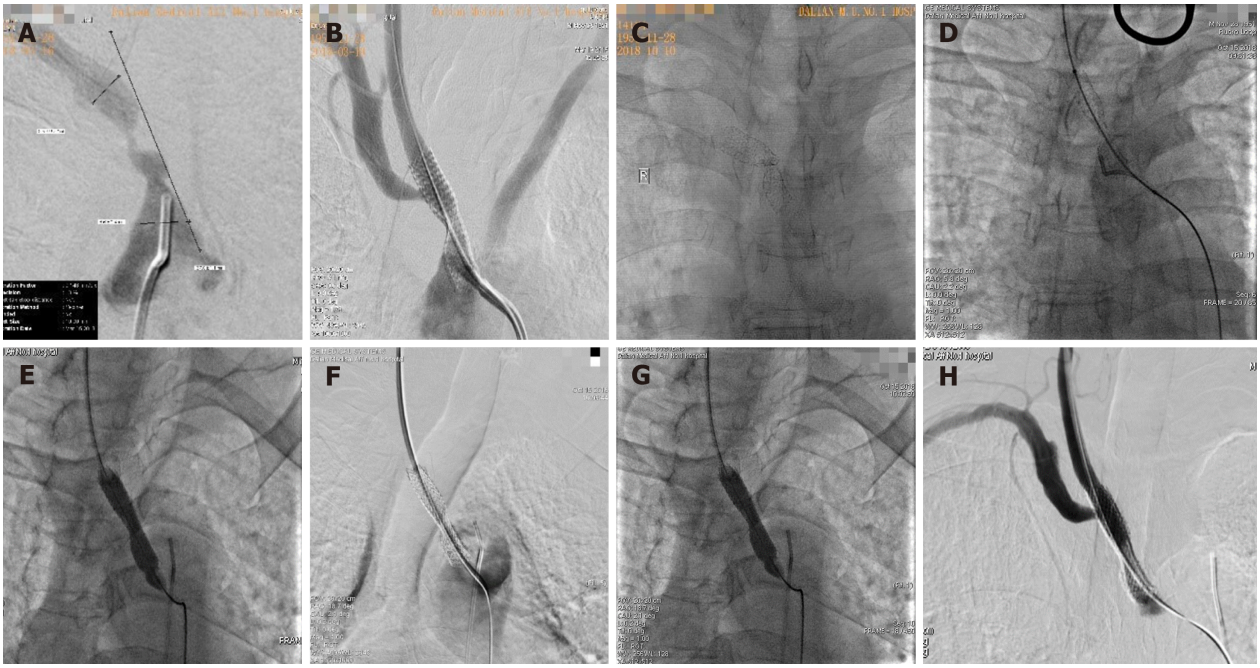

Figure 1 Cerebral angiography. A: Cerebral angiography showing severe stenosis at the beginning of the brachiocephalic artery; B: During the first procedure, the stent was placed in the brachial artery. Cerebral angiography showed a satisfactory stent position and shape, and the blood flow velocity returned to normal; C: During the second hospitalization, cerebral angiography showed severe stenosis in the brachiocephalic artery stent; D: A carotid approach was used to smoothly pass the guidewire through the stenosis section; E: An Evercross (6 mm × 40 mm) balloon was used to expand the stenosis section; F: A Wallstent (9 mm × 30 mm) stent was placed in the stenosis, and residual stenosis was observed in the stent; G: An Evercross (8 mm × 40 mm) balloon was used to expand the residual stenosis in the stent; H: The stent was opened satisfactorily.

cerebrovascular angiography. Cerebral angiography showed severe stenosis at the beginning of the brachiocephalic artery (Figure 1C). After clarifying the stenosis of blood vessels, we carefully studied the operation plan. During the operation, vascular access was conventionally established in the right femoral artery, and a 6F sheath tube was inserted. The guidewire and catheter were matched to reach the opening of the brachiocephalic artery. We repeatedly attempted but failed to use the guidewire to pass the stenosis segment. We believe that there were certain difficulties related to the surgical approach through the femoral artery, and we therefore determined that continuing attempts may have resulted in plaque detachment and affected the patency of distal cerebral blood vessels. Preoperative angiography confirmed that the patient's right carotid artery was unobstructed and showed no obvious stenosis or plaque. Therefore, we decided to use a right carotid artery approach to complete the operation. First, we punctured the right common carotid artery with a miniature puncture needle according to the Roadmap (the puncture point was located approximately 1 cm below the bifurcation of the carotid artery). After a 6F short sheath was inserted, we replaced the V-18 guidewire with a vertebral artery catheter and reversed the blood flow through the stricture to reach the ascending aorta (Figure 1D). Along the guidewire, we sent an Evercross (6 mm × 60 mm) (EV3, United States) balloon into the stenosis place to pre-expand it (Figure 1E). We placed a Wallstent (9 mm × 30 mm) stent (Boston, United States) in the stricture, and we then performed another angiogram. We found residual stenosis in the stent (Figure 1F), and we therefore sent an Evercross (8 mm × 40 mm) balloon (EV3, United States) through to expand the stenosis (Figure 1G). Angiography showed that the position of the stent was satisfactory, and the blood flow rate returned to normal (Figure 1H). We sutured the neck puncture point with a vascular stapler (Perclose Proglide, provided by Abbott Vascular, United States) and then ended the operation. After the operation, the patient recovered well, his symptoms related to dizziness disappeared, and his right radial artery pulsation could be detected. The blood pressure of the left upper limb was 135/88 mmHg, while that of the right was 128/80 mmHg. A follow-up performed 6 mo after the operation showed that there were no ischemic symptoms, such as dizziness, and no pulse.

OUTCOME AND FOLLOW-UP

Table 1 Abnormal laboratory test results

	First admission to hospital in March 2018	Second admission in October 2018
TG	2.14 mmol/L	2.07 mmol/L
TC	7.43 mmol/L	7.03 mmol/L
LDL-C	4.36 mmol/L	4.29 mmol/L

TG: Triglyceride; TC: Total cholesterol; LDL-C: Low density lipoprotein- cholesterol.

The patient continued oral aspirin (100 mg) and clopidogrel antiplatelet therapy (75 mg) after discharge. And we asked the patient to take the drug on time and in volume. A follow-up performed 6 mo after the operation showed that there were no ischemic symptoms, such as dizziness, and no pulse.

DISCUSSION

The brachiocephalic artery is the largest branch of the aortic arch and is also known as the brachial artery or the innominate artery. It extends distally into the right carotid artery and the right subclavian artery and supplies blood to the right cerebral hemisphere and right upper limb. Therefore, patients with brachiocephalic artery stenosis often have dizziness and no pulse in the right upper limb. Further development of this condition may lead to ischemic gangrene in the right upper limb and cerebral infarction caused by posterior circulation ischemia[7]. Common causes of stenosis of the brachiocephalic artery include atherosclerosis, multiple arteritis, and radiation arteritis. There are several treatments for patients with ischemic cerebrovascular disease who exhibit significant ischemic symptoms or are not treated with medicine. Traditional endovascular stripping, intracranial and extravascular revascularization, or interventional endovascular treatment can be selected. Endovascular stripping is one of the earliest surgical procedures that can be used in extracranial cerebral vascular stenosis. It is the first choice for the treatment of carotid stenosis in developed regions, such as Europe and the United States[8,9]. Several multicenter randomized controlled trials have confirmed the efficacy of endovascular stripping, such as the North American Symptomatic Carotid Endarterectomy Text[10], the European Carotid Surgery Test[11], the Asymptomatic Carotid Atherosclerosis Study, and the Asymptomatic Carotid Surgery Test. Resection of atherosclerotic plaques in the intima can reduce the incidence of cerebral infarction at low cost and with a high success rate. This is therefore one of the methods used to prevent and treat moderate and severe cerebrovascular stenosis[12]. However, this operation is more traumatic and has higher requirements regarding the patient's physical condition; it is therefore not suitable for patients with stenotic vessels that are too long or difficult to expose. Intracranial and extracranial revascularization can theoretically improve intracranial blood supply in patients with severe cerebral hemodynamic disorders; however, an international multicenter randomized controlled trial denied that this treatment method produced good effects. More recently, the Carotid Occlusion Surgery Study showed that the probability of recurrent cerebrovascular events occurring in patients undergoing bypass surgery has not decreased[13]. Due to the deep and complicated location of the brachiocephalic artery, it is very difficult to expose the operative field during surgery. In contrast, endovascular interventional therapy is widely used because of its advantages, which include a small amount of trauma, a fast recovery, a high success rate, a low rate of operation-related complications, and high mid and long-term patency rates[14]. Hüttl *et al*[15] reported 89 cases of brachiocephalic artery stenosis or occlusion treated with interventional therapy, and theirs is the largest case series published so far. The technical success rate was 96.6%, and the follow-up rate was 12%, with a follow-up period ranging from 12 to 117 mo. This shows that endovascular therapy is a simpler, safer, and more effective method for treating brachiocephalic artery stenosis. However, this approach is not perfect, and vascular stenting does have limitations. For example, in cases with inadequate brain protection, the incidence of postoperative cerebral infarction is higher[16-18]. In addition, the costs of this treatment are higher. With the improvement of interventional devices and techniques, the incidence of related complications has been significantly reduced, and an increasing number of patients therefore choose vascular interventional therapy[19-21].

The femoral artery approach is the most common approach used for endovascular exclusion of the aorta. However, in cases involving an abnormal aortic arch or

obvious distortion of the arteries, the trans-femoral approach is difficult to use because of its low success rate and high incidence of complications during the perioperative period. In addition, it is also difficult to apply the femoral artery approach in patients with thoracic aortic dissection, iliofemoral artery occlusive disease, or inguinal infection[22]. For the patient in this case, we tried the femoral artery approach first, but we could not pass the guidewire through the lesion after repeated attempts because of severe restenosis in the stent. An approach *via* the brachial artery and radial artery was also abandoned because of severe stenosis in the brachiocephalic artery, and his arterial pulsation was difficult to detect. Under these circumstances, the carotid artery approach, although unconventional, has become another option to establish vascular access. At present, no relevant articles have reported performing brachial arterioplasty *via* this approach. Some scholars have suggested that[23,24] compared with the conventional femoral artery approach, the carotid artery approach can reduce the risk of embolism because it avoids an abnormal aortic arch (type III aortic arch, long aortic arch, severe atherosclerosis of aorta, deformed aorta, *etc.*). Possible complications of using the trans-carotid approach include local nerve injury, local hemorrhage, or hematoma. Patients with severe atherosclerosis of the common carotid artery or stenosis at the puncture site are not suitable for this treatment if they also have a history of neck surgery or radiotherapy[25]. Bergeron[24] reported 52 cases in which carotid artery stenting was performed *via* the carotid artery approach, achieving a technical success rate of 100% and no occurrence of stroke, cardiovascular events, or hemorrhage. Ghosh *et al*[26] reported performing endovascular exclusion of abdominal aortic aneurysms *via* the carotid artery and also achieved satisfactory results. In our case, it was difficult to establish vascular access *via* conventional approaches, and the carotid artery approach was therefore adopted. The operation was successful without any serious complications. Drawing on the literature and the cases presented in our work, we propose that the carotid artery approach, although unconventional, can be used to complete surgeries on intracranial, extracranial, cerebrovascular, and even large blood vessels.

However, the carotid artery approach has disadvantages. If the condition of the carotid artery is poor or the carotid pulse weak due to stenosis and occlusion, puncture will be difficult. Moreover, no brain-protecting device has been specially designed for the carotid artery approach, which can cause plaque detachment during the operation. Therefore, the selection of a carotid artery approach should be carefully considered in these cases. It is suggested that cerebral angiography results should be refined preoperatively to clarify the condition of the bilateral carotid arteries. When puncturing the target carotid artery, the puncture should be performed using Roadmap or ultrasound[27]. On the one hand, this can clarify the puncture position and thereby avoid any damage to the carotid bifurcation. On the other hand, it can also avoid cerebral infarction caused by plaque detachment.

It is more difficult to apply compression hemostasis to a carotid puncture point than to the femoral artery. Bleeding and even subcutaneous hematoma can therefore easily occur. In severe cases, a huge cervical subcutaneous hematoma may even compress the esophagus, causing dyspnea[28]. To avoid the occurrence of this situation and achieve faster and more effective hemostasis, we used a Perclose Proglide vascular stapler to suture the carotid puncture point. Previous studies have reported that the Proglide vascular stapler is mainly used in the endovascular treatment of large vessels with the femoral artery used as the puncture approach[29]. Perclose prosglide vascular stitching devices can reduce postoperative recovery times and the time spent bed-bound. More importantly, it can also reduce subcutaneous hematoma and surgical scars[30]. Patients undergoing endovascular intervention often take antiplatelet or anticoagulant drugs for a long time before surgery, and this increases the risk of hemostasis complications at the puncture point. Since the 1990s, vascular suturing devices have been used in coronary interventions performed through the femoral artery, in which they have been shown to have advantages, such as reduced hemostasis and bed rest times[30]. Compared with traditional manual compression hemostasis, vascular suturing devices can also reduce the incidence of vagus nerve reflexes and deep venous thrombosis caused by excessive compression[31,32]. The main factors affecting the suture success rate include self-factors, such as obesity, severe calcification of the target vessel wall, and severe tortuosity of the blood vessels, as well as the size of the sheath. Therefore, before using a vascular stapler, whether the above situation exists should be clarified. The product instructions included with the Proglide Vascular Stapler state that for patients undergoing interventional catheterization or treatment, a 5F to 21F sheath is suggested to be used. The suture is delivered percutaneously after surgery to suture the common femoral artery puncture site. In this case, this approach was used to suture the carotid puncture points; while this is beyond the scope of the described applications, there were no complications,

such as vascular stenosis or subcutaneous hematoma formation. Finally, satisfactory hemostatic effects have been achieved. Compared with other hemostasis methods, such as manual compression hemostasis and vascular closure, using vascular suturing devices produces fewer complications[33,34]. This method also helps to reduce the time during which the puncture points must be pressed, shortens bed rest times, and improves patient comfort. Therefore, the authors believe that it is appropriate to carefully use a vascular stapler for the cervical vascular puncture point. The surgeons must be able to use the vascular suture devices skillfully. The puncture site must be adequately anesthetized to avoid vagus nerve reflex caused by local pain. The operation must be performed carefully to achieve safe and effective use of the vascular suture devices and make patients more comfortable[35].

CONCLUSION

In summary, in patients with brachial artery stenosis, when the femoral artery approach is difficult, the carotid artery is an unconventional but safe and effective approach. At the same time, the use of vascular suturing devices to suture a carotid puncture point is also commendable. Although it is beyond the published scope of the application, when used cautiously, it can effectively avoid cerebral ischemia caused by prolonged artificial compression, and improper suturing can lead to stenosis of the puncture site and improper blood pressure, resulting in the formation of a hematoma. Finally, satisfactory hemostasis can be achieved.

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CASE REPORT

An extremely rare pedunculated lipoma of the hypopharynx: A case report

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Abstract

BACKGROUND

Hypopharyngeal lipoma is a rare disease that can lead to asphyxiation after aspiration. Sclerotic lipoma in the hypopharynx is an extremely rare histological type. Hypopharyngeal lipoma should be resected in time after diagnosis.

CASE SUMMARY

An 86-year-old female patient presented to our department with a long pedunculated mass protruding from her mouth. Until this time, the patient had no dyspnea, dysphagia, or throat discomfort. Physical examination showed stable vital signs and clear consciousness. The pedicel was derived from the posterior wall of the hypopharynx. The tumor was smooth, hyperemic and dark red, about 10 cm long, and 4 cm wide. In order to prevent airway obstruction, the hypopharyngeal tumor was excised in emergent operation. The pharyngeal cavity was exposed by a mouth gag during the operation. A disposable plasma knife was used to completely remove the tumor along the base of the new organism, and no active bleeding occurred. The postoperative pathological results were sclerotic lipoma.

CONCLUSION

Lipoma in the pharynx is relatively rare. Patients with this condition must be referred immediately to Ear-Nose-Throat specialists and complete surgical excision should be performed as soon as possible to prevent serious complications, such as airway obstruction and death.

Key words: Hypopharynx tumor; Sclerotic lipoma; Plasma; Case report

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Core tip: Sclerotic lipoma in the hypopharynx is extremely rare. We report a case of hypopharyngeal sclerotic lipoma in a female patient. The lipoma was removed with plasma radiofrequency at low temperature under general anesthesia. The patient had no discomfort in the hypopharynx after surgery. The pathologic findings, clinical feature, and treatment of the disease are presented and discussed.

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INTRODUCTION

Up to date, less than 100 cases of pedunculated lipoma of hypopharynx have been reported[1]. Most of them are fibrous lipoma, as shown in histopathology. We here report a rare case of sclerotic lipoma. The first case of pedunculated lipoma of hypopharynx was reported by Colchester in 1952 in a patient who died of asphyxiation due to sucking in the lipoma[2]. Hypopharyngeal pedunculated lipoma grows slowly and generally has no obvious symptoms. When respiratory aspiration occurs, it can block the upper airway and kill the patient easily. The key to treatment is timely surgical resection.

CASE PRESENTATION

Chief complaints

An 86-year-old female patient presented to our department with a long pendulous mass protruding from her mouth (Figure 1).

History of present illness

The patient coughed up the mass in the morning and had no dyspnea or dysphagia until entering the hospital.

History of past illness

She had no history of surgery, chronic diseases, or allergies.

Personal and family history

She gave birth to two daughters, both *via* vaginal delivery, and she had no history of smoking or drinking. There was no similar history in the family.

Physical examination upon admission

A thick pendulous mobile mass was hanging outside the mouth, and the root was derived from the back wall of the hypopharynx. The surface of the mass was smooth and hyperemic. Other tests were normal.

Laboratory examinations

No abnormality was found in routine blood tests, biochemical tests, or electrocardiogram.

Imaging examinations

Postoperative chest computed tomography showed widened esophagus.

FINAL DIAGNOSIS

Sclerotic lipoma in the hypopharynx.

TREATMENT

The lipoma was removed with plasma radiofrequency at low temperature under

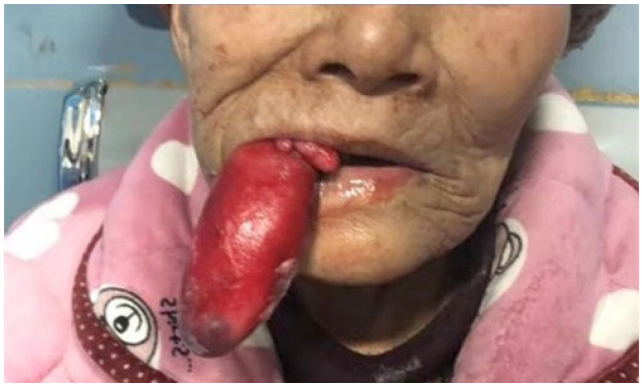

Figure 1 Mass protruding from the patient's mouth.

general anesthesia (Figures 2 and 3). The postoperative pathological results were fibrosclerosing lipoma, and immunohistochemistry was positive for vimentin, S100, and CD34 (Figure 4).

OUTCOME AND FOLLOW-UP

Electronic laryngoscopy showed good white membrane growth in the operative area 4 d after surgery. The patient had no discomfort in the hypopharynx.

DISCUSSION

Lipoma in the pharynx is relatively rare[3], and accounts for 0.6% of the benign tumors of the pharynx[4]. Lipoma is associated with endocrine factors, infection, chronic disease, infection, and heredity[5]. Lipoma of the hypopharynx grows slowly and generally has no obvious symptoms. Only a few patients may present with dysphagia, reflux foreign body sensation, or cough[6], but sudden airway blockage may occur[7]. Most of the patients do not visit the emergency department for treatment until a rapidly increased abdominal pressure appeared, such as cough, and the tumor came out of the mouth. Our patient, who had no special sensation for a long time, was admitted to the emergency department of our hospital after coughing out the mass. To our surprise, the large tumor did not cause swallowing and breathing difficulties. The reason may be that the narrow peduncle of the lipoma can pass through the pharyngoesophageal sphincter, and the tumor body grows slowly in the esophagus, resulting in expansion of the esophagus. The slow process makes the body adaptable to the tumor in this patient. Enlarged esophagus was seen on postoperative chest computed tomography (Figure 5).

The most serious complication of hypopharyngeal lipoma is asphyxia death. Once the tumor is diagnosed, the patient is likely to suffer from airway obstruction within a short period of time, which should be monitored closely. The first reported patient with hypopharyngeal lipoma died of asphyxia due to aspiration[4]. Therefore, timely surgical treatment is necessary. Currently, there are a variety of surgical approaches. Some authors recommend endoscopic resection for small lesions, while for tumors larger than 2 cm, open surgery is preferred[7]. Others suggest that endoscopic surgery has advantages of quick recovery and less trauma to patients, and endoscopic resection may also be used for larger masses[5,8]. In contrast to previous reports of similar cases, we used the plasma knife as the resection tool. The plasma knife has a good hemostasis function during the operation, keeping the field clear, and low temperature can minimize the damage to the surrounding tissues. Therefore, we recommend the plasma knife as a tool for tumor resection in similar cases. Specific tumor resection should refer to the size, location, and scope of the tumor as well as the experience of the surgeon. Considering that our patient was old and complicated with systemic diseases such as heart disease, we selected the plasma resection combined with endoscopic resection for tumor exposure by mouth gag. After the surgery, the patient was transferred to the ordinary ward and able to take a fluid diet. The patient and her family were satisfied with the treatment effect.

In this case, the pathologic type is sclerotic lipoma, which is a variant type in the pathological classification of lipoma and was first reported by Zelger *et al*[9] in 1997. It

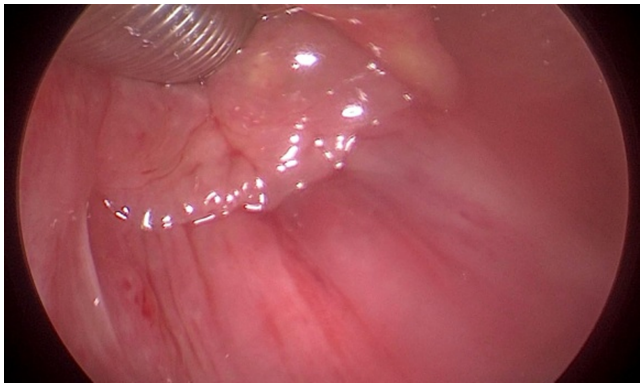

Figure 2 Root of lipoma was located in the posterior wall of the hypopharynx.

is characterized by spindle cells or fibroblast-like cells and dense intercellular matrix microscopically, in which fat cells are distributed[10]. The structure is similar to fibroma, except that there are different numbers of fat cells in the background of fibrosclerosis. To date, less than 30 cases of sclerotic lipoma have been reported worldwide[11], most of which occur in the limbs and scalp, and no literature has reported one on pharynx.

CONCLUSION

We report a rare case of hypopharyngeal pedunculated lipoma, and the pathological type is sclerotic lipoma. We recommend timely resection to prevent airway obstruction and death. Plasma resection is a good option during surgery.

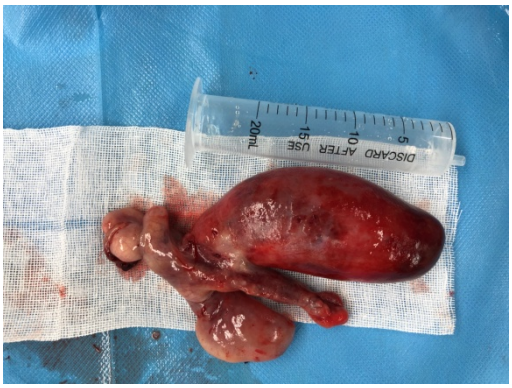

Figure 3 Lipoma in contrast with a 20 mL syringe.

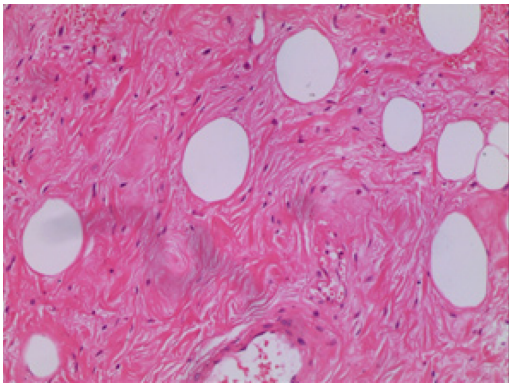

Figure 4 Histopathology revealed the distribution of adipocytes in dense fibrous tissue.

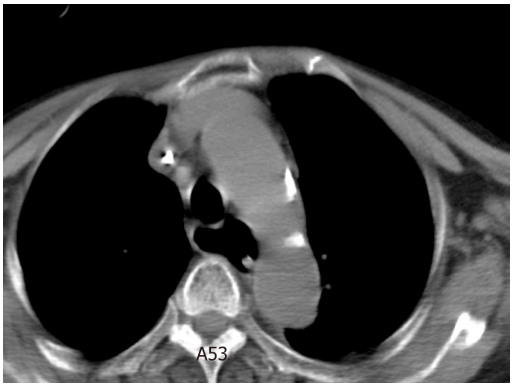

Figure 5 Postoperative chest computed tomography shows enlarged esophagus.

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