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ABOUT COVER

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EDITORIAL

Primary pulmonary meningioma and minute pulmonary meningothelial-like nodules: Rare pulmonary nodular lesions requiring more awareness in clinical practice

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Abstract

In this editorial, we comment on an article by Ruan *et al* published in a recent issue of the *World Journal of Clinical Case*. Pulmonary meningothelial proliferative lesions, including primary pulmonary meningiomas, minute pulmonary meningothelial-like nodules, and metastatic pulmonary meningiomas are rare pulmonary lesions. These lesions are difficult to differentiate from lung cancers based on clinical and imaging manifestations. Herein, we briefly introduce the clinical, imaging, and pathological characteristics of these lesions and discuss their pathogenesis to strengthen the current understanding of pulmonary meningothelial proliferative lesions in clinical diagnosis and therapy.

Key Words: Pulmonary meningothelial proliferation; Primary pulmonary meningioma; Minute pulmonary meningothelial-like nodule; Lung neoplasm; Rare pulmonary nodular lesion

Core Tip: Primary pulmonary meningiomas (PPM) and minute pulmonary meningothelial-like nodules (MPMN) are rare pulmonary lesions, which are difficult to differentiate from lung cancers due to similarities in clinical and imaging manifestations. To avoid misdiagnosis and overtreatment, PPM and MPMN should be considered in the differential diagnoses of pulmonary nodules of difficult clinical and/or imaging procedure diagnosis, particularly of asymptomatic patients. Differentiating PPM and MPMN from other pulmonary nodule diseases and assessing the malignancy of PPMs are difficult using only imaging-procedures, and histopathological examination thus remains the gold standard diagnostic procedure. Enhancing our understanding of MPMNs and PPMs and elucidating their pathogenesis will aid in the accurate differentiation of these lesions, to improve the clinical management of patients.

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INTRODUCTION

Pulmonary meningothelial proliferative lesions, including primary pulmonary meningiomas (PPMs), minute pulmonary meningothelial-like nodules (MPMNs) and metastatic pulmonary meningiomas (MPMs), are rare pulmonary lesions[1]. PPMs and MPMNs are usually discovered incidentally during physical examination or lung surgeries performed for other indications. In recent years, pulmonary nodules have become more commonly, due to the popularization of regular physical examinations and the development of medical imaging technology, thus raising the attention of clinical physicians and pathologists. Consequently, the incidence of MPMNs and PPMs have also significantly increased. Additionally, MPM is very rare, and diagnosis depends on whether the patient has a medical history of intracranial or spinal meningioma. These lesions are difficult to differentiate from lung cancers based solely on clinical and imaging manifestations. Furthermore, due to differences in biological behavior and treatment methods, it is also necessary to differentiate between PPM, MPMN, and MPM. In a recent issue of the *World Journal of Clinical Cases*, Ruan *et al*[2] reported a rare case of MPMN and explained its histomorphology and immunohistochemical features. In this editorial, we review the recent developments in the clinical, imaging, and pathological characteristics of PPM and MPMN and discuss their pathogenesis, in order to strengthen the current clinical understanding of pulmonary meningothelial proliferative lesion diagnosis and treatment.

CLINICAL FEATURES OF PPM AND MPMN

Meningiomas are common tumors of the nervous system originating from meningothelial cells of the arachnoid layer, often occurring in the intracranial or spinal canal. Meningiomas occurring in tissues and organs not covered by the meninges are termed ectopic meningiomas. PPM is defined as a primary meningioma in the lung tissue[3] and is classified as a rare condition under the category of lung tumors of ectopic tissues according to the World Health Organization (WHO) Classification of Thoracic Tumors[4].

Patients with PPMs and MPMNs usually present with no obvious symptoms, other than some atypical respiratory symptoms, although this can depend on tumor size, location, and accompanying diseases[5-7]. PPMs are usually found through imaging examinations[5,8]. Patients with PPMs are mainly middle-aged or older women[1,7,9]. The vast majority of PPMs are benign, well-circumscribed and solitary, with a favorable prognosis[5,10-12]. Therefore, the major therapeutic method for PPM is surgery, such as wedge resection or lobectomy[8,10,13,14]. It has also been suggested that a conservative approach, using close medical monitoring, is the best option for patients when the location, size, and number of smaller nodules challenge the accessibility for biopsy or resection[13,15]. Malignant PPMs are prone to recurrence or metastasis, leading to a poor prognosis[3,16,17]. Conversely, some reports have indicated that the prognosis of patients with malignant PPM is actually favorable owing to a typically slow progression[6].

IMAGING FEATURES OF PPM AND MPMN

Radiologically, PPMs most commonly appear in the form of pulmonary nodules[5]. However, the visual features of PPM nodules are not universal, for example, they can appear either as a solitary nodule or in clusters[7,15]. The distribution of nodules is frequently subpleural (less than 1 cm away from the visceral pleura), whereas others are intrapulmonary (greater than 1 cm away from the visceral pleura), with these two presentations accounting for 89.1% and 10.9% of cases, respectively[18]. The edges of PPM nodules can also either be close to pulmonary blood vessels or visually away from the bronchi, blood vessels, or pleura[7,18]. There is usually no preferred location for PPM in the lung[19].

PPM nodules usually manifest as a round homogeneous mass with well-demarcated borders on imaging examinations [5,7,13,18]. PPMs can appear with ground-glass opacity and cyst-like structures or calcifications, depending on the changes in the lesion[7,18]. Small, early-stage PPMs can manifest as ground-glass like lesions, which are easily confused with early-stage lung cancers. As the lesions grow, it can become difficult to differentiate them from other benign lung tumors, such as pulmonary hamartoma, sclerosing pneumonocytoma, lipoma, and certain infections (such as cryptococcal infection or virus infection). It is also difficult to differentiate PPMs from aggressive growths or multiple advanced lung cancer nodules[10].

Approximately 74.0% of PPMs are less than 3 cm in diameter[7]. The size of benign PPM tumors ranges from 0.4 to 6 cm in diameter (median: 2 cm), whereas malignant PPM tumors range in size from 1.5 to 15 cm in diameter (median: 6.4 cm)[7]. Although the average diameter of malignant PPMs is larger than that of benign PPMs, it is impossible to diagnose them based solely on tumor size. In one PPM case, the tumor measured 9.5 cm × 8.4 cm × 5.3 cm in size, but pathological examination confirmed it was benign[3].

MPMNs are usually smaller than PPMs, ranging from 2.5 to 5.0 mm in diameter on CT scans, with an average of 3.04 ± 1.12 mm[18]. Therefore, MPMNs are difficult to discover during imaging examinations. In addition, some larger nodules may be misrepresented as PPM due to their increasing prevalence[13].

PET/CT has been proven to be more accurate than traditional CT in evaluating solitary pulmonary nodules. Low uptake of 18F-fluorodeoxyglucose (18F-FDG), defined as a maximum standardized uptake value (SUVmax) less than 1.5-2.0, is generally associated with a benign diagnosis[20], however, PPMs can present with various CT manifestations in enhanced imaging[6,7,21]. Therefore, the pattern of enhancement may not help determine whether the PPM is benign or malignant[7,22,23]. PPMs exhibit anywhere from mild to high metabolic activity, and the average value of SUVmax is 4.36, ranging from 0.6 to 12.9, although this factor has no relevance for malignant evaluation[3]. A recent study reported increased 18F-FDG uptake in synchronous benign and malignant PPMs[23]. In patients with a history of cancer, PPMs or MPMNs can be easily mistaken as lung metastases due to deceptive increases in 18F-FDG uptake[24,25]. As such, a single 18F-FDG PET or contrast-enhanced CT examination may not be sufficient to evaluate patients with PPM.

Overall, the imaging manifestations of PPMs are often heterogeneous between different patients. Although accurate diagnoses based on imaging results is of great significance for developing appropriate treatment plans, it is currently impossible to differentiate PPM from other pulmonary nodule diseases or to differentiate between benign and malignant PPM through radiographic observation alone[6,10]. Thus, pathological examination is the most accurate method of diagnosis of PPM[7,8,10].

PATHOLOGICAL FEATURES OF PPM AND MPMN HISTOLOGICAL FEATURES

PPM, MPMN, and MPM have similar morphological and immunohistochemical features[1]. PPMs share the same histomorphology and WHO grading with that of central nerve system (CNS) meningiomas[8,19]. The premise underlying the diagnosis of PPM is that no CNS lesions are found in imaging modalities and that MPM can be ruled out[26]. In histopathological analyses, PPMs are typically categorized as epithelial, fibrous or transitional[13]. Further, they often exhibit spindle cells in whirlpool arrangements, while psammoma bodies can also be observed[5,6,8,13,15,19]. Pseudonuclear inclusions have also been reported in PPM histopathology[5,8,13]. No mitoses or necrosis has been identified in benign PPMs[5,8]. Finally, high proliferative activity with several mitotic figures and a high Ki-67 index may be indicative of malignant PPM[23].

MPMNs are interstitial cellular proliferations first identified in 1960[27]. MPMNs can often appear with no visible abnormal lesions, or sometimes as pale, reddish gray or brown, and regular or irregular solid nodules, with moderate or soft texture, and unclear boundaries[28]. Like PPMs, MPMN can also present as a solitary or multiple nodules. In cases of MPMN which present in a diffuse, miliary like distribution in both lungs (up to tens, hundreds, or uncountable), it is defined as “diffuse pulmonary meningeal epithelial neoplasia”. Under the microscope, MPMNs exhibit elliptical nodules ranging in size from 1.0 to 5.0 mm. Most lesions tend to be subpleural, or located in the pulmonary interstitium, and distributed along the alveolar septa. Tumor cells are spindle shaped or epithelioid and arranged in a nest or vortex shape around small veins. The nuclei are ovoid with delicate chromatin and indistinct nucleoli with a rich and eosinophilic cytoplasm and an ambiguous cell boundary. Pseudoinclusion bodies can be seen in some nuclei, and mitotic figures are rare[1]. It is difficult to differentiate MPMN from PPM because of their morphologic similarity, with an exception to their size differences[29].

Even though histological diagnosis of PPM may not appear challenging according to morphological and immunostaining characteristics, misdiagnosis remains an issue. When PPM contains psammoma bodies, it can be misdiagnosed as metastatic papillary thyroid carcinoma[30]. In addition, approximately 90% of patients with MPMNs have synchronous lung cancer-related lesions, including atypical adenomatous hyperplasia, adenocarcinoma *in situ*, minimally invasive adenocarcinoma, and invasive adenocarcinoma[1].

IMMUNOHISTOCHEMICAL FEATURES

PPM and MPMN often overlap in terms of histological and immunohistochemical phenotypes, which are consistent with the manifestations of CNS meningioma[31]. Specific immunohistochemical staining is useful for diagnosing PPM and MPMN and excluding other types of lung tumors.

Positive immunohistochemical staining for vimentin, epithelial cell membrane antigen, and progesterone receptor (PR) is common in most cases of PPM and MPMN[5,6,8,13,18], whereas markers such as S100, cytokeratin (CK), and CD34 may exhibit variable or inconsistent staining results[1,8,15,19,26]. The expression of thyroid transcription factor-1 and neuroendocrine markers, such as synaptophysin and chromogranin, are negative[6,31]. Tao *et al*[32] previously reported that MPMNs showed strong and diffuse cytoplasmic expression of somatostatin receptor 2A (SSTR2A) and that the expression rate of SSTR2A was higher than that of conventional markers of meningioma.

PATHOGENESIS OF PPM AND MPMN

The incidence of ectopic meningioma is very rare (2%) and can be found in various anatomical sites such as the head and neck region, and specifically in the sinonasal tract, ear and temporal bone, and scalp[33]. However, meningiomas originating from the lungs are even more rare. Although the pathogenesis of PPM and MPMN remains unclear, it is generally believed that ectopic meningioma is derived from pluripotential subpleural mesenchymal cells or heterotopic embryonic rests of arachnoid cells[3]. Some scholars believe that PPMs originate from MPMNs based on their similar morphological, immunohistochemical and ultrastructural features[8,34]. Kraushaar *et al*[35] suggested that PPM can appear as a giant form of MPMN. Presentation of MPMNs as a single lesion lacking genetic alterations may indicate its origin of reactivity. MPMN-omatosis syndrome, defined as the diffuse distribution of MPMN, may represent the transition between reactive and neoplastic proliferations[31].

PPM and MPMN are more common in females. Further, as both PPM and MPMN cells express PR, the occurrence of these tumors may be related to PR activity. Moreover, PR develop from normal meningeal epithelial cells and the expression in meningiomas has been well confirmed, with results indicating the potential presence of lung meningeal epithelioid cells in normal lung tissues[2].

Patients with malignant lung tumors tend to have a higher incidence of MPMN[18,36]. Further, the microenvironment theory suggests that the external environment is the main contributing factor to the occurrence of MPMNs. Therefore, lung diseases may provide a localized microenvironment that promotes the occurrence and development of MPMN[36]. One case report of a patient with a *BRCA2* germline mutation exhibited quadruple neoplasms, including PPM. *BRCA2* mutations can increase tumor sensitivity in patients, but further research is needed to determine whether the *BRCA2* germline mutation could be related to PPMs[37].

CONCLUSION

The accurate diagnosis of PPM and MPMN is challenging due to their rarity. To avoid misdiagnosis and overtreatment in clinical practice, PPM and MPMN should be considered as differential diagnoses of pulmonary nodules of difficult clinical and/or imaging procedure diagnosis, in particular asymptomatic patients. Differentiating PPM and MPMN from other pulmonary nodule diseases and assessing the malignancy of PPMs are difficult using only imaging procedures. As such, histopathological examination remains the gold standard for diagnosing PPM and MPMN. Moreover, as most PPM and MPMN have synchronous lung cancer-related lesions, ground-glass-like changes which PPM and MPMN often exhibit in imaging examinations may cause the primary malignant lung tumor to exhibit metastatic malignancy, leading to delayed or canceled treatment for the primary malignant lung tumor[29]. Wedge resection is so far the best option for the diagnosis and treatment of these lesions, as no recurrence has been reported in benign cases after complete resection. As PPM is usually benign, conservative monitoring by biopsy is also a good treatment strategy, particularly if the locations of the lesions are inconvenient for surgical operation. In these cases, asymptomatic patients can undergo long-term follow-up observation instead. Enhancing our understanding of MPMN and PPM features and elucidating the pathogenesis underlying the development of these lesions could help to increase the clinical accuracy of PPM and MPMN differentiation, thus improving the clinical management of patients.

FOOTNOTES

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Advances in clinical applications of bioceramics in the new regenerative medicine era

Noha Elshazly, Fayza Eid Nasr, Ayat Hamdy, Safa Saied, Mohamed Elshazly

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Abstract

In this editorial, we comment on the hard and soft tissue applications of different ceramic-based scaffolds prepared by different mechanisms such as 3D printing, sol-gel, and electrospinning. The new concept of regenerative medicine relies on biomaterials that can trigger in situ tissue regeneration and stem cell recruitment at the defect site. A large percentage of these biomaterials is ceramic-based as they provide the essential requirements of biomaterial principles such as tailored multisize porosity, antibacterial properties, and angiogenic properties. All these previously mentioned properties put bioceramics on top of the hierarchy of biomaterials utilized to stimulate tissue regeneration in soft and hard tissue wounds. Multiple clinical applications registered the use of these materials in triggering soft tissue regeneration in healthy and diabetic patients such as bioactive glass nanofibers. The results were promising and opened new frontiers for utilizing these materials on a larger scale. The same results were mentioned when using different forms and formulas of bioceramics in hard defect regeneration. Some bioceramics were used in combination with other polymers and biological scaffolds to improve their regenerative and mechanical properties. All this progress will enable a larger scale of patients to receive such services with ease and decrease the financial burden on the government.

Key Words: Regenerative medicine; Bioceramics; Chronic wounds; Bone defects; Clinical

applications

Core Tip: Some of the most common types of bioceramics used in regenerative medicine are solid prosthesis parts, bone-filling granules, metal prosthesis coatings, injectable bone cement, nanofibers, and porous scaffolds. Bioceramics can be bioactive (like bioactive glass) or resorbable ceramics (like β- and α-tricalcium phosphate, new forms of hydroxyapatite, and bioactive glass). This depends on the tissue's reaction to the grafted biomaterial. Bioactive and bioresorbable scaffolds form a stable bond and are gradually replaced with natural tissues. In this editorial, we discuss some clinical applications of bioceramics and the challenges that need suitable solutions.

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INTRODUCTION

Globally, nonhealing cutaneous wounds are a serious public health obstacle. According to the Global Burden of Disease (GBD) study, which gathered data from over 195 countries and territories, the prevalence of skin and subcutaneous diseases has increased dramatically over the past ten years, with a prevalence of 605036000 in 2015 compared to 492883000 in 2005[1]. An example of the most frequent causes of wounds are mechanical wounds (like persistent/Localized pressure), vascular deficiencies (like venous or arterial incompetence), or metabolic disturbances (like diabetes). In the United States, Chronic wounds affect the quality of life of approximately 2.5% of the population, costing healthcare services over 96 billion dollars with diabetes ulcers and surgical wounds being the costliest to treat[2].

In the same context, it was reported that bone defects resulting from nonunion fractures, trauma, osteomyelitis, surgical operation, segmental bone defects, and tumors are major causes of patient morbidity and impose a crippling financial strain on the healthcare system. An estimated $5 billion is spent annually in the United States on treating bone defects, while even more money is needed for bone grafts to treat tumors, damage to the bone, and other diseases linked to poor fracture repair[3]. Besides, a recent retrospective analytical study which was conducted in the United States reported that 7%–10% of long bone fracture cases that are surgically treated result in non-union with the younger population being at a declined risk when compared to the old population. Complex and shaft fractures were more likely to not unite[4]. It also reported that the estimated cost for treatment of such non-union cases varied from $33–$45K with an increased expense of $16–$34 due to non-union fracture reoperation. Costs were additionally raised due to coexisting infection by $46–86000[4].

The tissue engineering and regenerative medicine field was introduced to improve the quality of life. The new generation of tissue engineering was developed to produce new materials with 3D architecture and chemical characteristics similar to the tissue of interest. These scaffolds stimulate the endogenous body regeneration capacity in which stem cells from all over the body migrate to the site of injury and proliferate to restore the missed tissue[5]. Two accessions of tissue engineering have been introduced; the classic approaches in which a scaffold is used as a supporting structure to allow cell proliferation and the formation of a matrix to be ready for transplantation. The other one uses the scaffold as a 3D structure which provides the tissues with growth factors and required signals, so when it is included in the tissue it stimulates cell recruitment from all over the body to the site of the scaffold to form the required tissue matrix[6].

Scaffolds in tissue engineering have passed through various improvements. The first generation of tissue engineering scaffolds started as matrices that transfer cells and growth factors to the site of the defect and allow mechanical support until complete tissue formation. The next generation was developed to improve the performance of these materials and produce specific materials that can simulate the microenvironment of different tissue types with which the material interacts and produces intimate integration and communication with the surrounding tissue besides controlling the dynamics of cells. This includes the use of more complex biomaterials with a 3D architecture to mimic the ECM and affect cell behavior through distinct techniques. Scaffolds may be built from a wide range of natural and synthetic materials some of them bioresorbable or permanent, thanks to research and engineering efforts. Of these, bioceramics have received a lot of attention since, in general, their tissue reactions are advanced to those of metals and polymers[6,7].

Bioceramics possess lots of advantages that put them on top of the hierarchy of biomaterials utilized to stimulate tissue regeneration in soft and hard tissue wounds. Different types of bioceramics have been utilized to induce in-situ tissue regeneration due to their biocompatibility, multi-scale porosity, angiogenic, antibacterial, and mechanical properties[8,9]. In addition to that they could be designed using different techniques such as sol-gel, electrospinning, and 3D printing, which make them able to simulate any hard or soft ECM ultrastructure. For that reason, these scaffolds allow *in vivo* stem cell recruitment to the site of the defect, helping in building the cell niche which restores tissue integrity and function within a short frame of time[8,9]. The following sections will review different kinds of bioceramics and their clinical applications in hard and soft tissue engineering.

BIOCERAMICS IN HARD TISSUE REGENERATION

Bioceramics are categorized according to their bioactivity when implanted in a physiological environment into bioinert, bioactive, and bioresorbable[10]. Bioactive glasses, hydroxyapatite (HA), as well as tricalcium phosphate (TCP α and β), are the most studied bioceramics through the last 5 decades till the present. These bioceramics are the cornerstone of bioceramics that have regenerative potential concerning hard and soft tissues.

Recent investigations have demonstrated a wide range of advanced bioceramics that have been created by combining these three bioceramics with other biomaterials to enhance their regenerative properties for hard tissue applications[11]. Bioactive glasses attract interest in bone regeneration as they bind intimately with mineralized tissue. During the last 50 years, various types of bioactive glasses have been developed by altering their ions' composition, ratio, ultrastructure, and mechanism of action. Furthermore, some bioglasses are commercially available and FDA-approved[12].

Anesi and his research group investigated the osteogenic capacity of two novel bioglasses, BGMS10 and Bio-MS when implanted in a rabbit's femur in comparisoncompared to 45S5 BG[13]. Histomorphometric and histological observations of the implanted sites demonstrated that the neo trabeculae were thicker and uniformly distributed in the BGMS10/Bio-MS treated group when compared withthan in the 45S5 BG group. However, the quantitative amount of new bone was the same in all groups during 30- and 60-d post-grafting. Moreover, BGMS10 and Bio-MS showed preference over 45S5 BG as they possess slower dissolution rates, permitting the occurrence of two cascades of osteogenesis during the long-term implantation. Another study conducted by Liao *et al*[14] investigated the fast healing of rabbits' long bone segmental defects (radius and ulna) within 4 and 12 weeks after implanting Cu/Mg BGs. The group reported that Cu/Mg BGs appended advantages on the mechanical strength and porosity assessed in decreasing its degradation rate. As a result-Consequently, they sustained the released ions to maintain osteogenesis. Further, Cu/Mg BGs extract encourages the function of osteoclasts concurrently with upregulating the expression of osteopontin that is diminished in the late stage of ossification[14]. Gravina *et al*[15] demonstrated a case report of a 27 years old male with distal forearm laceration and loss of soft tissues where the ulna fracture was damaged by pseudoarthrosis six months post-surgery. Bioglass A bioglass spacer was implanted in the defect site after biological activation. Three and six months post-implantation, the defect spontaneously healed without the need for a bone graft[15].

Kresakova *et al*[16] have demonstrated HA implants in 12 female sheep with critical size defects in the load-bearing bone. During 6 months of follow-up, there was were no clinical signs of infection, inflammation, or pathological wound damage. At the histomorphological analysis level, the defect area showed no fibrous tissue formation and islets of osteoblasts and osseous tissue that indicate bone remodeling. In addition, the neo-bone showed similar organization of to the cortical and trabecular bone. On the other hand, one case showed no degraded and noor resorbed HA with a thin layer of cortical bone on its surface, which is evident that the shape and structure of the implant significantly influence significantly the biodegradability and resorbability of the implant. Histological analysis showed revealed tight connection and integration of the new bone inside the HA implant. Meanwhile, the new bone showed incomplete mineralization comparable to the physiological bone as well as the density of the neo-bone is was lower. Another study investigated the regenerative potential of a 3D printed brushite scaffold in an equine model with tuber coxae defect. In this study, the wounds of five horses were healed without complications, except for one that was infected at 3 days post-operation. The hHistomorphometric and histological analysis at 6 months post-operatively showed that, the newly formed bone fully grew inside the microporous brushite implant with tight contact with the host bone. As well a high amount of collagen and mineralized tissues were deposited inside and on the surface of the scaffold[17].

The osteoconduction and osseointegration capabilities of a novel constructed 3D porous hydroxyapatite (3DP-HA) were evaluated by Kijartorn *et al*[18]. In this clinical trial, 3DP-HA was grafted around dental implants after teeth extraction from 30 patients to enhance ridge preservation. The regenerative ability of the HA scaffold was compared with that of a commercially available bone graft[18]. Histological/ histomorphometric results showed the apical and coronal distribution of the new bone in the sockets. Furthermore, 3DP HA3DP-HA minimized the ridge resorption and increased the stability of the implant. Another study used a mixture of biphasic tricalcium phosphate and HA in the Maxilla for sinus lifting in elderly patients. Bone biopsies showed the formation of lamellar bone with the presence of osteoblast in the peripheral and woven bone after 6 months post-after material implantation. High expression of osteocalcin protein in the areas of grafting was also observed[19]. It is important to mention that the ionic portion of bioceramics influences various osteogenic and angiogenic genes such as HIF-1α and TNF-α for bone regeneration and PI3K/AKT and MAPK/ERK cascades for vascularization[14]. Conversely, the porosity of the material is considered a critical characteristic which has to be controlled for inadequate nutrient delivery and determining the mechanical strain required for cellular attachment and proliferation[20]. One of the obstacles to use clinically the bioceramics is the complexity of matching patient–specific destruction besides the alteration in the degradability behavior of some bioceramics *in vitro* or *in vivo*. The formation of the HA layer may decrease the rate of implant resorption and decrease its solubility[17]. Recently this obstacle has been resolved by constructing of implants *via* 3D printing technology[21]. Another significant impediment is bacterial infection transmission after-surgical implantation. Zhao *et al*[22] summarized recent strategies of providing the antibacterial ability tobioceramics with preservation of bone healing encouraging.

BIOCERAMICS IN SOFT TISSUE REGENERATION

Soft tissues represent an extensive part of the human body. Injuries to soft tissues are common as they are exposed organs [23]. ECM of soft tissues is mainly composed of fibrous proteins (*i.e.*, collagen, elastin), glycosaminoglycans (GAGs: *i.e.*, hyaluronic acid, chondroitin sulfate), and proteogly-cans (*i.e.*, aggrecan, versican), which contribute to the elasticity of

these tissues[24]. Regeneration of the skin, orbit, cardiac, nerves, lung, and many other examples of soft tissues requires the introduction of several biomaterials that meet the required criteria, especially in immunocompromised models and critical-sized defects[23]. Tissue engineering scaffolds proposed for soft tissue applications must acquire general criteria including biocompatibility, biodegradation, and proper mechanical properties; in addition to specific criteria according to the site of application as angiogenesis and electrical stimuli transmission. Bioceramic scaffolds offered promising results in that area[25].

Different generations of bioactive glasses were introduced for skin regeneration and showed promising results. An example of this was a mixture of different types of bioactive glass prepared in an ointment form[26]. Another form was borosilicate bioactive glass nanofibers, which were applied in full-thickness skin defects in rabbit animal models, where the very early ion release since the first day enhanced the cascade toward cutaneous regeneration[27]. The results were in agreement with those of an earlier study conducted on dogs[28] where 13–93Borate-based bioglass promoted full-thickness wound healing. A recent study also evaluated the incorporation of gold nanoparticles into bioactive glass on skin wounds in rats to accelerate its healing cascade[29].

In the ocular regeneration field; glass ceramics were proposed as orbital implants in rabbits as early as 1999s, showing an accelerated fibrovascular effect. Trials were made to add bioactive glass particles to polyethylene implants to produce MedporR Plusr spheres. In human clinical trials, these implants showed satisfying results with no conjunctival inflammation or thinning. Biosilicate®-derived implants were first introduced in 2010, and since then animal and early clinical trials have shown favorable biointegration, biocompatibility, and antibacterial effect[30].

Bioceramics showed interesting results in the nervous system regeneration. Phosphate glass microfibers showed improvement in different functions when applied to transacted spinal cords in a rat model[31]. Beta-tricalcium phosphate allowed nerve regeneration and restoration of functions among a swine model with a 35 cm long nerve injury[32]. Hydroxyapatite nanoparticles were reported to remarkably accelerate nerve regeneration in an induced experimental model[33].

Bioactive glass repaired induced ulcerative colitis wounds in rats through significant upregulation of some inflammatory pathways[34]. Despite the wide range of applications of bioceramics in soft tissue regeneration, the introduction of bioceramics in lung and cardiac tissue regeneration research is still uncommon[24].

Bioceramics have been proven to be good candidates for soft tissue regeneration through the byproducts resulting from biodegradation. Calcium ions for example; increase the pH of the site resulting in antibacterial activity. Silica and calcium target many cellular behaviors, whereas copper and boron enhance angiogenesis and anti-inflammatory effects. whereas silver ions play a crucial antibacterial role[23].

The promising results of bioceramics in soft tissue regeneration have encouraged their use in immunocompromised models as those reported by Elshazly *et al*[35]; in testing the regenerative capacity of borosilicate bioactive glass nanofibers in oral mucosal defects in diabetic-induced rabbits. The mucosal wounds grafted with BGnf showed inflammation-free wound closure, increased cellular activity, and neo-vascularization since the first week opposite to what happened in the wounds that were left empty, where infection and open wounds persisted. These exciting results introduced a new soft tissue scaffold in a wet area borne with microorganisms as the oral cavity and in a diabetic model [35]. Fibrous 13-93B3 borate bioactive glass having the trade as “Dermafuse” [Mo-Sci Corporation (United States)], “ReadiHeal TM” and Mirragen®(ETS Wound Care, MO, United States) with “cotton candy” like appearance have also achieved promising results in wound healing applications with interesting results in chronic wounds in diabetic patients [24].

Introducing hard bioceramics for soft tissue regeneration was faced with many challenges. From the physico-mechanical point of view, the inconsistency between the bioceramics and the delicate nature of these tissues; in this context, they were produced in fibrous forms as the cotton-like 13-93B3 borate bioactive glass used in wound healing applications, or they were used as composites with other polymeric scaffolds. Another aspect is that there is a structural variation between different types of soft tissues that makes one type of bioceramic that is suitable for all soft tissue applications a very difficult choice[24]. For example, in cardiac tissue applications concerns were reported about using bioactive glasses, claiming that they are electrical insulators as well as promote calcifications in the cardiac apparatus[24].

BIOCERAMICS FROM BENCH TO CLINICAL APPROVAL

In the last five years, bioceramics have shown promising results in hard and soft tissue repair; *in vitro* and *in vivo*. However, evaluation of its impact on humans is insufficient compared to the abundance of preclinical studies and the diversity of the bioceramic products. Even though clinical trials of bioceramics applications in diseases implying tissue loss; excluding oral diseases, are few, the results demonstrated a well-tolerated capability of governing tissue regeneration with and without autologous cells.

In a randomized phase I clinical trial, Deinsberger *et al*[36] reported the effect of topical administration of zeolite-mineral purified clinoptilolite-tuff (PCT) on artificial cutaneous wounds. Improved wound healing without pain stimulation or signs of severe inflammatory response subsequent to the application of PCT was observed. In periodontitis, Bodhare *et al*[37] used 45S5 bioactive glass (BG) morsels to treat intrabony defects in a randomized controlled trial. A decrease in the defects' depth, mesiodistal, and buccolingual width, in addition to the elevation of the alveolar crest level was detected which refers to periodontal restoration. These results were enhanced by the application of BG with autologous platelet-rich fibrin.

Bioceramic products aid in the acceleration of bone healing by providing a matrix that facilitates cell attachment and hence regeneration as in the case of applying MBCP+™, a bone graft prepared of 20% Hydroxyapatite (HA) and 80% beta-

tricalcium phosphate (ß-TCP), coupled with autologous mesenchymal stromal cells to reconstruct long bone fracture in phase I/II clinical trial conducted by Gómez-Barrena *et al*[38]. Healing of tibial, femoral, and humeral non-unions was displayed with no adverse events as a result of the treatment. Herr *et al*[39] found that far-infrared ceramic wraps help in curing lower limb venous ulcers which were represented by a decrease in ulcer dimensions and enhancement of tissue type. It is worth mentioning that some individual cases involve bone defects such as heel osteomyelitis in a Guillain-Barré Syndrome and Charcot foot in a diabetic patient, and sternal cleft showed bone regeneration in the presence of bioactive glass and alumina[40-43].

CAPTURING THE OVERALL IMAGE

Bioceramic scaffolds have a large variety of forms and formulas which consequently results in many applications. Indeed, this opens up new horizons of hard and soft tissue applications, but at the same time results in fewer biomaterial approvals for clinical use. In the past years, testing of bioceramics in large animals was a common scene. Scaffolds such as Hydroxyapatite and bioglass were tested in animal models as goats, sheep, monkeys, and pigs. Over the years this number has declined to a fewer number of studies due to the increased cost of animal welfare and the rise in ethical standards across years. In a recent study, the percentage of bioceramics applications in large animals was estimated at 28% of the studies with the dog animal model representing the highest percentage at 11.11. In the same context, the small animal models occupied the largest percentage with 33.33% of studies conducted in rabbit animal models and 41.27% of studies conducted using rodent animal models[43]. When it comes to clinical studies, they might be categorized more as case studies or case series with a few numbers of clinical trials that were mentioned in the previous section. Each of these clinical studies adopted a different type of bioceramic scaffold according to the required properties.

One of the main challenges in the application of bioceramic materials is adjusting the balance between the mechanical properties and the level of porosity. This enables the scaffold to be used in the load-barring area and large-size defects. Commonly, this goal is difficult when using bioceramics alone; therefore, in most cases, the bioceramic material is combined with a polymeric material to achieve this difficult equation of bioactivity, hardness, and biodegradation. An example of that, is the work conducted by Kim *et al*[44] in which bioactive glass(BGS 7) was incorporated with polycaprolactone as a 3D printed scaffold. This composite was investigated in craniofacial reconstruction in patients with craniofacial defects in load-bearing areas. This composite possesses bioactivity gained from the ionic dissolution of bioactive glass on the surface of the scaffold and sufficient strength thanks to the polymer scaffold[44]. The same was observed in the soft tissue application where researchers reported the disappearance of bioactive glass from the wound surface at day one postoperatively[27,28]. One of the main advantages of bioceramics is the antibacterial effect at the site of application. This allows the use of this material in sites subjected to infection as in the oral cavity or immunocompromised conditions such as diabetic wounds[35]. Indeed, the new technologies used in the fabrication of bioceramics will help improve their properties and as a result their application range[45].

CONCLUSION

Bioceramics has an advanced effect on stimulating in situ tissue regeneration in hard and soft tissues. The variation in ultrastructure and chemical composition gives the bioceramics different degrees of porosity, biodegradation, mechanical, antibacterial, and angiogenic properties. This allows bioceramics to be utilized in different body sites providing the required niche for tissue regeneration and initiating the stem cell recruitment required for wound healing. Despite that, more investigations and studies are required to encourage the use of bioceramics as a substitute for grafts in all suitable applications to reduce the cost of medical services and improve patients' quality of life.

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EDITORIAL

Climate change and human health: Last call to arms for us

Antonio Corrente, Maria Caterina Pace, Marco Fiore

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Abstract

Climate change, now the foremost global health hazard, poses multifaceted challenges to human health. This editorial elucidates the extensive impact of climate change on health, emphasising the increasing burden of diseases and the exacerbation of health disparities. It highlights the critical role of the healthcare sector, particularly anaesthesia, in both contributing to and mitigating climate change. It is a call to action for the medical community to recognise and respond to the health challenges posed by climate change.

Key Words: Climate change; Carbon footprint; Sustainability; Greenhouse gases; Anaesthetic gases; Environmental impact; Disposable laryngoscope blades

Core Tip: This editorial sharply focuses on the interplay between climate change and health, advocating for a proactive healthcare response, especially highlighting the environmental impact of anaesthesia and critical care medicine. This editorial is intended to be a call to action for the medical community to acknowledge and address the health challenges posed by climate change.

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INTRODUCTION

Climate change, which was once a looming threat, has rapidly transformed into the largest health danger humanity has ever faced. Recent data reveals that the last decade was the hottest on record, a stark indicator of the escalating climate crisis[1]. The evolving climate scenario is a mosaic of environmental catastrophes, each contributing to a complex array of health challenges. The World Health Organization predicted that between 2030 and 2050 climate change will directly or indirectly cause approximately 250000 more deaths *per* year. The direct damage costs to health are estimated to be between USD 2-4 billion/year by 2030[2]. Despite any denial or scepticism, this data confirms that climate change is an essential public health concern. Interestingly, the healthcare sector plays a dual role in this narrative–both as a victim and a contributor. Specifically, anaesthesia, a cornerstone in medical procedures, has an often-overlooked environmental impact. This editorial aims to galvanise collective action and foster a dialogue on sustainable solutions. We will explore the multifaceted impact of climate change on health, the urgency of immediate and coordinated action and the role and responsibilities of healthcare systems, with a special focus on anaesthesia.

THE IMPACT OF CLIMATE CHANGE ON HUMAN HEALTH

Climate change, in conjunction with various environmental stress factors, both natural and anthropogenic, significantly affects human health. Since 2016, The Lancet has annually published The Lancet Countdown on Health and Climate Change, a report based on international contributions that tracks the impact of climate change on health. This document is recognized as one of the most pivotal indicators of the health consequences of climate change and global warming[3]. Additionally, the Centers for Disease Control and Prevention highlights the health risks associated with an increasingly unstable climate[4]. Key threats identified in recent reports include the increasing frequency of heat waves and extreme weather events, such as heavy rainfall, floods, droughts, more intense storms like hurricanes, sea level rise and air pollution. These changes have the potential to have a negative impact on health[3,4]. The increased frequency and severity of heat waves correlate with increased morbidity and mortality, especially in vulnerable groups like the elderly and children. Heat-related illnesses, such as heat stroke, often have fatal outcomes and exacerbate chronic conditions, including respiratory, renal and cardiac diseases. They also indirectly impact health by limiting physical activity, which can lead to obesity[5,6]. The deterioration of air quality due to global warming and the increase of atmospheric particulate matter, have led to an increase in respiratory diseases, such as asthma and chronic obstructive pulmonary disease[5,7]. Climate change is facilitating the spread and geographical expansion of infectious diseases such as dengue, zika, chikungunya and malaria. Variations in temperature, rainfall and humidity aid the proliferation of disease vectors like Aedes and Anopheles mosquitoes, leading to increased disease incidence and their extension into previously unaffected areas, further accelerated by the global movement of people and goods[5,8]. Rising temperatures amplify the risk of waterborne bacterial diseases, notably cholera and gastroenteritis, due to the enhanced survival and proliferation of pathogens in warmer waters. This risk is exacerbated by frequent torrential rains and floods, which compromise potable water access and cause the destruction of sewerage infrastructure, elevating pathogen exposure[9]. Moreover, these infectious diseases, often lead to diarrhoea, and increase malnutrition by impairing nutrient absorption and utilisation. Climate variability adversely affects agricultural production, impacting food availability and quality, thus directly affecting human health[10]. Beyond physical health, climate change profoundly affects mental health. Extreme climate-related events, like floods and wildfires, are linked to increased mental health disorders, including anxiety, depression, and post-traumatic stress disorder[11,12]. It is critical to underline that the health impacts of climate change are neither uniform nor equitable. These effects disproportionately burden the most vulnerable and least resilient segments of the population, including low-income communities, minorities, people with pre-existing medical conditions and children[3, 13]. In particular, early childhood exposure to pollutants and climate changes can have long-lasting effects on physical and cognitive development[14,15].

HEALTHCARE SYSTEMS AND CLIMATE CHANGE: A TWO-FACED JANUS

Carbon footprint is a key metric that, more effectively than any other variable, enables us to assess the environmental consequences of human activities on climate change and, consequently, on global warming[16]. It quantifies the total greenhouse gas (GHG) emissions, mainly carbon dioxide, resulting from individual, organisational or product-specific activities. This measure is central to understanding and mitigating the impact of human actions on the environment[17]. The healthcare sector, often perceived as a beacon of healing and care, ironically contributes significantly to environmental degradation primarily due to energy-intensive operations, waste production, and resource utilisation[18,19]. It has been estimated that if the healthcare industry were a country, it would be the fifth-largest GHG emitter on the planet[8]. Globally, the healthcare sector is accountable for a substantial share of GHG emissions, ranging from 4.4% to 4.6% of total emissions, primarily due to energy-intensive operations, waste production and resource utilisation[20]. Notably, emissions vary based on the nature of the institution, with a significant gap between public and private healthcare facilities. The public healthcare sector, often expansive and government-managed, has a substantial carbon footprint due to its extensive operations. However, it also has the capacity for impactful change through policy and regulation[17,21]. The United Kingdom of National Health Service, for instance, has set ambitious targets to become carbon neutral by 2040, demonstrating the potential of public healthcare systems to lead in environmental sustainability[22]. The geographical dimension adds another layer of complexity. Developed countries like the United States and Europe contribute dispro-

portionately to health emissions compared to regions like Africa and Latin America[3]. This highlights a crucial aspect of global environmental and health equity. Healthcare institutions in developed nations, with their financial and technological resources, can generate higher GHG but also invest in mitigation strategies. This contrasts with their counterparts in developing countries, which often lack the means to reduce their emissions. The harsh consequence is that low-income countries, which contribute much less to the problem, often bear more of the negative impact of climate change on health [3,23].

In this context, the role of anaesthesia is particularly noteworthy. Nearly half of GHG healthcare emissions are attributed to hospitals[24]. About one-third of hospital waste is generated by operating rooms, with a daily rate of 13.6 kg *per* patient and a total carbon intensity of 160 kg CO_2 *per* operation[25,26]. A similar rate applies to intensive care units [27].

So how can anaesthetists concretely contribute to reducing the environmental impact of operating rooms and Intensive Care Unit? First, the ongoing mantra must be 'Reduce, Reuse, Recycle'. To minimise healthcare's carbon footprint, specifically in pre-operative evaluations, anaesthesiologists can limit redundant or unnecessary tests and examinations, often performed for defensive medicine. By implementing initiatives like 'Choosing Wisely', which target the reduction of healthcare waste and unnecessary procedures, they can decrease both patient risks and costs[28]. The same principles apply to avoiding ineffective critical care admissions. It is about balancing environmental considerations with clinical accuracy. Anaesthesiologists are at a crossroads of patient care and environmental responsibility. According to a survey conducted in Australia and New Zealand, only 10% of anaesthesiologists consider environmental impact when choosing anaesthetics[29]. This is a critical area for improvement, especially considering the environmental toll of inhalation anaesthetics. For instance, in a seven-hour surgical session utilizing inhalational anaesthetics at a fresh gas flow rate (FGF) of 0.5 L/min, the CO_2 equivalent emissions from 2% sevoflurane, 1.2% isoflurane, and 6% desflurane are analogous to a car traveling 783 km, 667 km and 3924 km, respectively[30]. When it is clinically safe, anaesthesiologists should prefer intravenous, regional or neuraxial anaesthesia. If inhalation anaesthetics are necessary, sevoflurane or isoflurane are preferable over desflurane, which requires higher gas concentrations for general anaesthesia. Additionally, minimizing FGF, even during induction, is a vital strategy[31]. Medication waste is an inevitable aspect of anaesthesia care. In daily practice, propofol is the most wasted drug by volume[31], whereas emergency medications (*e.g.* atropine, epinephrine) see a high percentage of waste after being opened but not used[32]. To mitigate environmental impact, several strategies can be implemented. These include employing pre-filled syringes for emergency drugs and requesting pharmacy services to divide vials in sterile conditions to minimise waste, particularly beneficial during drug shortages. Additionally, keeping medications accessible yet unopened when feasible, utilising paediatric-specific vial sizes and ensuring the proper disposal of controlled substances is crucial. This is particularly important to prevent illegal sewer disposal, in compliance with legal regulations[31]. In recent years, there has been a significant rise in the use of disposable devices within healthcare, particularly in anaesthesia. Examples include disposable laryngoscope blades and single-use fibre-optic endoscopes. This trend has significant environmental repercussions[33]. To mitigate these impacts, the adoption of reusable devices, which can be cleaned and sterilised after each use should be promoted. Additionally, an emerging practice in many hospitals is the reprocessing of single-use devices, encompassing both anaesthesia and surgical equipment, *via* third-party vendors. This involves a comprehensive process of sterilisation, tracking and repackaging[31, 32].

CONCLUSION

The interconnection between climate change, carbon footprint and healthcare, particularly anaesthesia, is an area that demands immediate attention and action. While healthcare is a vital sector for human well-being, its role in contributing to climate change cannot be overlooked. The poor or insufficient information on this topic, the trivialisation of the problem and the low perception of genuine risks, could lead to postponement of the adoption of measures, which are individually and collectively necessary to effectively combat the climate crisis. Unfortunately, we are in a code red and there is no more time to waste. In this era marked by a pervasive crisis of trust in institutions and the scientific community, physicians uniquely maintain high levels of trust among the majority of the population, being perceived as the most reliable professionals. However, it is crucial to acknowledge that this trust is not unconditional and can be influenced by demographic, socioeconomic and geographical factors[34]. Studies show that patients of colour[35], Hispanic patients[35], women[34] and those from lower socioeconomic backgrounds[36] are more likely to report lower trust in physicians compared to the general population. This can stem from multiple factors, such as previous negative experiences, language, cultural barriers and imbalanced power dynamics, where the physician's perceived authority might impede trust and open communication. These insights underscore the importance of recognising the complex dynamics of trust within global healthcare systems, which could critically influence the response to public health challenges posed by climate change. Through the construction and strengthening of trust in the doctor-patient relationship, all of us doctors are called upon to provide clear answers to our patients about the incurred risks due to climate change. It is our responsibility to deliver information about how to change habits, for example, our eating habits, to combat this emergency. It is also our fundamental role to identify those subjects who are susceptible to diseases related to pollution and at risk for the contribution of medical-environmental-social factors. In addition, all health professionals must lead the way in adopting sustainable practices; considering this point of view, anaesthesiologists can do a great deal to reduce the carbon footprint related to their daily practice. Health professionals should also stimulate institutions to implement primary prevention policies that counteract environmental risk factors. Finally, another important action is to train future medical classes on climate change as well as its effects on human health. Some public health schools at universities, such as Yale, Harvard and Washington, have already integrated curricula dedicated to this topic into their

teaching offerings[37]. To paraphrase the words of Bruce Chatwins, to wound the earth is to wound yourself, and if others wound the earth, they wound you. This is our last call to arms! It is time to act, not only for us, but for the smiles of our children on this planet, which they will inherit.

FOOTNOTES

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EDITORIAL

Protocol for lower back pain management: Insights from the French healthcare system

Lea Evangeline Boyer, Mathieu Boudier-Revéret, Min Cheol Chang

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Abstract

In this editorial we comment on the article published in a recent issue of the *World Journal of Clinical Cases*. This article described a novel ultrasound-guided lateral recess block approach in treating a patient with lateral recess stenosis. The impact of spinal pain-related disability extends significantly, causing substantial human suffering and medical costs. Each county has its preferred treatment strategies for spinal pain. Here, we explore the lower back pain (LBP) treatment algorithm recommended in France. The treatment algorithm for LBP recommended by the French National Authority for Health emphasizes early patient activity and minimal medication use. It encourages the continuation of daily activities, limits excessive medication and spinal injections, and incorporates psychological assessments and non-pharmacological therapies for chronic cases. However, the algorithm may not aggressively address acute pain in the early stages, potentially delaying relief and increasing the risk of chronicity. Additionally, the recommended infiltrations primarily involve caudal epidural steroid injections, with limited consideration for other injection procedures, such as transforaminal or interlaminar epidural steroid injections. The fixed follow-up timeline may not accommodate patients who do not respond to initial treatment or experience intense pain, potentially delaying the exploration of alternative therapies. Despite these limitations, understanding the strengths and weaknesses of the French approach could inform adaptations in LBP treatment strategies globally, potentially enhancing patient outcomes and satisfaction across diverse healthcare systems.

Key Words: Lower back pain; Protocol; France; Treatment; Chronic pain

Core Tip: The treatment algorithm for low back pain in France, recommended by the French National Authority for Health, prioritizes early patient activity and minimal medication use. While it promotes daily function and non-pharmacological therapies for chronic cases, it may not adequately address acute pain, relying heavily on caudal epidural steroid injections. The fixed follow-up timeline may also hinder exploring alternative therapies for non-responsive or intensely painful cases. Despite these limitations, understanding the strengths and weaknesses of this approach could inform global adaptations, potentially improving patient outcomes and satisfaction across diverse healthcare systems.

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INTRODUCTION

In this editorial we comment on the article "Novel approach of ultrasound-guided lateral recess block for a patient with lateral recess stenosis: A case report" published in a recent issue of the *World Journal of Clinical Cases*[1]. This article described a novel ultrasound-guided lateral recess block approach in treating a patient with lateral recess stenosis. The impact of spinal pain-related disability extends significantly, causing substantial human suffering and medical costs. Each county has its preferred treatment strategies for spinal pain.

Lower back pain (LBP) is one of the most common musculoskeletal disorders. More than 80% of the population experience LBP at some point in their lives, and 10%-20%-up to 40% in some reports-of acute LBP cases become chronic [2]. Thus, treating LBP is crucial; several treatment approaches have been implemented in clinical settings, with ongoing research on effective treatment approach strategies. Treatment approaches for LBP may vary globally due to differences in healthcare systems and the general perception of various treatments in each country.

Here, we will explore the LBP treatment algorithm recommended in France. In France, the French National Authority for Health (Haute Autorité de santé) was established in August 2004 and has since been responsible for setting patient care guidelines and improving the quality of healthcare in France. We will examine the LBP treatment algorithm by this agency edited in 2017 and 2019 (Figure 1)[3].

SUMMARY OF THE TREATMENT ALGORITHM RECOMMENDED FOR PATIENTS WITH LBP IN FRANCE

The treatment algorithm recommended for patients with LBP in France can be summarized as follows: Patients visiting a clinic or hospital for LBP are encouraged to continue their daily activities as much as possible and are advised to engage in appropriate physical activity. Depending on the patient's needs, pain management medications, such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), may be prescribed for less than a week.

At the first visit, patients are informed that radiological evaluation is not always necessary, and clinicians do not conduct it.

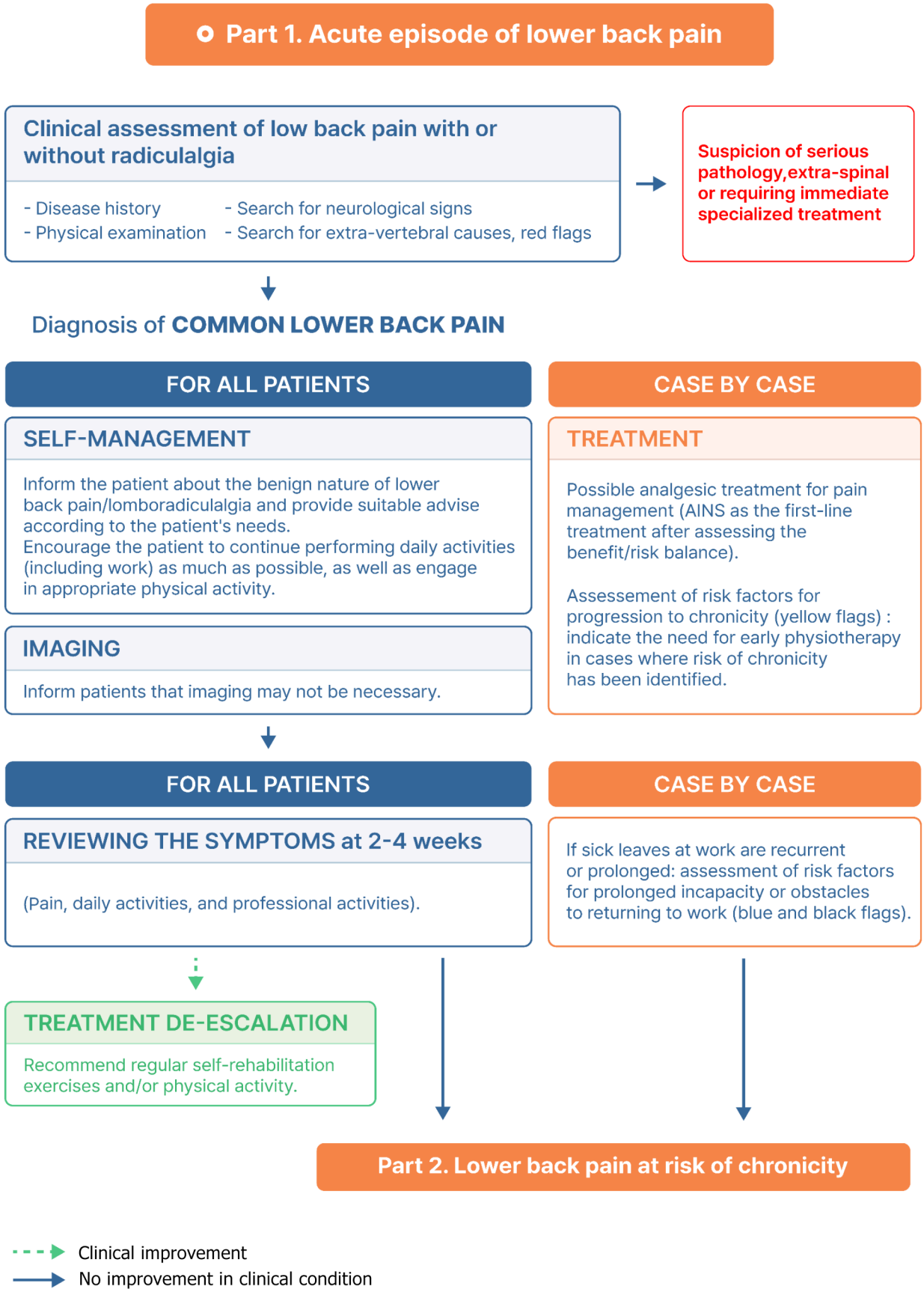
Red flags are ruled out at each step to eliminate acute pathologies necessitating further specialized assessments and imaging (Figure 1).

A follow-up is conducted 2-4 wk after the initial visit. If pain persists, exercise and physiotherapy are recommended and prescribed. In addition, pharmacotherapy is considered for pain control. Yellow flags, factors of chronicization, are assessed (Figure 1). If radicular pain is present, a radiological evaluation is performed, and epidural caudal injection may be considered.

Another follow-up occurs 6-12 wk later. If pain persists, spinal imaging tests are conducted and a multidisciplinary approach is implemented, as well as addressing blue flags to assess the barriers to return to work (Figure 1). The family doctor can refer to a specialist or a pluridisciplinary center for back rehabilitation can be considered. This approach can include a psychological assessment, nutritionist, cognitive-behavioral therapy, relaxation techniques, mindfulness, and hypnosis. If depressive symptoms are present, the use of antidepressants is considered. For patients with radicular pain, gabapentinoids or antidepressants [serotonin norepinephrine reuptake inhibitors (SNIRs) or tricyclics] may be considered, as well as stepping up with infiltrations. If necessary, symptoms are evaluated in correlation with radiological images; surgery may be considered.

CONSIDERATIONS ON THE ALGORITHM

There are several positive aspects of this treatment algorithm. First, it encourages patients to continue their daily


Part 1. Acute episode of lower back pain
Clinical assessment of low back pain with or without radiculalgia
- Disease history
- Physical examination
- Search for neurological signs
- Search for extra-vertebral causes, red flags
Suspicion of serious pathology,extra-spinal or requiring immediate specialized treatment
Diagnosis of COMMON LOWER BACK PAIN
FOR ALL PATIENTS
CASE BY CASE
SELF-MANAGEMENT
Inform the patient about the benign nature of lower back pain/lomboradiculalgia and provide suitable advise according to the patient's needs.
Encourage the patient to continue performing daily activities (including work) as much as possible, as well as engage in appropriate physical activity.
TREATMENT
Possible analgesic treatment for pain management (AINS as the first-line treatment after assessing the benefit/risk balance).
Assessement of risk factors for progression to chronicity (yellow flags) : indicate the need for early physiotherapy in cases where risk of chronicity has been identified.
IMAGING
Inform patients that imaging may not be necessary.
FOR ALL PATIENTS
CASE BY CASE
REVIEWING THE SYMPTOMS at 2-4 weeks
(Pain, daily activities, and professional activities).
If sick leaves at work are recurrent or prolonged: assessment of risk factors for prolonged incapacity or obstacles to returning to work (blue and black flags).
TREATMENT DE-ESCALATION
Recommend regular self-rehabilitation exercises and/or physical activity.
Part 2. Lower back pain at risk of chronicity
Clinical improvement
No improvement in clinical condition

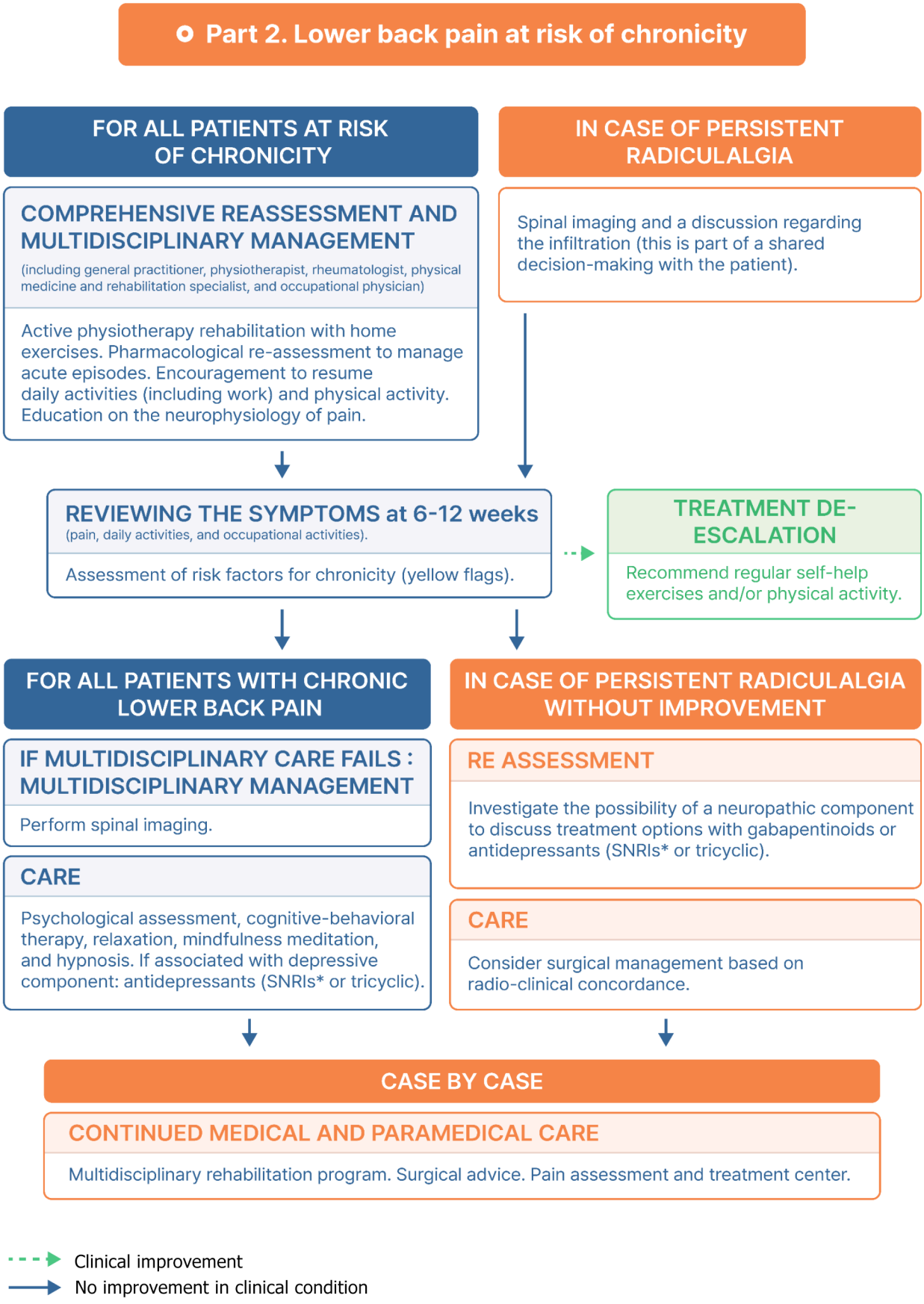


Figure 1 The protocol for management of lower back pain established by the French National Authority for Health.

activities. Most clinicians are aware that patients with LBP should not necessarily be on bedrest and that they may continue with their daily lives without straining too much; however, they may not explain this to the patients unless asked. Therefore, making this a clear part of the treatment protocol would ensure clinicians consistently inform patients about the safety and benefits of maintaining normal activities.

Second, the algorithm is designed to limit the excessive use of oral medications and spinal injections. It recommends NSAIDs at the first visit only when necessary; spinal injections are considered only after an initial period if required. These measures help minimize potential drug side effects and complications of spinal injection, thus encouraging natural healing processes. Moreover, such measures may lead to reduced medical costs.

Third, for chronic cases, the algorithm recommends performing psychological assessments and using antidepressants when necessary, allowing for the treatment of depression that is common in many patients with chronic LBP. By suggesting treatments such as cognitive-behavioral therapy, relaxation, mindfulness, and hypnosis, the algorithm not only addresses the emotional aspects of chronic pain, but also helps to decrease dependency on drugs and injections. Additionally, the use of gabapentinoids or antidepressants (SNIRs or tricyclics) is recommended only for chronic pain with radicular symptoms, which can reduce the incidence of side effects associated with these medications.

While the treatment algorithm for LBP in France has these advantages, there are also some keys disadvantages to be considered.

First, it may not address the patient's pain aggressively enough in the early stages. This approach overlooks the acute discomfort caused by LBP, and the resulting impact on daily life and work. In cases of severe pain, a more proactive use of medications or spinal injections early on could alleviate suffering, while earlier imaging could allow for more proactive treatments, such as spinal injections, in cases of significant herniated lumbar discs, thus reducing patient suffering[4]. Early aggressive treatment could prevent the pain from becoming chronic; treatment success rates are typically lower once pain becomes chronic[5].

Second, recommended infiltrations are predominantly caudal epidural steroid injection in cases of radiculalgia. Other injection procedures are not recommended and not usually conducted in clinical settings in France. Current recommendations do not endorse transforaminal or interlaminar epidural steroid injections due to concerns over side effects. However, we think that caudal epidural steroid injection is limited in that it cannot deliver injectates selectively to the lesion site. For caudal epidural steroid injection, 20-25 mL of a mixed solution with steroids, anesthetic, and saline is injected through the sacral hiatus into the lumbosacral epidural space[6]. Because the total amount of steroid in mixed solution is only 1-2 mL, it is significantly diluted. Therefore, only a small portion of the injected steroid reaches the target lesion. Third, the follow-up timeline is not flexible. In situations where the patient does not respond to the treatment recommended by clinicians and suffers from intense pain, it would be desirable for patients to seek medical attention earlier to explore alternative treatments.

CONCLUSION

Each country has its preferred treatment strategies for LBP; these approaches are bound to differ depending on the country's healthcare system and culture. By considering the strengths and weaknesses of the French treatment algorithm, LBP treatment strategies in other countries or healthcare facilities could be adapted to enhance patient outcomes and satisfaction.

FOOTNOTES

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EDITORIAL

Removal of intrahepatic bile duct stone could reduce the risk of cholangiocarcinoma

Gowthami Sai Kogilathota Jagirdhar, Yatinder Bains, Salim Surani

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Abstract

Hepatolithiasis (HL) poses a significant risk for cholangiocarcinoma (CCA) development, with reported incidences ranging from 5%-13%. Risk factors include older age, smoking, hepatitis B infection, and prolonged HL duration. Chronic inflammation and mechanical stress on the biliary epithelium contribute to CCA pathogenesis. Hepatectomy reduces CCA risk by removing stones and atrophic liver segments. However, residual stones and incomplete removal increase CCA risk. Kim *et al* identified carbohydrate antigen 19-9, carcinoembryonic antigen, and stone laterality as CCA risk factors, reaffirming the importance of complete stone removal. Nonetheless, challenges remain in preventing CCA recurrence post-surgery. Longer-term studies are needed to elucidate CCA risk factors further.

Key Words: Hepatolithiasis; Cholangiocarcinoma; Biliary stone; Common bile duct stone; Cholangitis

Core Tip: Hepatolithiasis (HL) poses a significant risk for cholangiocarcinoma (CCA), with factors like stone location, recurrence, and incomplete removal influencing risk. While hepatectomy reduces CCA risk, residual stones and incomplete removal pose challenges. Kim *et al*'s study identifies carbohydrate antigen 19-9, carcinoembryonic antigen, and stone laterality as CCA risk factors, supporting prior findings. Nonetheless, discrepancies in bile duct stricture's impact on CCA risk highlight the need for further research. Understanding these factors aids in refining CCA risk assessment and optimizing management strategies for HL-associated CCA.

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INTRODUCTION

The incidence of hepatolithiasis (HL) associated cholangiocarcinoma (CCA) appeared to range from 5%-13% in the literature. Risk factors for development of CCA include older age > 40 years, history of smoking, family history cancer, more extended history of HL > 10 years, history of weight loss, history of hepatitis B infection, high levels of serum alkaline phosphatase, low serum carcinoembryonic antigen (CEA) level > 4.2 ng/mL, low serum albumin, high serum carbohydrate antigen 19-9 (CA19-9) > 22 U/mL, duct stricture, focal atrophy, atrophy of liver parenchyma, and bilateral HL[1,2]. History of gastrectomy and choledochoenterostomy were also the risk factors for CCA development[3]. HL associated CCA (HL-CCA) has been grouped into concomitant-CCA (C-CCA) or subsequent-CCA (S-CCA) based on its diagnosis with HL. C-CCA ranges from 5%-12%. S-CCA has been reported up to 10% of the population[4-6]. Removal of stones decreases the risk of CCA. We discuss the study's results by Kim *et al*[7] and expand on the topic.

Mechanism of HL associated with CCA

HL-CCA occurs in areas of stone location. HL may include persistent mechanical stress and chronic inflammation of the biliary epithelium. The process of CCA appears to be a complex process involving pro-inflammatory cytokines, growth factors, cancer associated fibroblasts and biliary tract and liver microbiome changes[8-10]. This creates a tumor microenvironment with increased expression of cell surface receptors and disruption of intracellular signaling pathways, causing cell proliferation and aberrant development. Banales *et al*[8] describes common mutated genes including FGFR2 fusions, BAP1, BRAF, ARID1A, KRAS, TP53, SMAD4, PBRM1 and IDH1 and IDH2. Molecular alterations including p16 inactivation, increased expression of cyclooxygenase-2, prostaglandin E2, proto-oncogene c-met and decreased caudal-related homeobox gene 2 have been recognized in precursor lesions of CCA[10]. Wang *et al*[11] found that peripheral inflammation parameters that indicate systemic inflammation and immune response like neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and systemic immune inflammation were higher in the HL group compared to the non-HL group and without biliary stricture group. Systemic immune response was hyper-activated in HL-CCA patients. Helper and cytotoxic T cells were involved in the inflammatory process. This resulted in the bile ducts in this area becoming fibrosed, thickened, and stenosed, causing recurrent attacks of acute cholangitis. The stone-involved segments became damaged and atrophic over time. The recurrent attacks of acute cholangitis can cause CCA in stone-involved segments. Therefore, hepatectomy for the involved segments decreases the risk of CCA. Hepatectomy removes the stones, atrophied liver segments, and stricture tissue. S-CCA development is an important prognostic factor in predicting survival in these patients. Often, patients with S-CCA have advanced disease and poor prognosis at presentation.

Can removal of intrahepatic bile duct stone reduce the risk of CCA?

Studies describe continued risk of stone formation even after initial stone removal[5]. Residual stones continue to pose an increased risk for CCA by up to 16%[12]. Inflammation of the liver tissue due to Chronic proliferative cholangitis from residual stones may lead to bile duct epithelium dysplasia and cancer[12]. The 10-year recurrence rate was doubled in the bilateral group compared to the unilateral group[12-14]. These patients continued to be at increased risk of CCA, with risk ranging up to 6.25%[12,13]. Patients with recurrent HL post hepatectomy still have a high risk of C-CCA and S-CCA. Studies often showed that S-CCA developed post-resection in the lobes closest to the resected hepatic segments. This may be due to biliary intraepithelial neoplasia from long-term inflammation in the adjacent bile ducts. Bilateral HL can also be associated with a limited ability to clear stones in diffuse distribution during hepatectomy with intraoperative lithotomy and lithotripsy. To preserve part of the liver, conservative resection can increase the risk of S-CCA.

Some studies also describe the extent of liver resection (ELR) compared to stone-affected segments. When the ELR < stone affected segments (SASs), patients are at increased risk of CCA development (20%-21.5%). When the ELR = stone - affected segments, the risk was comparably lower in unilateral and bilateral groups (3%-4.3%)[12,15]. Often, patients have incomplete stone removal on initial hepatectomy and require repeated procedures such as segmentectomy, Cholangioscopic lithotomy, or lithotripsy for stone removal[15]. There is a high chance of residual and missing stones. These can further contribute to continued atrophy, thickening, and hepatocyte fibrosis of the stone-bearing ducts, with the adjacent unaffected segments having compensatory hypertrophy. This process can also predispose to CCA[13]. Further isolated peripheral stones and varied involvement of intrahepatic duct distribution can make cholangioscopic procedures

challenging and impact complete stone removal, affecting the ELR = SAS ratio and increasing residual stones. In the absence of symptomatic HL, residual stones, biliary stricture, and hepatic atrophy after initial stone removal, careful close follow-up can be done after discussing risks and benefits with patients[16]. Ultrasound and Computed tomography imaging are primary modalities for diagnosis of HL diagnosis and for monitoring recurrence during the follow-up period. They can detect biliary dilations, strictures, and stones. Magnetic resonance imaging and magnetic retrograde cholangiopancreatography are often additional tests for abnormalities in liver enzymes or tumor markers or to define ultrasound or computed tomography abnormal findings better[6]. Monitoring liver enzymes, serological tumor markers such as CA19-9 and CEA for 6-month follow-up after stone removal and with less frequent intervals after. Endoscopic retrograde cholangiopancreatography is used to treat biliary dilation and obtain tissue for diagnosis. Endoscopic ultrasound with biopsy may be used to assess locoregional extension of CCA, evaluate biliary obstruction, and obtain tissue for diagnosis[17].

In the most recent issue of the *World Journal of Clinical Cases*, Kim *et al*[7] attempted to replicate the prior research on stone removal and the risk of CCA in a retrospective study and identify risk factors for its development.

Kim *et al*[7] found CA19-9, CEA, and bilateral stones to be risk factors for CCA, similar to prior studies. Stone removal was associated with a lower incidence of CCA. They also found complete removal without recurrence to decrease the risk of CCA, similar to prior studies. The authors found atrophy of the liver parenchyma to be a significant risk factor similar to prior studies. Some studies, like Liu *et al*[2] showed left-sided stones associated with a higher risk of CCA, and others, like Suzuki *et al*[1] showed predominant right-sided stones associated with high risk[1,2]. It is postulated that since the right intrahepatic duct is shorter and wider it is more prone to stasis, stone formation and inflammation thereby increasing risk of CCA. In the study by Kim *et al*[7] results showed left-sided stones to be at high risk. The left sided hepatic duct is anatomically at an acute angle with the common bile duct thereby more prone to stasis. The right segmental bile ducts also branch from the left hepatic thereby increasing left sided stone and CCA risk. Based on the study by Kim *et al*[7] and prior studies there may be no strong correlation between stone location and intrahepatic CCA. The varied study results may also be due to reasons specific to the study population[7].

The authors found that bile duct stricture did not increase the risk of CCA. However, these results differ from prior literature on larger patient populations. Strictured bile ducts are atrophied, fibrosed, and postulated to increase the risk of CCA. Non-surgical methods of stone removal were associated with remnant stones, recurrent stones, and increased cholangitis episodes. However, this did not reflect the decreased risk of CCA. They also found that complete removal with recurrence and incomplete removal with remnant showed a decreased risk for CCA. However, the results were not significant. Considering these groups were 6.4% and 5.6% of the study population, the small size may have yielded different results than prior literature. Further, the follow-up duration of 7 years may not have been long enough to detect further cases of CCA. Compared to patients who underwent stone removal, the risk of CCA was higher by 3 times in the patients who did not undergo removal in the study by Kim *et al*[7] (5% *vs* 15.3%). Even after complete stone removal, the risk of CCA in the study was 4.6%, similar to prior studies that showed high risk from adjacent inflamed biliary ducts. The study adds to prior literature on risk factors for CCA. A longer follow-up period of > 10 years and a larger group of patients with CCA could have yielded more information on risk factors and supported the evidence from prior studies.

CONCLUSION

HL is a risk factor for CCA. Post hepatectomy and procedures for stone removal, patients continued to be at increased risk if there were recurrent stones or incomplete stone removal. Complete removal of stones without recurrence decreases the risk of CCA but does not eliminate the risk.

FOOTNOTES

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REVIEW

Unexpected focal fluorodeoxyglucose uptake in main organs; pass through or pass by?

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Abstract

Since the inception of fluorine-18 fluorodeoxyglucose (F-18 FDG), positron emission tomography/computed tomography (PET/CT) utilizing F-18 FDG has become widely accepted as a valuable imaging modality in the field of oncology, with global prevalence in clinical practice. Given that a single Torso PET/CT scan encompasses the anatomical region from the skull base to the upper thigh, the detection of incidental abnormal focal hypermetabolism in areas of limited clinical interest is both feasible and not uncommon. Numerous investigations have been undertaken to delineate the distinctive features of these findings, yet the outcomes have proven inconclusive. The incongruent results of these studies present a challenge for physicians, leaving them uncertain about the appropriate course of action. This article provides a succinct overview of the characteristics of fluorodeoxyglucose, followed by a comprehensive discussion of the imaging findings and clinical significance associated with incidental focal abnormal F-18 FDG activity in several representative organs. In conclusion, while the prevalence of unrecognized malignancy varies across organs, malignancies account for a substantial proportion, ranging from approximately one-third to over half, of incidental focal uptake. In light of these rates, physicians are urged to exercise vigilance in not disregarding unexpected uptake, facilitating more assured clinical decisions, and advocating for further active evaluation.

Key Words: Incidental; Focal; Incidentaloma; Fluorodeoxyglucose; Positron emission tomography; Hypermetabolism

Core Tip: Unexpected incidental focal fluorine-18 fluorodeoxyglucose uptake on positron emission tomography/computed tomography is not an uncommon finding. The nature of this uptake has been the subject of various studies, with outcomes varying depending on the organ in which it manifests. A noteworthy finding from these investigations reveals that over one-third of such uptakes were determined to be malignant. This observation underscores the importance of conducting further examinations in cases where incidental uptake is identified, as it could potentially serve as a crucial indicator for malignancy.

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INTRODUCTION

The role of fluorine-18 fluorodeoxyglucose (F-18 FDG) is pivotal in establishing positron emission tomography/computed tomography (PET/CT) as a preeminent imaging modality within the realm of oncology. This radiopharmaceutical is readily available and routinely employed worldwide on a daily basis. Unlike conventional radiological images such as those obtained through computed tomography (CT) or magnetic resonance imaging, nuclear medicine images offer a functional perspective, enabling the assessment of molecular-level changes. Given that biochemical alterations precede observable physical changes such as alterations in size[1,2], PET/CT assumes a crucial role in the early detection of disease states. Presently, this imaging technique serves various purposes, including diagnosis, treatment planning, post-treatment evaluation, and follow-up.

Torso PET/CT scans encompass a range extending from the skull base to the upper thigh, with the possibility of conducting whole-body PET/CT scans contingent upon the capabilities of the scanner. The extensive scan range introduces the potential inclusion of regions with diminished clinical interest, leading to the observation of increased fluorodeoxyglucose (FDG) uptake (hypermetabolism) at unexpected sites. Such incidental uptake can pose a challenge for physicians in their interpretation. Studies have been undertaken to investigate incidental hypermetabolic regions, yielding diverse outcomes. This article delves into the distinctive characteristics of F-18 FDG, elucidates imaging findings, and explores the clinical significance of incidental hypermetabolism in several organs where unexpected uptake is relatively commonplace.

F-18 FDG INTO CELLS

The initial synthesis of F-18 FDG was accomplished by Pacák *et al*[3] in 1968, followed by the successful preparation of F-18 FDG by Ido *et al*[4] in 1978, thereby facilitating its utilization as a radiopharmaceutical for positron emission tomography (PET) imaging[3-6]. FDG has found extensive applications in diverse fields such as oncology, neurology, and cardiology. Structurally, FDG closely resembles glucose, with the key distinction being the substitution of the hydroxyl group on the 2-carbon of a glucose molecule with a fluorine-18 radionuclide[7,8]. This glucose analogue is actively transported into cells through glucose transporters, primarily GLUT1 and GLUT3, mirroring the cellular uptake of glucose[7-9]. However, owing to its structural dissimilarity, FDG cannot complete the glucose metabolic pathway and becomes trapped within cells[10]. Despite this metabolic divergence, the initial stages of FDG uptake closely parallel those of glucose, enabling FDG to assess and depict cellular glucose metabolism due to their shared metabolic behavior.

Living cells rely on glucose as a primary energy source. Notably, cancer cells exhibit a heightened uptake of glucose, a phenomenon well-described by the Warburg effect[11]. In terms of energy production, cancer cells predominantly favor glycolysis over oxidative phosphorylation, despite its lower efficiency in adenosine triphosphate yields when compared to the latter. The preference for glycolysis, despite its lower efficiency, is attributed to its faster rate, effectively meeting the energy demands of cancer cells[12-15]. This accelerated glycolytic activity contributes to the increased uptake of both glucose and FDG in cancer cells, visualized through PET[16]. However, it is essential to note that FDG, while commonly used as a marker, lacks specificity for cancer cells. Organs with naturally high glucose metabolism, such as the brain or liver, exhibit elevated FDG uptake. Moreover, benign conditions characterized by increased glycolysis also result in the accumulation of FDG in cells[17-21]. Consequently, FDG cannot be considered a selective agent for distinguishing between malignant and benign cells.

The assessment of accumulated FDG in PET images involves both visual interpretation and quantitative analysis. One widely used semi-quantitative index is the standardized uptake value (SUV), a representative dimensionless ratio indicating the relative concentration of FDG in a region of interest[22]. The calculation of SUV is outlined as follows:

$$\text{SUV} = \frac{\text{Tissue radioactivity concentration (decay-corrected) mCi/mL}}{\text{Injected tracer dose mCi/body weight (g)}}$$

The popular application of SUV is evident in the differentiation between malignant and benign lesions. A cutoff value is investigated for specific cancers; subsequently, this determined cutoff serves as a reference value. Furthermore, SUV finds frequent use in the evaluation of treatment efficacy, involving a comparison of values obtained from pre- and post-therapy images. SUV can be quantified in various ways. Noteworthy methods include the determination of the highest

SUV for a single pixel (maximum SUV or SUV_{max}), the average SUV for a freely drawn region (mean SUV or SUV_{mean}), and the average SUV for a small fixed-sized region centered on a highly uptake area (peak SUV or SUV_{peak}). While SUV_{max} remains consistent regardless of the evaluator, it is susceptible to noise interference[23,24]. Conversely, SUV_{mean} is prone to alterations based on the delineated area[25,26]. SUV_{peak} encompasses a relatively larger volume, making it less influenced by noise; however, its application becomes challenging for small or tiny lesions that do not attain a certain size [27-29]. In addition to these parameters, various SUV-derived metrics such as SUV corrected for lean body mass, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) are employed. Acknowledging the imperfections inherent in each parameter, it becomes apparent that no single parameter can entirely substitute others.

F-18 FDG AVIDITY TO CANCER CELLS

The elevated glycolytic activity observed in cancer cells contributes to an increased uptake of FDG, resulting in pronounced visualization on PET imaging[30-32]. This uptake can be quantified, with SUV serving as a widely used metric in clinical settings. While SUV has inherent limitations, a generally accepted threshold is an SUV of 2.5 or higher, indicating a potential malignancy. It is crucial to acknowledge that non-specific FDG uptake can lead to elevated SUV values in normal physiological or benign inflammatory/infectious conditions[33-37].

The degree of FDG uptake varies depending on several factors. In solid tumors, low cellularity or reduced glucose metabolism may result in diminished FDG uptake, as observed in well-differentiated thyroid cancers, low-grade lung adenocarcinomas, low-grade lymphomas, well-differentiated neuroendocrine tumors, renal cell carcinoma, clear cell carcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, low-grade hepatocellular carcinoma, pancreatic cancer, prostate cancer, and so on[38-45]. However, these tumors may exhibit heightened FDG uptake during progression, marked by dedifferentiation or transformation[46-51]. Factors such as the cell cycle phase, oxygen levels, and the surrounding environment, particularly acidity, are implicated in influencing FDG uptake[52-57]. The level of FDG uptake also varies based on cancer cell type and degree of differentiation. Complementary to FDG, other PET radiopharmaceuticals structurally derived from amino acids or choline can be employed for a more comprehensive assessment of cancer avidity[58-61].

F-18 FDG UPTAKE IN BENIGN/NORMAL CONDITIONS

The transport of both glucose and FDG across cell membranes is facilitated by common plasma membrane proteins. Consequently, blood glucose concentration plays a pivotal role in influencing FDG transport dynamics. Numerous studies have elucidated that elevated blood sugar levels adversely affect image quality, attributing this phenomenon to the competitive inhibition of FDG transport by blood glucose across cell membranes[62-65]. Recognizing the significance of this relationship, guidelines outlined by the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine recommend conducting F-18 FDG PET/CT scans under stringent blood glucose control, specifically targeting concentrations lower than 11 mmol/L (approximately 200 mg/dL)[16,66]. Although a subset of recent literature suggests a limited impact of blood glucose levels on imaging outcomes[67-73], it is noteworthy that adherence to the established guidelines remains prevalent in the field.

The non-specific uptake mechanism of FDG renders it susceptible to uptake in both malignant and non-malignant cells, with a particular affinity for those exhibiting elevated glycolysis. Non-malignant cells, akin to their malignant counterparts, may avidly seek out glucose. Notably, active infectious or inflammatory lesions, as well as benign polyps, can manifest high FDG uptake, thereby mimicking the metabolic patterns observed in malignant lesions[74-78]. Consequently, relying solely on heightened FDG uptake poses challenges in accurately differentiating between malignant and non-malignant lesions. FDG, in this context, remains impartial, lacking discriminatory specificity.

The human body harbors several tissues and organs exhibiting noteworthy physiological FDG uptake. The brain, characterized by its elevated glucose metabolism, typically manifests robust FDG uptake, constituting approximately 6% of the administered dose[36]. The liver, too, engages in active facilitated glucose transport, resulting in a discernible FDG uptake. Hepatic FDG uptake generally surpasses that of the blood pool, and owing to the relatively stable metabolic activity of the liver, it frequently serves as a reference for FDG uptake[36,79]. Physiological uptake of FDG in the gastrointestinal tract is a commonly observed phenomenon, and there is a well-documented association between metformin use and heightened FDG uptake in the colon[80-85]. The excretion of FDG predominantly occurs through the urinary system, leading to discernible radioactivity in the kidneys, renal pelvis, ureters, urinary bladder, and urethra[86,87]. Additional biodistribution sites encompass skeletal muscles, the heart (with a notable concentration in the left ventricle), brown adipose tissue, and various other tissues.

Studies noted the usefulness of SUV in differentiation between primary and metastatic lesions[88-90], however, challenges persist when confronted with intense FDG uptake.

F-18 FDG UPTAKE PATTERN, FOCAL VS DIFFUSE

When elevated FDG metabolism is evident in imaging, the observed uptake manifests as either focal or diffuse[91-94]. In certain organs, diffuse uptake is more likely to be benign or physiological when compared to focal uptake[34,36,95-100].

Conversely, focal uptake holds greater clinical significance; it necessitates careful consideration, as it may indicate the presence of a malignant lesion[101-104]. The pattern of uptake becomes crucial in evaluating the potential pathology.

INCIDENTAL FOCAL F-18 FDG UPTAKE BY ORGANS

F-18 FDG PET/CT is a widely performed imaging modality encompassing various anatomical regions, not rarely revealing incidental focal FDG uptake outside the primary area of interest. However, it is imperative to acknowledge that non-FDG-avid or diminutive malignant lesions may be inherently excluded due to the inherent limitations of F-18 FDG PET/CT. The degree of FDG uptake serves as a crucial parameter, with higher uptake correlating with an elevated likelihood of malignancy or advanced disease[105-107]. Consequently, these incidentally observed uptakes should not be casually disregarded. The subsequent discussion delves into the clinical implications of incidentally observed focal F-18 FDG uptake within several organs that are frequently affected[108].

Thyroid

Approximately 85% of thyroid cancer is composed of well-differentiated cancer including papillary and follicular carcinomas[109,110]. They are relatively indolent than other subtypes such as poorly differentiated carcinoma or Hürthle cell cancer. F-18 FDG PET/CT is not routinely engaged in diagnosis and follow-up evaluation of well-differentiated cancer, unless the situation with elevated serum thyroglobulin (generally > 10 ng/mL) and negative radioiodine-131 whole body scan[111]. The prevalence of incidental FDG uptake, including both diffuse and focal, is up to 8%[112], and that of focal uptake is around 2%-4%[113-116]. Diffuse FDG uptake has more chance to be benign diseases such as thyroiditis than cancer[96,117], while approximately up to 60% of focal uptake proved to be malignant[112,116,118-120]. Noticeably, benign Hürthle cell adenoma show focal high FDG uptake as well mimicking a malignant lesion[121-123].

In healthy men with a mean age 55.5 ± 13 (min 28, max 75), the SUV of thyroid ranges from a minimum of 1.2 to a maximum of 2.2 with a mean of 1.5 ± 0.2. In healthy women with a mean age 49 ± 17 (min 18, max 73), it is from 1.1 to 2.4 with a mean of 1.5 ± 0.3[124]. Although studies show some differences in findings, most focal thyroid uptake had SUV greater than 3, and it was able to differentiate malignant from benign lesions in many instances. Other PET parameters such as MTV or TLG are under discussion for differentiation.

Of those malignant lesions, well-differentiated cancers accounted for a large part[102]. These FDG-avid well-differentiated cancers are possibly related to the dedifferentiation or mutation. The upregulation of glucose transporters is one of the possible mechanisms of increased FDG avidity[125,126]. BRAF V600E mutation is also the possible cause of elevated expression of glucose transporters and glycolysis, resulting in high FDG uptake[127-130]. Therefore, incidentally visualized focal thyroid uptake on FDG PET possibly has more aggressive features than non-visualized occult lesions. Also, the fact that more than half (from one-third to two-thirds) of incidental focal uptake turned out to be malignant suggests that further evaluation should be weighted to identify the nature of the uptake.

Breast

The incidence of breast cancer in the year 2020 is the overwhelming number one in women, and the mortality rate is the highest among the types of malignant tumors[131,132]. Breast cancer is classified into many subtypes. The two main histological subtypes are invasive and preinvasive[133-135]. Invasive breast cancer is about three times more common than preinvasive one. Ductal carcinoma no special type of invasive breast cancer (also known as invasive ductal carcinoma) makes up close to 80% of all breast cancers. Invasive lobular carcinoma is the other subtype of invasive breast cancer. Preinvasive breast cancer includes ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). DCIS accounts for about 80% of preinvasive breast cancer and may develop into invasive breast cancer, whereas LCIS rarely exhibits invasive features. Many molecular subtypes area known including triple-negative, human epidermal growth factor receptor 2 positive, luminal B, luminal A.

The prevalence and incidence of breast cancer is obviously much higher in woman than in man[136-138]. The prevalence of incidental focal breast FDG uptake in woman is varying in some extent, several studies documented it around 1.0%[103,139-143] and the highest was about 23% in a study[144]. Possibly over 50% of the focal uptake proved to be malignant and common histologic type was invasive ductal carcinoma[103,145-148].

As expected, homogeneously diffuse and low breast FDG uptake appears to be a normal finding, and SUV_{max} is less than 2.5. A study reported that in the age group of 50.9 ± 9.70 (range 32-77), the average SUV_{max} of normal dense breasts was 1.243, while that of normal nondense breasts was 0.997. Similar results have been reported in other studies[149-151]. Due to low SUV in normal breast, focal uptake can be observed without great difficulty. However, DCIS was reported to have an average SUV_{max} between 2.0 and 2.4[152,153], which may not be visually distinguishable on images. Moreover, the SUV may be affected by physiological states (density change) such as pregnancy, breastfeeding, menstrual cycle[154, 155], and age. Enlarged breast during pregnancy may show SUV similar to liver which has the value from 2 to 5[124]. Suckling of the lactating breast may be associated with increase in expression of glucose transporters resulting in high FDG uptake[156]. SUV decreases as age increases (with diminished breast density).

Breast cancers with lobular feature or small size limit the role of FDG PET/CT in evaluation[157-160]. F-18 FDG PET/CT is not indicated for the routine use except when standard studies bring equivocal results or in advanced disease[161]. In evaluation of breast, axillary lymph node uptake may be a challenge too. Focal FDG uptake in the breast and/or axilla may be observed in the situations such as infection/inflammation[37], primary/metastatic disease[162-164], benign neoplasm (fibroadenoma, intraductal papilloma, ductal epithelial hyperplasia, sclerosing adenosis, and so on)[165], gynecomastia[166], and artefacts[167]. These should be included in differential diagnosis. The most common benign

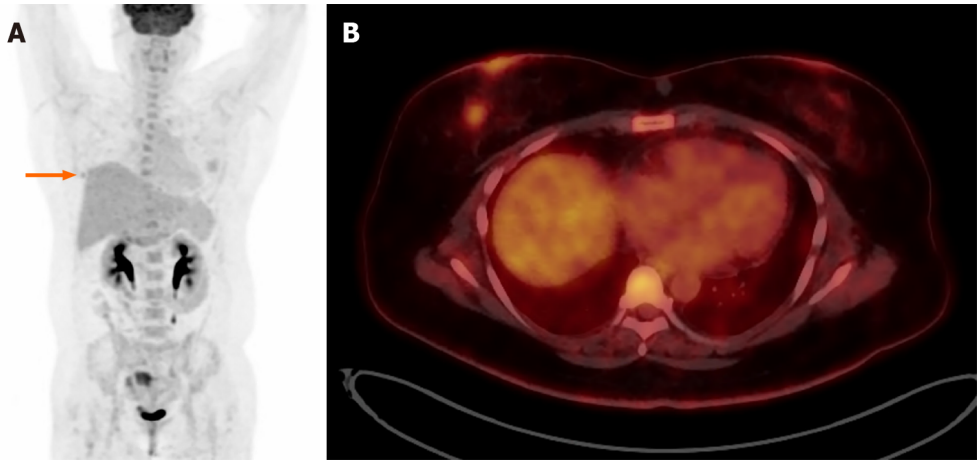

Figure 1 Incidental focal right breast fluorine-18 fluorodeoxyglucose uptake. A: Focal mild to moderate uptake (arrow) is observed in the right chest on the maximum intensity projection image of a 32-year-old woman diagnosed with endometrial cancer; B: Axial image of fused positron emission tomography/computed tomography showing hypermetabolism (maximum standardized uptake value 3.3) in her right breast and the uptake was histopathologically confirmed as a ductal carcinoma in situ.

breast tumor, fibroadenoma, often shows low FDG uptake, but it may have high uptake mimicking a malignant lesion [168,169]. Asymmetrical or nodular appearance of gynecomastia also can mimic malignancy. SUV failed in differentiation between malignant and benign lesions in a study[139]. Nevertheless, incidental focal breast FDG uptake has up to more than 50% of malignancy, therefore, a thorough appropriate evaluation is needed.

Figure 1 shows incidental right breast uptake in a 32-year-old woman who was diagnosed with endometrial cancer. Increased uptake in the right pelvic cavity indicates primary cancer lesion, and another focal moderate uptake is observed in her right breast unexpectedly (SUV_{max} 3.29). The uptake turned out to be a coincident malignant lesion which was confirmed as DCIS histopathologically.

Colon and rectum

Incidental colorectal FDG uptake is up to around 5%[170-172]. Focal uptake has more chance to be malignant[173]. Diffuse and segmental uptake may be due to inflammation, physiological uptake, or FDG excretion[174,175]; and considered to have a low risk of malignancy. The prevalence of focal uptake is up to around 16%[176]. The malignant and premalignant lesions were up to 68% of focal uptake[101,176,177]. Premalignant lesions are not yet malignant; however, they have more chance to develop into malignant lesions. Adenomas (tubular adenomas, villous adenomas, tubulovillous adenomas) are the most frequent premalignant lesions and others include chronic inflammatory bowel diseases, hereditary syndromes (familial adenomatous polyposis, Peutz-Jeghers syndrome, and juvenile polyposis). Colorectal adenomatous polyps are known to develop in up to 40% of people over the age of 60[178].

Different genetic mechanisms are suggested for cancer development by the location (distal or proximal)[179-181]. Proximal colon cancer (up to splenic flexure) accounted for 41%; distal colon cancer 22%; and rectal cancer 28% in the United States from 2009 to 2013[182]. Other paper observed that the most frequent site (42%) of malignant and premalignant lesions was the ascending colon[173], while another reported it as the rectum (60.0%), followed by the sigmoid colon (17.4%)[183]. The distribution of colorectal cancer appears to vary by country, region, race, and age[184-186]. It also varies with sex. Women are more likely to experience proximal colon cancer compared with men[187,188]. Because specific colorectal regions are more likely to involve malignancy than others, consideration of patient characteristics is recommended in reading FDG PET/CT.

Often, mixed single/multiple focal and diffuse uptake is observed together in colorectal region. In this case, diffuse uptake may not preclude further evaluation including colonoscopy and histopathological confirmation. The role of SUV to differentiate malignant/premalignant from benign lesions is still in debate[170,189-193]. Again, more than 50% of malignancy is observed in the incidental focal FDG colorectal uptake.

Figure 2 shows F-18 FDG PET/CT images of a 79-year-old woman who was diagnosed with pancreatic body cancer. Suspicious focal uptake is observed in the right lower abdomen. With an aid of CT, it was revealed as urine radioactivity at the right ureter. Another interesting thing is the multiple foci of hypermetabolism along the descending and sigmoid colon. Colonoscopy was conducted and it found no significant abnormal lesion. The uptake is probably due to normal physiological uptake.

Figure 3 shows a maximum intensity projection image of a 76-year-old woman diagnosed with cecal cancer and multiple metastases/seeding nodules. The primary cecal cancer is observed in the right lower abdomen and diffuse intestinal uptake is also shown. The diffuse uptake may be physiological; however, the possibility of hidden pathological lesions, which may be obscured by the intense intestinal uptake, cannot be ruled out.

Prostate

With the recent advent of United States Food and Drug Administration-approved prostate-specific membrane antigen-targeted PET imaging radiopharmaceuticals, PET/CT has become actively used in the evaluation of prostate cancer. In

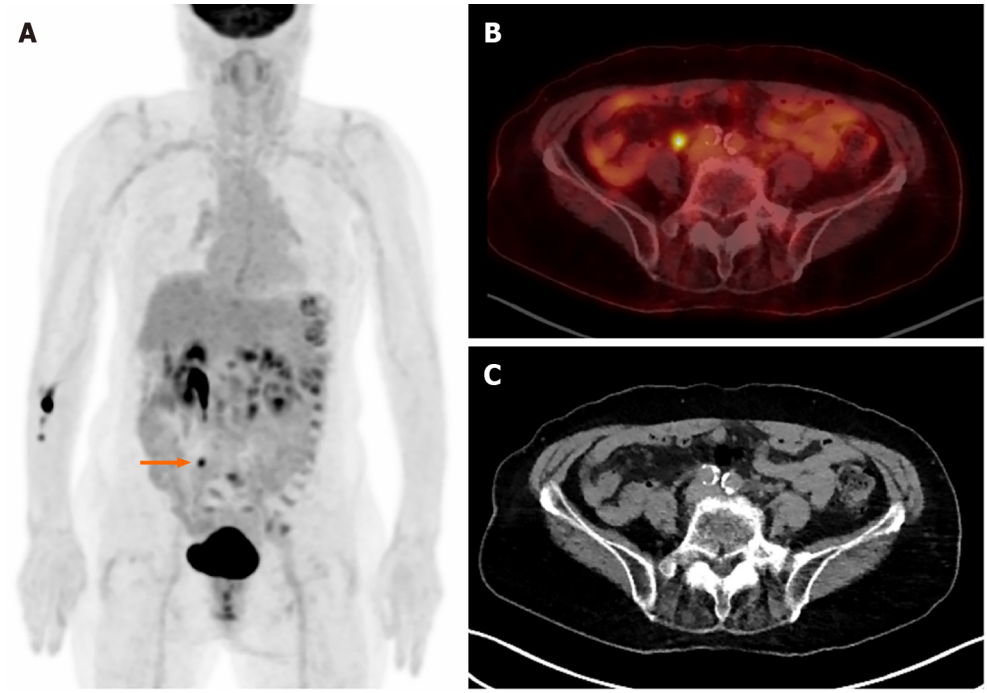

Figure 2 Multiple foci of physiological fluorine-18 fluorodeoxyglucose uptake. Images of a 79-year-old woman diagnosed with pancreatic body cancer. A: Focal uptake is observed in the right lower abdomen (arrow); B: Suspicious uptake as a lesion; C: No lesion but right ureter. Multiple hypermetabolic areas are observed along the descending and sigmoid colon in image A. Colonoscopy found nothing abnormal, and the uptake is probably due to normal physiological uptake.

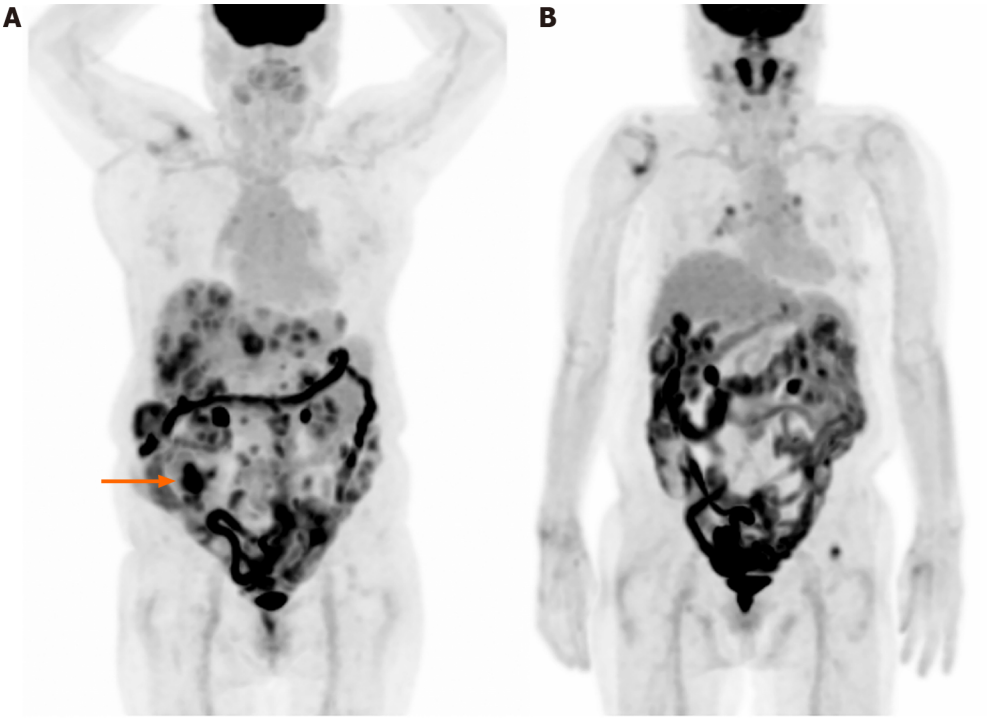

Figure 3 Diffuse intestinal fluorine-18 fluorodeoxyglucose uptake. A: 76-year-old woman diagnosed with cecal cancer and multiple metastases/seeding nodules. Primary cecal cancer is observed in the right lower abdomen (arrow) and diffuse intestinal uptake is also shown. The diffuse uptake may be physiological; however, pathological lesions may be obscured by the intense intestinal uptake; B: 79-year-old woman diagnosed with mantle cell lymphoma, and also had a history of colon cancer about three decades ago. Mixed focal and diffuse intestinal uptake is challenging.

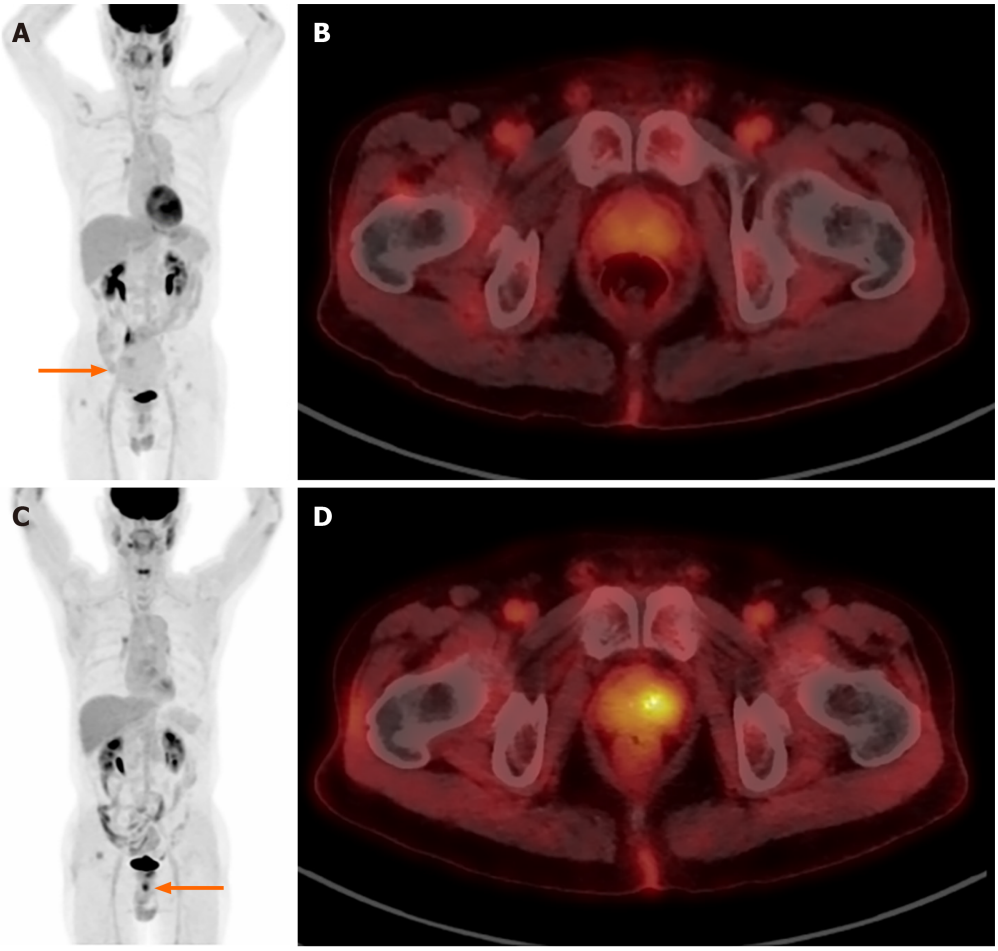

Figure 4 Incidental prostate fluorine-18 fluorodeoxyglucose uptake. A 74-year-old man diagnosed with small bowel gastrointestinal stromal tumor. A: On the initial image, known small bowel gastrointestinal stromal tumor with low uptake is observed (arrow); B: Also, nearly symmetrical low prostate uptake is shown; C: An incidental focal uptake is observed beneath urinary bladder (arrow) on the five-year follow-up image; D: The uptake is at the left side of prostate (maximum standardized uptake value 5.6) and it was proved histopathologically as an adenocarcinoma of prostate.

terms of FDG, prostate is one of the organs that shows low FDG uptake even if it is cancerous. In a group of men with a mean age of 63.6 years (range 22-97), SUV_{mean} and SUV_{max} in normal prostate were reported as 1.3 ± 0.4 (range 0.1-2.7) and 1.6 ± 0.4 (range 1.1-3.7), respectively[194]. The degree of uptake may overlap among prostate cancer, benign prostate hyperplasia, and normal prostate. SUV showed questionable or suboptimal performance in differentiation between malignant and benign lesions. As a result, F-18 FDG PET/CT is not routinely recommended and performed in detection or initial staging of primary prostate cancer[195,196]. However, incidentally observed focal uptake may have clinical implications[100,104,197,198], particularly in the peripheral zone[199,200]. The prevalence of uptake is up to around 2% [200,201] and malignant rate is up to over 60%[197,201-203]. Multifocal uptake is not a significant differential diagnostic criterion between malignant and benign lesions[204]. The location of focal uptake may be the key in differentiation, that is, focal uptake in the peripheral zone is possibly related with malignancy[204,205]. Although with low FDG uptake in both malignant and benign prostate diseases, focal and peripheral uptake should be noted and lead to further evaluation.

Figure 4 shows F-18 FDG PET/CT images of a 74-year-old man who was diagnosed with small bowel gastrointestinal stromal tumor. Initial maximum intensity projection image Figure 4A shows a large pelvic mass with low FDG uptake (arrow). Also, nearly symmetrical low prostate FDG uptake is observed (Figure 4B). F-18 FDG PET/CT conducted in five years for a suspicious recurrent pelvic mass noticed on CT show an incidental focal FDG uptake (SUV_{max} 5.6) in the left side of prostate (Figure 4C and D). The uptake was proved as an adenocarcinoma of prostate histopathologically.

CONCLUSION

This article comprehensively addresses the characteristics of FDG, discusses imaging findings, and outlines the clinical implications of incidental focal FDG uptake across various organs. Existing literature consistently reports that a significant proportion, ranging from approximately one-third to over a half, of incidental focal FDG uptake is indicative of yet unrecognized malignancy. Considering the malignancy rate associated with incidental focal uptake in diverse organs, it is imperative for healthcare professionals not to disregard such unexpected findings. By doing so, they can make more informed and confident clinical decisions, prompting a proactive approach towards further comprehensive

evaluation.

FOOTNOTES

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MINIREVIEWS

Research progress on venous thrombosis development in patients with malignant tumors

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Abstract

The coexistence of venous thromboembolism (VTE) within patients with cancer, known as cancer-associated thrombosis (CAT), stands as a prominent cause of mortality in this population. Over recent years, the incidence of VTE has demonstrated a steady increase across diverse tumor types, influenced by several factors such as patient management, tumor-specific risks, and treatment-related aspects. Furthermore, mutations in specific genes have been identified as potential contributors to increased CAT occurrence in particular cancer subtypes. We conducted an extensive review encompassing pivotal historical and ongoing studies on CAT. This review elucidates the risks, mechanisms, reliable markers, and risk assessment methodologies that can significantly guide effective interventions in clinical practice.

Key Words: Malignant tumor; Venous thromboembolism; Cancer-associated thrombosis; Research progress

Core Tip: Treatment-related risks involve therapies such as chemotherapy, endocrine therapy, angiogenesis inhibitors, immunotherapy, protein kinase inhibitors, blood transfusions, and cell line stimulants, all contributing to venous thromboembolism. This review summarizes the pathogenesis of cancer-associated thrombosis and treatment approaches for this condition. This review elucidates the risks, mechanisms, reliable markers, and risk assessment methodologies that can significantly guide effective interventions in clinical practice.

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INTRODUCTION

With demographic shifts and an aging population, the global incidence of tumors has steadily risen, establishing malignant tumors as a leading cause of disease mortality in the 21st century[1-3]. Cancer-associated thrombosis (CAT) stands out as a common complication of malignant tumors, affecting up to approximately 20% of individuals, according to relevant studies[4,5]. The risk of CAT is multifaceted, lacking a singular predictive risk factor or biomarker for its occurrence[6,7]. The correlation between venous thrombosis and malignancy was initially suggested by Baptiste Builaud, and later confirmed 44 years afterward by the French physician Armand Trousseau[8,9]. Among CAT patients, the risk of tumor recurrence and bleeding post-anticoagulation is notably higher than patients without tumor. Specifically, the risk of venous thromboembolism (VTE) recurrence is three times higher than that in the general population without tumor, while the risk of bleeding escalates three to six times higher than in the population without tumor[10].

The risk of recurrent VTE (rVTE) in patients with tumor significantly amplifies within one month of experiencing VTE [11]. Numerous factors may influence the risk of CAT, including patient-related, tumor-related, and treatment-related risk factors[12]. Patient factors include age, gender, smoking, alcohol consumption, obesity, and nutritional requirements [13]. Tumor-related risks are closely associated with the type and stage of malignant tumors, with brain tumors[14], pancreatic cancer[15], and gastric carcinoma[16]posing the highest CAT risk, followed by lung[17], liver[18], ovarian cancers[19], and certain hematologic tumors such as multiple myeloma[20] and acute leukemia[20].

Treatment-related risks involve therapies such as chemotherapy, endocrine therapy, angiogenesis inhibitors, immunotherapy, protein kinase inhibitors, blood transfusions, and cell line stimulants, all contributing to VTE. Chemotherapy, notably, elevates thrombotic events nearly sevenfold compared with patients with cancer who do not undergo chemotherapy[21,22]. Additionally, other treatments (*e.g.*, surgeries) and factors related to treatment (*e.g.*, hospitalization and central venous catheters) heighten VTE risk in patients with cancer.

Epidemiology of CAT

The paradigm of cancer treatment has undergone a significant shift in the past decade with the emergence of precision medicine and the development of various targeted therapies[23]. As medical care quality has improved, cancer patient survival rates have seen a proportional increase, leading to the emergence of new CAT risk groups. The GARFIELDVTE study revealed that 10.1% of patients had an active tumor upon VTE diagnosis, and patients with active tumors exhibited higher rates of mortality, rVTE, and major bleeding than patients without tumor[24]. A recent study involving 150000 cancer diagnoses during 2006-2007 identified approximately 7200 cases of VTE, showcasing substantial variations in CAT prevalence based on patient characteristics, follow-up duration, and detection/reporting methods for venous thrombosis [25]. A registry study in Denmark assessed the survival duration of patients with general tumors *vs* CAT tumors, demonstrating that CAT patients had a notably lower 1-year survival rate, at least 24% lower than those with general tumors, and a 11% higher rate of distant metastases than patients without CAT tumors[26]. Intriguingly, this study also illustrated that patients with bilateral deep vein thrombosis (DVT) had lower survival rates than those with unilateral DVT, with a 2-year survival rate of approximately 70% for unilateral proximal DVT, 64% for bilateral proximal DVT, and 66% for bilateral distal proximal DVT[27].

Although certain factors such as patient age, gender, history of VTE, and various metastatic diseases have been recognized as predictive factors in some studies, the comprehensive understanding of risk factors contributing to CAT within this population remains incomplete.

Risk factors for CAT

The primary clinical presentations of malignancy-associated thromboembolism encompass DVT[28], pulmonary embolism (PE)[29], wandering thrombophlebitis, arterial thromboembolism, nonbacterial thrombotic endocarditis, portal vein thrombosis, and disseminated intravascular coagulation[30]. However, the etiology of CAT varies among cases and primarily involves stagnant blood flow due to the hypercoagulable state of blood, vessel wall injury, and tumor compression[31]. The presence of additional risk factors contributes significantly to VTE development, primarily including patient-related factors, tumor-related factors, and treatment-related factors. Patient-specific factors encompass age, gender, obesity, and history of VTE, where a prior history of VTE can independently elevate the risk for recurrent CAT, notably more prevalent in patients with malignant tumors compared to common VTE cases[32]. For instance, in the general population, the incidence of VTE escalates notably with advancing age. One study findings suggest that patient age may universally influence VTE occurrence and could impact the location of thrombus presentation[33]. Correspondingly, aging emerges as a substantial risk factor for VTE in cancer patients. In retrospective cohort analyses, cancer patients aged ≥ 65 years were notably more prone to VTE development compared to younger patients. In a case control study, Matern *et al*[34] conducted a multifactorial analysis of data related to patients with cervical cancer, and the results showed that age is an independent risk factor for CAT formation, and that attention should be paid to screening for DVT in patients of advanced age[34]. Furthermore, systemic infections also pose a risk for CAT development[35]. In a controlled study, hospitalized patients with malignant tumors who acquired infections demonstrated a 3- to 5-times

higher risk of developing CAT than non-infected patients. Infections such as respiratory, skin, intra-abdominal infections, and bacteremia all contributed to this heightened risk[35]. The second risk factor, specifically linked to malignancy-related VTE, includes the anatomical location of the tumor, tumor stage, and tissue origin. Some studies highlight that the incidence of VTE is significantly higher in patients with advanced tumors developing distant metastases than in patients whose lesions do not progress to distant metastases[36]. The third risk factor emanates from the therapeutic dimension of tumor treatment, encompassing systemic chemotherapy, hormonal therapy, anti-angiogenic therapy, major surgery, postoperative bed rest, and other factors capable of influencing CAT development. Among the predictive factors for VTE in hospitalized patients with malignancies are blood transfusions and central venous cannulation The development of blood clots from central venous catheters may be related to venous stasis and endothelial injury after the procedure. The formation of blood clots from central venous catheters may relate to venous blood stasis and endothelial injury post-procedure[37].

Mechanisms of CAT occurrence

Malignant tumors disrupt the body's coagulation, anticoagulation, and fibrinolytic systems through various mechanisms, inducing hypercoagulability and pre-thrombotic alterations. This disruption promotes the growth and metastasis of the tumor, forming a vicious circle. Numerous reports delve into the mechanisms underlying CAT occurrence, and this review consolidates four potential aspects involved in CAT formation: Tissue factor (TF)[38], podoplanin (PDPN)[39], neutrophil extracellular traps (NETs)[40], and plasminogen activator inhibitor-1 (PAI-1)[41] (Figure 1).

TF: Endothelial cells, monocytes, and tumor cells express TF. TF is now widely acknowledged as a major contributor to cancer-associated coagulation disorders and CAT. TF directly triggers the conversion of coagulation factor VII to coagulation factor VIIa, playing a pivotal role in activating the exogenous coagulation pathways. TF, a transmembrane protein, exhibits heightened expression on the plasma membrane of cancer cells or microvesicles derived from circulating cancer cells[42]. In cancer patients, TF's expression and activity are significantly elevated compared to normal tissues, often correlating with thromboembolic complications and a poorer prognosis. Several ongoing clinical studies indicate a correlation between CAT incidence and TF in pancreatic cancer, glioma, and other tumors[14]. Activated TF is frequently released from tumor cells in the form of extracellular vesicles (EV), specifically termed EVTF[43]. Patients with tumors have higher levels of EVTF activity than healthy individuals, and intriguingly, patients with tumors of different histological origins have different levels of EVTF activity, with patients with tumors originating from adenocarcinomas also having higher levels of EVTF activity than those with other histological types of tumors. Elevated EVTF activity levels are associated with an increased CAT risk in patients with multiple tumors. A recent study on the relationship between EVTF activity and VTE in patients with glioblastoma showed no direct association between EVTF activity and VTE in patients with glioblastoma during a 2-year follow-up. Notably, patients with glioblastoma and wild-type IDH1/2 displayed higher levels of TF expression and a greater CAT incidence than the mutant type[44]. However, further investigation is needed to determine whether tumor-derived TF + EV contributes to VTE in patients with glioblastoma[45]. Nick *et al*[45] collected autopsy specimens from 180 patients, including 66 patients without tumor and 114 patients with tumor. Among the patients with tumor, 30 (26.3%) showed CAT formation. Upon analyzing TF expression in this group, their results revealed that 23 (76.7%) patients exhibited higher TF levels[45]. Collectively, these TF-expressing tumor cells likely contribute to CAT formation through various pathways in this patient cohort.

PDPN: PDPN represents a class of cell surface glycoproteins that play a pivotal role in tumor development. Overexpressed in various tumors such as hepatocellular carcinoma, lung cancer, and breast cancer[46,47], PDPN induces platelet aggregation through specific binding to platelet receptors. Additionally, PDPN participates in the proliferation, differentiation, epithelial mesenchymal transition and maintenance of tumor stem cell-like properties of malignant tumor cells.

Several studies have investigated PDPN's regulatory mechanisms. Hantusch *et al*[48] initially analyzed the base-rich region upstream of PDPN's promoters and identified multiple transcription factors promoting its transcription, including SP1, AP4, NF-1, among others. Moreover, in lymphatic endothelial cells, the transcription factor PROX-1 was recognized as a potential regulator for transcription factor for the transcriptional regulation of PDPN. Interestingly, analysis confirmed by chromatin immunoprecipitation confirmed the recruitment of SP1/SP3 to the upstream promoter region of PDPN, suggesting the presence of additional transcription factor complexes in this region. Peterziel *et al*[49] demonstrated a negative correlation between PDPN expression levels in primary human glioblastoma and glioma cells at the cellular level. At the same time, they experimentally observed increased PDPN expression in the ventricles of the brain in phosphatase and tensin homolog (PTEN) knockout mice and confirmed using western blot, that the PI3K/AKT/AP-1 signaling axis activation and PTEN loss of function led to PDPN expression in glioblastoma.

The tumor microenvironment (TME) comprises extracellular matrix (ECM), cytokines, and numerous stromal cells. Oncogenic stromal cells significantly contribute to TME construction, involving ECM production, activation of cancer-associated fibroblasts (CAFs), immune suppression, and angiogenesis promotion[50]. PDPN-positive CAFs actively participate in tumor malignancy by modifying the TME. Furthermore, PDPN acts as a co-inhibitory receptor expressed on T cells[50]. Understanding this mechanism elucidates PDPN's role in immunosuppression, offering new directions for cancer immunotherapy.

NETs: In 2004, Brinkmann *et al*[51] identified a network of DNA-histone complexes and proteins released by activated neutrophils, naming it NETs[51]. NETs formation represents a specific cellular process leading toward death, involving the release of granule proteins and chromatin depolymerization[52]. The mechanisms underlying NETs formation primarily stem from two aspects. First, the cleavage of NETs is induced by fopperol acetate myristate or cholesterol crystals, leading to histone arginine citrullination. Subsequently, neutrophils undergo rapid actin cleavage, detachment of cytosolic membranes, and reestablishment of microtubules and the cytoskeleton, followed by rupture of the cytoplasm

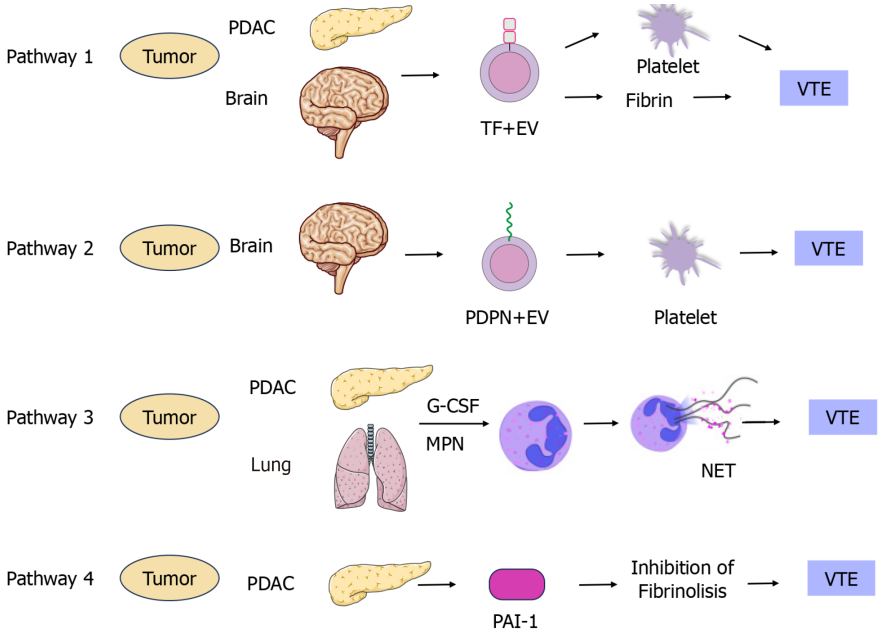

Figure 1 Pathways of cancer-related thrombosis. PDAC: Pancreatic ductal adenocarcinoma; PDPN: Podoplanin; TF: Tissue factor; EV: Extracellular vesicles; VTE: Venous thromboembolism; G-CSF: Granulocyte colony-stimulating factor; MPN: Myeloproliferative-neoplasms; NET: Neutrophil extracellular trap; PAI-1: Plasminogen activator inhibitor-1.

and nucleus to release the chromatin. Finally, NET is released after cytoplasmic membrane rupture and release of the cytoplasmic contents. Another mechanism is the formation of nonlysing NETs, mediated by the activation of Toll-like receptors by certain bacteria or by the activation of a few complement-mediated reactions, all of which occurs independent of the oxidative activity of nicotinamide adenine dinucleotide phosphate [53] (Figure 2).

Previous studies have highlighted NETs' role as a defense mechanism for host cells and their involvement in non-infectious diseases such as rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus, atherosclerosis, and periodontitis[54]. Notably, several investigations have linked NETs to tumor cells, indicating their involvement in the tumor immune microenvironment, proliferation, metastasis, and CAT[55]. NETs further facilitate tumor cell metastasis by degrading extracellular stromal components.

Interestingly, NETs are closely associated with tumor progression and metastasis, with significantly higher expression levels detected in the plasma of patients with pancreatic, bladder, and lung cancers compared to healthy individuals[56]. In colorectal cancer patients, heightened *in vitro* stimuli correlate with increased NETs expression, linking to poor patient prognosis. Park *et al*[57] demonstrated the highest expression of NETs in metastatic triple-negative breast cancer patients through immunofluorescent staining.

PAI-1: PAI-1 acts as a serine protease (serpin) inhibitor and the principal regulator of the plasminogen activation system [58]. Studies conducted since the 1990s have consistently found high levels of PAI-1 protein in human primary malignant tumor extracts, serving as a significant biochemical marker for poor prognosis across various human cancer types. Recent research highlighted PAI-1's influence on the transition of tumor cells from G1 to S phase by regulating cell cycle proteins D1/CDK3/4 and, consequently, the transition of tumor cells from G1 to S phase[59]. However, conflicting findings exist; in breast tumor cells, PAI-1 exhibited an inhibitory effect on proliferation. The exact molecular mechanisms confirming PAI-1's direct regulation of malignant tumor cell cycles lack validation, although its role in inhibiting apoptosis is extensively reported and characterized. PAI-1's anti-apoptotic effect involves inhibiting cell adhesion to waveform proteins, prompting tumor cell separation and migration, thereby exerting its anti-apoptotic effect[60].

Extensive literature underscores PAI-1's pro-cancer role in malignant tumors. Surprisingly, despite numerous studies, there remains insufficient evidence supporting the therapeutic efficacy of targeting PAI-1 on tumor cells[60]. Notably, recent investigations over the past 3 years have seen the development of several small molecule inhibitors of PAI-1, tested in animal models. While these inhibitors have shown promise in promoting thrombus recanalization in some models, their significant impact on tumor cell growth and metastasis in animal tumor models remains limited. Placencio *et al*[61] reported that PAI-039, also known as tiplaxtinin, an inhibitor of PAI-1, demonstrated antitumor activity in T47 bladder cancer and HeLa cell tumors in mice. However, another PAI-1 inhibitor, TM554, displayed activity in certain preclinical cancer models but lacked antithrombotic activity in other models.

Treatment of CAT

Conventional anticoagulation for CAT: The current treatment program for CAT is based on DVT treatment. All patients who are considered for VTE should commence anticoagulation therapy alongside diagnostic assessments. Guidelines advocate for low-molecular-weight heparin (LMWH) as the preferred choice for both initial and prolonged anticoagulation in CAT patients. Several guidelines support LMWH as the primary option for initial and ongoing anticoagulation

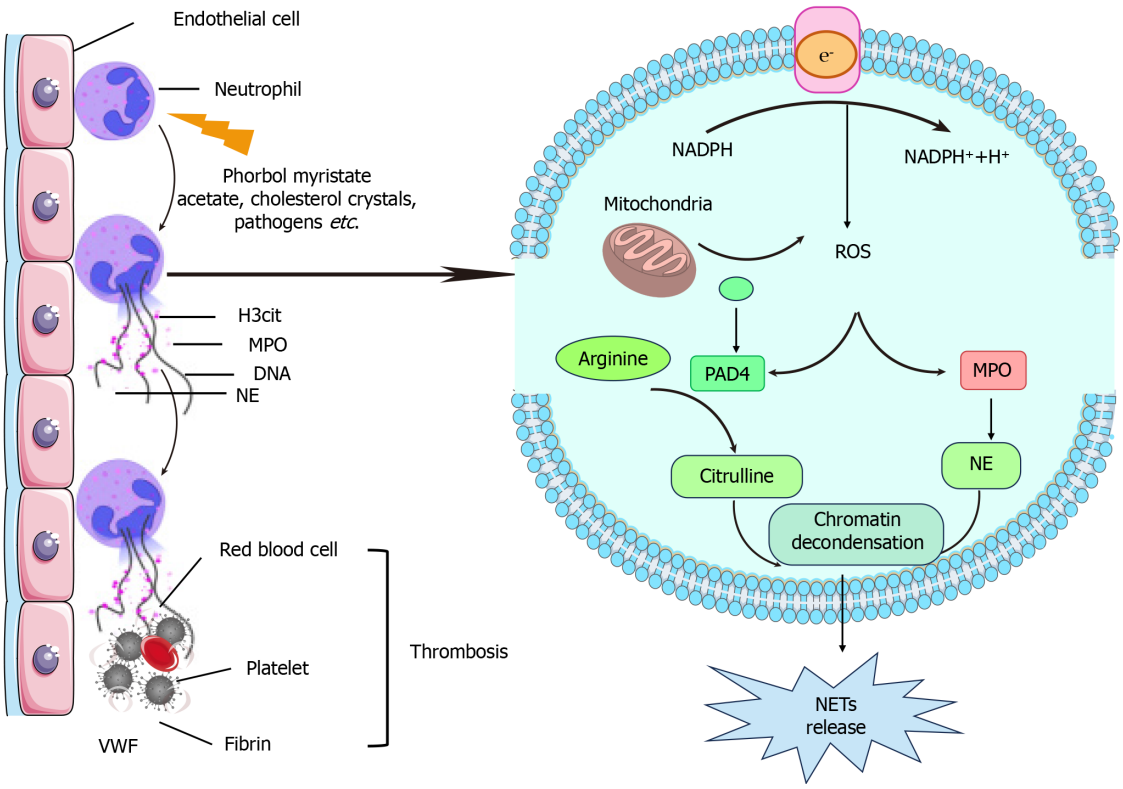

Figure 2 Diagram showing the mechanisms of neutrophil extracellular trap formation. MPO: Myeloperoxidase; NE: Neutrophil elastase; NADPH: Nicotinamide adenine dinucleotide phosphate; PAD: Peptidyl arginine deiminase; VWF: Von willebrand factor; NET: Neutrophil extracellular trap; ROS: Reactive oxygen species; H3cit: Histone 3 citrullination.

in CAT patients. According to a randomized controlled study comparing low molecular heparin to oral anticoagulants in preventing rVTE in cancer patients, a 6-month LMWH treatment notably reduced the risk of rVTE from 17% to 9% compared with conventional treatment (LMWH bridged to warfarin)[62].

While many guidelines support LMWH therapy for CAT, some analyses propose VKA bridging after 6 months of LMWH might be effective in patients with tumor. A study of 1502 patients with tumor treated with LMWH for 6 months demonstrated similar rates of rVTE [hazard ratio (HR) = 0.67, 95%CI: 0.44-1.02] and major bleeding (HR = 1.05, 95%CI: 0.79-1.55) for those continuing LMWH *vs* those transitioned to VKAs. Optimal anticoagulation duration remains inconclusive; guidelines suggest its continuation during active tumor presence or ongoing antitumor therapy[63].

ASCO guidelines recommend starting pharmacological prophylaxis preoperatively, ITAC recommends starting 2 to 12 h preoperatively[64], and ASH recommends starting postoperatively; for patients with malignancies treated with outpatient chemotherapy, risk stratification using the Khorana Risk Assessment Model recommends rivaroxaban as a primary prophylaxis for thrombosis[65]. These guidelines are applicable to all patients with malignancies, but how to more accurately individualise the regimen for gynecological patients with malignancies in different risk strata is a major challenge in prophylactic anticoagulation for a wide range of malignancies, including gynecological oncology patients.

Novel oral anticoagulation therapy for CAT

Recent advancements in novel oral anticoagulants (NOACs) mark a significant breakthrough in CAT prophylaxis and treatment, presenting an alternative to heparin and vitamin K antagonists (VKAs)[66]. However, efficacy and safety data for patients with tumor using NOACs are limited. Despite the advantages of NOACs over other anticoagulants, such as ease of administration (oral and fixed-dose regimens), no need for frequent testing, half-life similar to that of heparin, predictable anticoagulant efficacy, and minimal adverse effects, their safety and effectiveness in patients with tumor require further exploration[66].

Subgroup and meta-analyses of six phase III clinical trials investigating long-term oral anticoagulant therapy using NOACs in patients with CAT who have a prior history of tumor or are currently in an active tumor stage (approximately 5% of the total population) revealed that NOACs exhibit comparable safety and efficacy in both patients with and without tumor[67]. In the Zhang *et al* study[68], a randomized subgroup meta-analysis examining the treatment of active CAT with rivaroxaban (15 mg/dose, twice daily), compared to the Select-D study-a randomized, unblinded trial contrasting rivaroxaban (15 mg/dose, twice daily for 21 d, followed by 20 mg/dose once daily) with dalteparin (200 IU/kg for the initial month, then 150 IU/kg/d)-explored the efficacy of prolonged anticoagulant therapy. This evaluation assessed the incidence of hemorrhagic events and clinically relevant non-major hemorrhagic events in patients over 6 months, revealing that the rVTE at 6 months stood at 4% in the rivaroxaban group and 11% in the dalteparin group. Moreover, major and non-major clinically relevant bleeding rates were 17% and 6% in the rivaroxaban group, respectively. A meta-analysis indicated a decrease in rVTE following LMWH treatment in contrast to patients treated

with VKAs [relative risk (RR) = 0.52, 95%CI: 0.36-0.74]. However, direct oral anticoagulants (DOACs) did not exhibit a significant reduction in rVTE (RR = 0.66, 95%CI: 0.39-1.11). Neither LMWH nor DOACs were linked to the development of major bleeding events[69]. Contrary to these findings, the International Society on Thrombosis and Haemostasis Guidance Statement suggests that NOACs might not be suitable for use in all patients with CAT due to the elevated risk of gastrointestinal bleeding. The statement emphasizes the necessity for more comprehensive and rigorous examination of the efficacy and safety of these medications through randomized, controlled trials.

Endoluminal therapy for CAT

In situations where anticoagulation is contraindicated for CAT, caution should be exercised when placing an IVCF in patients with CAT because of the high risk of thrombotic recurrence risks in this population[70]. IVTE treatment strategies encompass mechanical thrombus removal, catheter-directed thrombolysis, angioplasty, and other endoluminal therapies[71].

In cases where CAT leads to severe functional impairment or significantly affects the quality of life, such as when a tumor compresses nearby major blood vessels or metastasizes in lymph nodes, more aggressive treatment approaches may be considered. These may involve venous stenting, either with or without Contact thrombolysis with preserved catheter. The aim is to prevent further deterioration in patients' quality of life[72] due to tumor-related issues. For acute malignant superior vena cava obstruction syndrome, the primary treatment is endovascular stenting of the superior vena cava, either solely or in conjunction with radiotherapy and/or chemotherapy[72].

Although endovascular interventions prove effective and safe in alleviating symptoms and enhancing the quality of life, there's a scarcity of comprehensive data from international researchers on endoluminal treatment for tumor-related VTE. Existing data are mainly obtained from of case reports and studies with small sample sizes. This limited information might be attributed to the shorter life expectancy of most patients with tumor, where preventing potentially fatal PE becomes a therapeutic priority. Additionally, patients with advanced tumors often lack sufficient survival time to develop post-thrombotic syndrome post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension[73]. Moreover, individuals with tumors have a heightened risk of rVTE and are more susceptible to in-stent reocclusion post-thromboplasty than patients without tumor. Hence, the risk-benefit analysis of angioplasty in patients with CAT should be thoroughly evaluated.

CONCLUSION

The risk associated with CAT varies based on the malignancy type, stage of development, and the patient's susceptibility to both thrombosis and anticancer therapies. However, CAT significantly impacts patient survival, mortality rates, and the overall quality of life in individuals with tumors. Consequently, enhancing risk assessment models to predict thrombosis risk and comprehending the pathogenesis of CAT are crucial. These steps aid in identifying high-risk CAT patients and devising suitable preventive measures.

Therapeutic approaches for CAT remain uniquely challenging, demanding tailored anticoagulation durations aligned with tumor activity and ongoing anticancer treatments. In the era of personalized medicine, frequent individualization of drugs, doses, and durations is imperative. While endoluminal therapy gains attention in CAT research, various aspects of its clinical application require further exploration.

FOOTNOTES

Author contributions: Wang TF and Chen Q conceived and presented the idea; Deng J, Xu Y and Ma SX wrote the manuscript with the support of Ma SX, Xu Y, Li SL and Wang TF; Ma SX supervised the results of this work; Ma SX oversaw the process and was responsible for the overall planning and management. All authors discussed the results and contributed to the final manuscript.

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MINIREVIEWS

Splenic hamartomas in children

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Abstract

Splenic hamartomas (SHs) are uncommon, benign vascular lesions of unclear etiology and are mostly found incidentally on abdominal images, at surgery, or at autopsy. Since the first case description, in 1861, less than 50 pediatric SH cases have been reported in the literature. In this article, we have performed an analysis of all SH cases in children published in the literature to date and presented our case of an 8-year-old male with SH. These lesions in children were shown to cause symptoms more often than in the adult population. The observed SH sizes in children ranged from a few millimeters to 18 cm, and the symptomatic lesions were mostly larger or multiple. The most common clinical finding was splenomegaly. Signs of hypersplenism were present in children with a single SH larger than 4.5 cm (diameter range: 4.5-18.0 cm) and in those with multiple hamartomas, ranging from a few millimeters to 5 cm. Eighty percent of patients with available laboratory findings had hematological abnormalities such as anemia, thrombocytopenia, or pancytopenia. Other symptoms and signs included abdominal pain, recurrent infections, fever, night sweats, lethargy, growth retardation, and weight loss. The use of multiple imaging modalities may suggest the preoperative diagnosis of a splenic mass in children and determine the therapeutic approach. However, the final diagnosis of SH relies on histopathological evaluation. Surgery, including total or partial splenectomy (PS), is the mainstay of SH management.

Although total splenectomy carries a greater risk of overwhelming post-splenectomy infection than PS it has remained the most performed surgical procedure in children with SH. In the majority of pediatric patients with symptomatic SH, resolution of symptoms and resolution or improvement of cytopenias occurred after surgical treatment.

Key Words: Splenic hamartoma; Pediatric; Splenoma; Clinical features; Radiological features; Histopathology; Treatment

Core Tip: This article provides a comprehensive analysis of all splenic hamartoma (SH) cases in children published in the literature until 2023 and presents our case of an 8-year-old male with SH. The relevant literature in English on pediatric SH was searched with special reference to demographic, clinical, radiological, and pathological features and treatment. The literature search was performed using Medline *via* the PubMed database, Google Scholar, and Cochrane Database, using the following terms: "splenoma"; "hamartoma"; "spleen"; "masses"; "lesion" and "children". Forty-six histopathologically confirmed SHs in children were found in the literature.

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INTRODUCTION

Splenic hamartoma (SH) is a rare, benign vascular proliferation and is mostly found incidentally on abdominal images, at surgery, or at autopsy. These lesions vary in size, ranging from a few millimeters to 20 cm. SHs have also been referred to as splenomas, spleen within a spleen, posttraumatic scars, fibrotic nodules, tumor-like congenital malformations, and hyperplastic nodules. The first case was described by Rokitansky in 1861 and about 200 cases have been reported so far[1-3]. The incidence varies according to the results of different studies, ranging from 0.024% to 0.13% in autopsy specimens [4,5] and 0.17% to 9.7% in spleens of patients who underwent splenectomy[4,6]. However, the frequency of these lesions could be underestimated due to the splenic fragmentation that is performed as a way to ease extraction in laparoscopic splenectomy (LS)[6].

The etiopathogenesis of SH is not clear. While it is considered a congenital malformation by some authors, others claim that it might be an acquired proliferative process, being a neoplasm or developing as a response to trauma, infection, or ischemia (Figure 1)[7-9].

SH may be a diagnostic challenge because it is often asymptomatic or presents with non-specific symptoms and has no pathognomonic radiological appearance. Therefore, histopathological analysis represents the cornerstone of correct diagnosis[2,10,11].

These lesions may be identified in all age groups[2], with only about 20% of cases occurring in children[12]. Some clinical features differ between adult patients and children with SH[2,13]. We present a comprehensive overview of SHs in children by analyzing all the cases presented in the literature and reporting our case of an 8-year-old male with SH.

CASE REPORT OF AN 8-YEAR-OLD MALE WITH SH

An 8-year-old male complained of intermittent pain in the left hypochondrium. His other past medical history was unremarkable. Physical examination showed no abnormalities, and laboratory blood analyses were within reference ranges. An abdominal ultrasound examination revealed an oval-shaped, clearly defined, slightly hypoechoic lesion (36 mm in diameter) in the lower pole of the spleen, with discrete posterior amplification. A complete removal of the lesion was achieved by partial splenectomy (PS). Grossly, the resected part of the spleen was 7.5 cm × 3.5 cm × 2.5 cm. On the cut surface, there was a 2.7 cm × 2.5 cm nodule, lighter than the surrounding normal splenic tissue (Figure 2). Histopathological examination revealed a nodular mass compressing the surrounding splenic parenchyma. The mass was composed of disorganized vascular channels lined by inconspicuous endothelial cells. No lymphoid follicles were detected in the lesion. Moreover, there was no atypia, mitotic activity, or necrosis (Figure 3). Immunohistochemistry of sinusoidal lining cells showed positive staining for CD8, CD31, and CD34 antigens and negativity for CD21 antigen (Figure 4). All this led to a diagnosis of SH. After 5 years of follow-up, the patient was doing well.

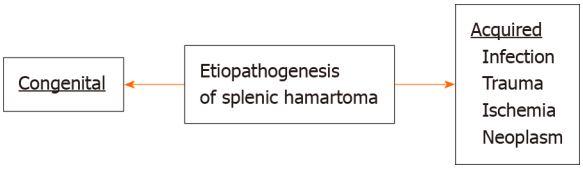

Figure 1 Possible etiopathogenesis of splenic hamartoma.

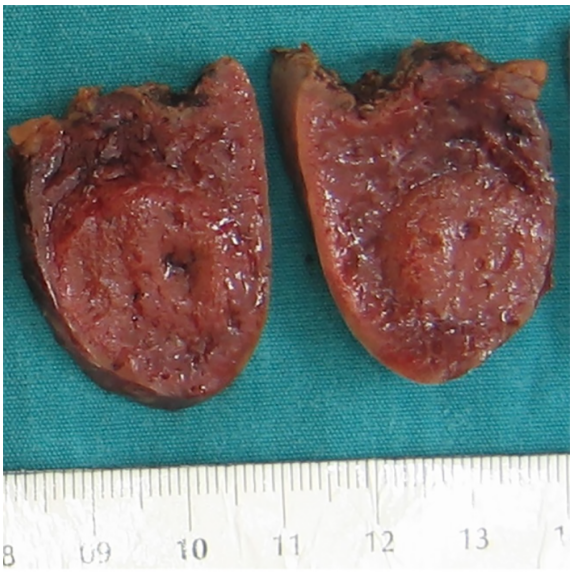

Figure 2 Gross appearance of splenic hamartoma. A nodular circumscribed unencapsulated lesion is visible on the cross-section, representing splenic hamartoma.

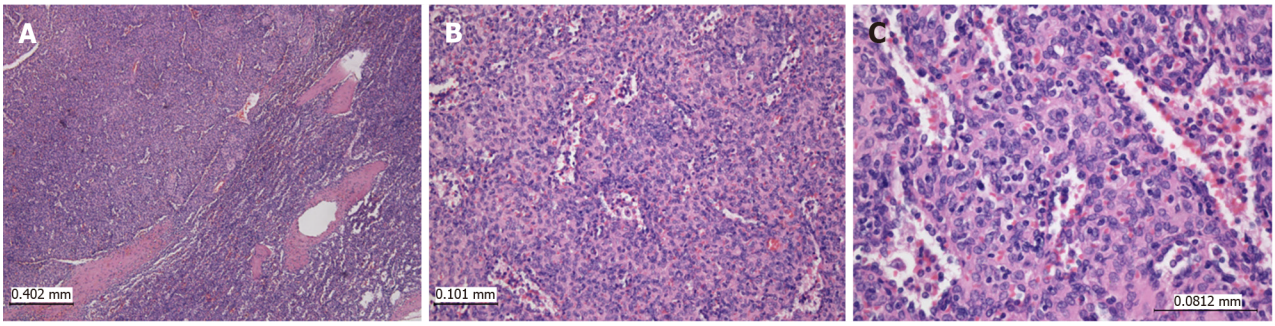

Figure 3 Microscopic images of the splenic hamartoma. A: Splenic hamartoma adjacent to normal splenic parenchyma was observed in the upper left of the panel, and compressed splenic parenchyma was observed in the lower right [hematoxylin and eosin (HE) × 50]; B: The lesion was composed of disorganized vascular channels lined by endothelial cells without significant cytological atypia (HE × 200); C: No mitosis or atypical cells were observed (HE × 400).

LITERATURE SEARCH

A literature search was performed *via* the PubMed database (www.pubmed.gov), Google Scholar (www.scholar.google.com), and the Cochrane Database up to 2023, using the following terms: "splenoma"; "hamartoma"; "spleen"; "masses"; "lesion" and "children". Data were collected on age, sex, number, size, and location of hamartomatous nodules, clinical signs and symptoms, laboratory findings, imaging, indication for surgery, type of operation, and outcomes. The search revealed 47 cases described as SH in children[5,6,8,11-33].

All the cases analyzed in this review were diagnosed with SH by histopathological examination. A report by Raouani *et al*[34] was excluded due to a lack of histopathological confirmation of the diagnosis of SH. Data on all included cases found in the literature (46 patients), as well as on our case, are listed in Supplementary Table 1. Data in some cases were incomplete because they were extracted from an abstract or cited text without having insight into the entire original article. The statistical analysis was performed using IBM SPSS Statistics software (IBM Corp., Armonk, NY, United States).

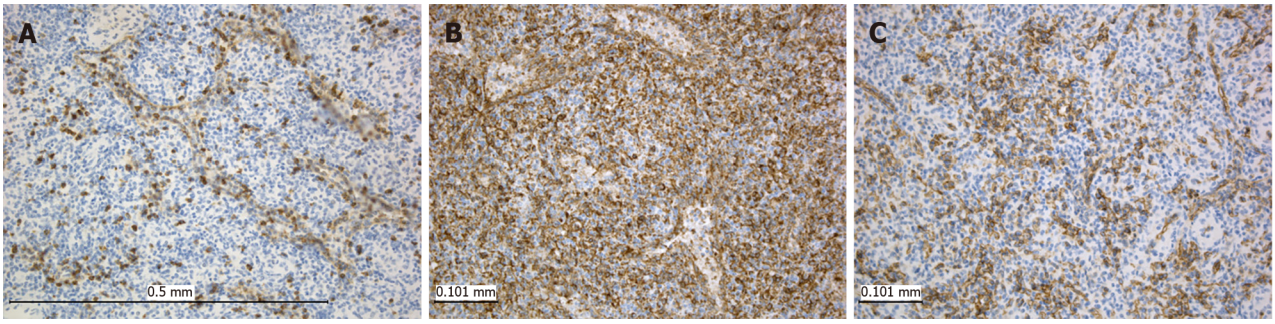

Figure 4 Immunohistochemical staining of the splenic hamartoma. A: CD8 was positive in the lining cells of vascular channels and in rare lymphocytes (× 200); B: Strong staining for CD31 was observed in the lesion (× 200); C: The lining cells of sinus-like spaces in the hamartoma were immunoreactive for CD34 (× 200).

DEMOGRAPHIC AND CLINICAL FEATURES OF PEDIATRIC PATIENTS WITH SHS

The age data were available for 42 patients. Among them, the mean age was 8.3 years (range: 0.4-18.0 years). Sex data were available for the 42 patients (18 females and 24 males) and showed no significant difference in SH occurrence between the sexes. Thirty-five patients had solitary nodule whereas ten patients had multiple nodules, indicating the frequency of patients presenting with a solitary lesion was 78% (35/45). For 2 patients, there were no data regarding the number of nodules. The previously reported share of cases presenting with a single SH in adults was 55.5% in one study [35] and 88.9% in another[29]. The size of SH in children varied from a few millimeters to 18 cm in diameter[15,20]. Unlike the adult population, in which a higher frequency of large lesions was observed in female patients[4,9,36], there was no difference in SH size between males and females in our analysis of pediatric cases.

Approximately 80% of SH cases in adults are asymptomatic[37]. However, larger lesions may cause abdominal discomfort and pain, symptoms of compression on surrounding structures, or may be associated with hypersplenism. Although SHs are less common in the pediatric population compared with the adult population, the percentage of affected children having symptoms was higher than in adult patients[8,13]. In this study, different data regarding clinical presentation were available for 34 children. Over 94% (32/34) of patients had symptoms. However, it is unclear whether these symptoms were specifically related to SH[5,8,11-18,20-24,26,28,30-33,38,39]. Two patients were asymptomatic[25,27], and there were no data regarding clinical presentation in thirteen patients[6,10,13,15,16,19,40]. Although, in general, symptomatic SHs were usually large or multiple[38], Kassarijan *et al*[21] presented a case of a child with a single 3.5 cm SH associated with hypertension, proteinuria, weight loss, multiple cutaneous lobular capillary hemangiomas, and membranoproliferative glomerulonephritis type I. On the other hand, these symptoms may not be specifically related to SH.

Over 32% (11/34) of patients experienced some kind of abdominal pain[11,12,17,18,20,22,24,28,33]. Splenomegaly was observed in 22 patients[5,8,12-17,20,22,23,26,30-32,38,39]. In 1 patient, congestive splenomegaly was a consequence of liver cirrhosis, whereas two small SHs were additional findings[15]. Splenomegaly associated with hepatomegaly was present in 3 patients, and in 1 of them a splenorenal shunt was performed in addition to splenectomy[5,8,38]. However, a specific pathological process on the liver was not noted in these patients.

Signs of hypersplenism were present in 8 patients. These children had either a single SH larger than 4.5 cm (diameter range: 4.5-18.0 cm) or multiple splenomas, ranging from a few millimeters to 5 cm[5,8,13,17,20,32,38,39]. Although symptomatic SHs causing hypersplenism in children and adults were mostly larger, Tsitouridis *et al*[1] reported a 64-year-old patient with a SH 3.5 cm in diameter that caused abnormal splenic overactivity, mimicking hypersplenism. Spleen size and histology were normal and blood counts returned to normal after splenectomy.

Laboratory data were provided for 31 patients. Eighty percent of patients (25/31) had a hematologic abnormality such as anemia[5,8,13,14,16,17,21,23,25,26,32,39,40], thrombocytopenia[8,13,17,18,39], or pancytopenia[8,13,20,32,38], and specific associated diagnoses included bone marrow hyperplasia[8,13,32,38], sickle cell anemia[8,23,27], hereditary spherocytosis[8,16], congenital dyserythropoietic anemia[8], and β thalassemia[17,26]. One patient was diagnosed with splenic lymphoma[16].

Systemic symptoms and signs such as recurrent infections, fever, night sweats, lethargy, weight loss, and growth retardation were reported in 5 patients. These symptoms resolved after splenectomy in all patients[8,17,20,38]. One patient with a 5.4 cm SH presented with parotid swelling accompanied by fever and anorexia[13].

Urinary symptoms and signs in patients with SHs are rare. Serra *et al*[28] reported a case of a child with 5.5 cm SH that presented with lumbar pain, fever, and microhematuria. Urinary tract infection (UTI) was diagnosed in 2 patients. The first patient underwent radiological evaluation of the UTI, which included ultrasonography (US) and computed tomography (CT), and SH with a diameter of 4.0 cm was found[8,19]. The other patient suffered from recurrent UTIs, which, interestingly, resolved after the removal of the 6.0 cm large SH by PS[22]. Furthermore, proteinuria together with anemia and splenomegaly was reported in a patient with a 7.0 cm SH[13].

The most severe complication of SH is rupture. Such was described in a 3-mo-old child. Despite urgent splenectomy, massive blood loss caused acute renal failure and disseminated intravascular coagulation leading to a fatal outcome on the fourth day of hospitalization[30].

There were 3 pediatric patients with SH associated with a genetic disorder. In a patient with Alagille syndrome, two SHs (2.5 cm and 4.0 cm) were postmortem findings. The genetic disorder in this syndrome consisted of *JAG1* mutations and impaired Notch signaling. Disruption of Notch signaling affects angiogenesis and arteriogenesis and might lead to various cardiovascular anomalies observed in Alagille syndrome including ventricular septal defects, tetralogy of Fallot, peripheral pulmonic artery stenosis, and coarctation of aorta. In addition, disruption of this signaling pathway is also related to the development of some vascular tumors including infantile hemangiomas and angiosarcomas[31]. Subsequently, it might be possible that the SHs in this patient were also a consequence of the Notch signaling disorder. The second patient suffered from Wiscott-Aldrich syndrome, a disorder characterized by immunodeficiency and microthrombocytopenia[13]. The third patient from this group was diagnosed with tuberous sclerosis, a genetic disease characterized by non-cancerous tumors that may appear in many vital organs. There is a possibility that the SH in this patient might be part of the tuberous sclerosis complex[6].

RADIOLOGICAL FEATURES OF SH IN CHILDREN

Although the final diagnosis of SH depends on histopathological evaluation, advances in imaging modalities provide the possibility of a preoperative assumption of the diagnosis. SH is often discovered incidentally during radiological evaluation for other reasons. Although it is a rare benign entity, it can be challenging to differentiate from some malignant splenic diseases[25,29,41]. Adequate preoperative diagnosis helps a surgeon to decide whether to proceed with a spleen-preserving procedure, sparing essential functions of the spleen and avoiding complications of a total splenectomy (TS), especially in the pediatric population[42-44]. In patients presented in this review, various imaging modalities including US[6], color Doppler[12], contrast-enhanced US[24], CT[29], positron emission tomography-CT[25], scintigraphy, angiography[14], and magnetic resonance imaging (MRI)[6] were used for the evaluation of SH.

Twenty-five patients from this review, including our case, underwent US[8,11-14,17,18,20-22,25,27,28,30,33,45]. In 5 patients, this diagnostic modality detected only splenomegaly but not a focal lesion[8,13]. On the US, SH is usually a well-defined solid mass but may have varying echogenicity[13,41,45,46]. Rarely, it may contain calcifications, cysts, or hemorrhage, appearing heterogeneous to normal splenic parenchyma[47,48], as presented by Thompson *et al*[20] and Serra *et al*[28]. Some SHs appeared as hyperechoic solid lesions compared to the adjacent normal splenic parenchyma[6,22,27]. In contrast, in multiple cases including ours, SHs were hypoechoic, most likely due to the predominant composition of red pulp with a lack of white pulp and fibrous trabeculae[6,11,12,21,25,33]. Finally, Zhang *et al*[12] presented a patient with a well-defined isoechoic mass representing SH.

On color Doppler images, SH is often characterized by increased blood flow representing the hypervascularity of the red pulp[12,24,25,28]. Tatekawa *et al*[24] performed contrast-enhanced US using Levovist, confirming the hypervascularity of SH previously detected on color Doppler imaging. Some authors detected the hypervascular appearance of the lesion by performing an angiogram[14,18], while in the case presented by Silverman *et al*[5], a large, relatively avascular mass was demonstrated.

CT was performed in 15 children with SH[8,12,13,17,18,20-22,24,26,29,31-33,40]. On plain and contrast-enhanced CT images, SHs usually appeared as heterogeneous masses[12,17,20,24,26,29], sometimes containing areas of lower density suggesting necrosis or hemorrhage as presented by Havlik *et al*[17] or calcifications as reported by Giambelluca *et al*[26]. In some cases, CT could not delineate the lesion[8,13,21] or demonstrate a focal lesion with decreased attenuation[32]. Avila *et al*[25] performed positron emission tomography-CT, showing a moderate uptake of fluorine 18-labeled fluorodeoxyglucose in a low-attenuating splenic mass.

Scintigraphy was performed in 6 cases[13,14,17,18,20,21]. In a patient presented by Hayes *et al*[13], only splenomegaly without a shift in radionuclide uptake was noted. Similarly, Kassarjian *et al*[21] reported a case with a focal area of absence of uptake at the spot of SH. Furthermore, a faint uptake was noted in 3 patients[14,17,20], while Okada *et al*[18] reported a SH case with increased activity on radionuclide scintigraphy correlating with a hypervascular mass detected by other imaging methods.

Among 47 patients presented in this article, MRI was used in a diagnosis of SH in 14[6,8,11,12,20,21,24,28,30,31]. Most authors found that SH appeared hyperintense on T2-weighted (T2W) MRI[6,12,20,21]. Less frequently, hypointense or intermediate signal compared to normal splenic tissue was described[6,11]. The appearance of SH on T1-weighted MRI was inconsistent, presenting as a hypointense[12,21], isointense[20], or hyperintense mass[10,12]. Postcontrast images usually showed diffuse homogenous or heterogeneous enhancement, indicating the vascular nature of the lesions[6,12,21]. Tatekawa *et al*[24] performed superparamagnetic iron oxide-enhanced MRI that showed a decrease in signal intensity on T2W gradient-echo imaging. These distinct MRI findings are considered to represent different histological types including fibrous and non-fibrous SH[20,41,49,50]. In a recent paper, Sabra *et al*[11] demonstrated no significant restriction of diffusion on diffusion-weighted imaging MRI.

The most common radiological differential diagnoses of SH are hemangioma[12,21,28] and some other benign lesions like inflammatory pseudotumor[12,25]. Sometimes, SH may resemble some malignant lesions, which makes it hard to choose the appropriate therapeutic approach. Malignancies that are often mentioned as possible differential diagnoses are lymphoma[12,25,27], angiosarcoma[12,27], or metastases in cases of multiple lesions[27].

PATHOLOGICAL FEATURES OF SH

Gross

SHs are represented by one or more well-circumscribed, unencapsulated, solid nodules[27].

Microscopic

SHs are composed of an abnormal cluster of the splenic red pulp presenting as irregularly arranged vascular channels of varying sizes, lined by splenic sinus endothelium (littoral cells) surrounded by fibrotic splenic (Billroth) cords. These lesions lack the white pulp. Scattered lymphocytes and histiocytes may be present throughout the stroma, along with other inflammatory cells and extramedullary hematopoiesis. Other features that may be found are fibrosis, calcified areas, hemosiderin, and adipocytes. The transition of the lesion to the surrounding parenchyma of the spleen is gradual[8]. The splenic parenchyma around the lesion is compressed without the formation of a pseudocapsule[51]. In rare case reports, stromal cell proliferation in SH has been described with the presence of larger, atypical, mononuclear cells[25] or bizarre stromal cells[3].

Immunohistochemistry

Immunohistochemistry is important in distinguishing hamartoma from other vascular neoplasms of the spleen. As endothelial cells of SH originate from splenic-type endothelial cells, their key feature is CD8 positivity[9]. Along with this, these cells are positive for CD31, vimentin, and factor VIII–related antigen but negative for CD21 antibody. CD34 exerts inconsistent staining of vascular spaces in SH according to different studies, but it is mostly negative. CD68 is positive in stromal macrophages but negative in the lining cells of the vascular spaces. The Ki-67 (also referred to as MIB-1) proliferative index is low, being expressed in less than 5% of endothelial cells in the nodule[8].

The main pathological differential diagnosis is with benign vascular tumors such as hemangiomas and littoral cell angiomas. In hemangiomas, endothelial cells are positive for endothelial markers including CD31 and CD34 and negative for CD8, CD21, and CD68. In littoral cell angiomas, the lining cells are positive for both endothelial and histiocytic markers CD31 and CD68 and negative for CD8 and CD34. CD21 is reported to be exclusively positive in littoral cell angiomas[9].

TREATMENT OF SH IN CHILDREN

A need for histopathological specimens and the possibility of complications of the SH in children make surgery the first choice in the treatment of this lesion. Surgical resection can be achieved by TS or PS. The choice of surgical procedure must be based on the number, site, and size of the lesions, the patient's age, and possible postoperative impairment to immune function. The indications for splenectomy in our study included splenic mass, severe anemia in hematological disorders, sequestration crisis, hypersplenism, splenomegaly, and spontaneous splenic rupture. Splenectomy was performed in 46 children, whereas in 1 patient SH was a postmortem finding.

TS ensures the complete removal of the pathological process in the spleen but makes patients susceptible to a variety of different infections, especially the ones caused by encapsulated organisms as they are more resilient to phagocytosis. The most concerning complication of TS is overwhelming post-splenectomy infection, which is associated with significant morbidity and mortality rates. The incidence of fatal infection in asplenic children is about ten times higher than in the control population[52]. Younger age at splenectomy is an important risk factor for infection[53]. In addition, TS is associated with a higher risk of thromboembolic events, such as portal vein thrombosis, deep venous thrombosis and pulmonary embolism, and according to some studies-pulmonary hypertension[54-56]. Still, TS is the most frequently performed procedure for the treatment of SHs. The factors that usually indicate TS are large size, central localization, and unclear etiology of the lesion, as well as the experience of the operator[44,57,58]. In children with SH, 35 TS were performed. Open TS (OTS) was performed in 21 patients. Among these, 7 cases specifically stated that OTS was performed[5,11,14,18,27,33,40]. The next 14 cases were reported before the first publication of LS. Therefore, we presumed that the open approach was applied[13,15,16,30,38,39]. The remaining 14 cases were reported after the first report of LS and there were not enough data to conclude whether an OTS or laparoscopic TS was performed[6,8,12,13,20,23,26,32].

LS is the technique of choice for the surgical treatment of SHs, offering the benefits of a minimally invasive approach. However, LS may be very hard to perform in an extremely large spleen when the space in the child's abdomen limits the handling of laparoscopic instruments and the spleen. Moreover, LS requires a highly trained surgeon and adequate laparoscopic equipment. In children with SH, four laparoscopic TSs were performed[10,24,25].

PS comprises removing 70%-80% of the spleen. It has been shown in experimental models that the remaining 25%-30% of the initial splenic tissue may provide sufficient immune activity[59]. PS is suitable for small-to moderate-sized lesions, not centrally located, and having well-defined margins[10]. However, PS may be a difficult surgical procedure requiring familiarity with the end-vascular distribution of intrasplenic vessels and the competence to deal with significant bleeding that may occur during tissue dissection.

In children with SH, five open PSs, including our case[17,19,21,22], and two laparoscopic PSs (LPSs) were performed [10,28]. Although the LPS seems to be the most beneficial procedure for SH treatment, reliable data on the risk-benefit ratio of LPS has not yet been precisely defined[60]. An accurate preoperative image study enables PS planning. Furthermore, the risk of bleeding during dissection of the spleen parenchyma in PS may be prevented by preoperative angiography and embolization of the affected spleen pole. This procedure was performed in a child with upper pole SH presented by Serra *et al*[28]. Malignancy was ruled out by intraoperative histological examination of the frozen section,

and then a LPS was performed.

Furthermore, malignancy may be ruled out preoperatively by minimally invasive diagnostic procedures such as fine needle aspiration cytology or image-guided core needle biopsy. However, there is the possibility of diagnostic inaccuracy and procedural complications, such as bleeding or seeding the neoplastic cells into the abdominal cavity in case of malignancies[25,28,61].

In the majority of patients with symptomatic SH or hematological laboratory abnormalities, there was a resolution of symptoms and resolution or improvement of laboratory findings after PS or TS[5,8,12,13,17,20-22,28,32,38]. However, when TS is performed, it is not clear whether the hematological resolution or improvement results from spleen removal or from the hamartoma elimination. On the other hand, case reports of PS (nodulectomy) in children with SH, such as our case, suggest that a favorable clinical-hematological response to splenectomy may be related to the removal of these "tumors"[17,21,28].

CONCLUSION

SHs in children may be asymptomatic or present with abdominal pain, splenomegaly, systemic symptoms such as fever, night sweats, lethargy, growth retardation, and weight loss, or signs and symptoms that result from hypersplenism and subsequent cytopenias.

SH may be indicated by the presence of a well-circumscribed homogenous solid mass in US imaging with increased blood flow on color Doppler images. On non-enhanced CT, SH is usually a heterogenous mass while appearing hyperintense on T2W MRI and showing diffuse post-contrast enhancement.

Surgical treatment, including PS or TS, represents the cornerstone of the management of SH. Most of the children analyzed in this review underwent symptom resolution and improvement or resolution of cytopenias after surgical removal of the SH. However, in some cases, it was not clear whether the hematological resolution or improvement was a consequence of the splenectomy or the removal of the hamartoma. PS preserves the immunologic functions of the spleen and is suitable for small-to moderate-sized peripherally located lesions with well-defined margins. Still, TS is the most frequently performed procedure for the treatment of SHs in pediatric patients, and it is usually indicated by large size, central localization, unclear etiology of the lesion, and the experience of the operator.

Finally, the definitive confirmation of SH is based on histopathological analysis. The main differential diagnosis comprises benign vascular tumors such as hemangioma and littoral cell angioma, that may be differentiated by immunohistochemistry.

This review has some limitations. First, the study included a small number of cases and not all analyzed characteristics were available for all patients. Moreover, data in some cases were extracted from an abstract or cited text without having insight into the entire original article.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Chaiqin Chengqi Decoction as an adjuvant treatment for mild/moderately severe hypertriglyceridemic acute pancreatitis: A retrospective study

Hai-Fu Zhang, Ze-Xuan Su, Yong-Hang Feng, Shuo-Jun Li, Bi-Yun Xie

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Abstract

BACKGROUND

Hypertriglyceridemia is the third leading cause of acute pancreatitis (AP), and its incidence is increasing. Due to its relatively insidious etiology, it is easy to be ignored in the early stages. In China, Chaiqin Chengqi Decoction (CQCQD) has long been employed for treating AP.

AIM

To evaluate the effectiveness of CQCQD in patients diagnosed with mild/moderately severe hypertriglyceridemic AP (HTG-AP).

METHODS

In this study, the clinical data of 39 patients with HTG-AP admitted from January 2019 to November 2022 were collected. The changes of blood lipids, gastrointestinal symptoms, and abdominal pain before and after treatment were analyzed and compared between the two groups.

RESULTS

Twenty patients were treated with the conventional HTG-AP regimen, and 19 patients were additionally treated with CQCQD. After receiving treatment, the triglycerides (TG) level of the CQCQD group was lower than that of the CQCQD group (3.14 ± 0.25 mmol/L *vs* 4.96 ± 0.47 mmol/L, $P < 0.01$). After 3 d of treatment, the patients in the CQCQD group had more bowel movements than the control group (2.51 ± 0.25 times *vs* 1.00 ± 0.17 times, $P = 0.01$). The gastrointestinal function of most patients returned to normal, and the acute gastrointestinal injury score was significantly lower than that of the control group (0.11 ± 0.07 *vs* 0.42 ± 0.11, $P < 0.01$).

CONCLUSION
In patients with HTG-AP, CQCQD can significantly reduce the TG level, shorten the recovery time of defecation, significantly improve the gastrointestinal function.

Key Words: Hypertriglyceridemic acute pancreatitis; Chinese medicine; Chaiqin Chengqi Decoction; Serum lipid; Triglycerides

Core Tip: Applying Chaiqin Chengqi Decoction (CQCQD) for treating acute pancreatitis (AP) has a long-standing history in China. To validate the efficacy of CQCQD in treating hypertriglyceridemic AP (HTG-AP), we conducted a retrospective analysis of patients with HTG-AP treated at our hospital. We compared and analyzed changes in blood lipid levels, gastrointestinal symptoms, and abdominal pain before and after treatment. Following treatment, the CQCQD group exhibited significantly lower triglyceride levels compared to the control group (3.14 ± 0.25 mmol/L *vs* 4.96 ± 0.47 mmol/L, $P < 0.01$). Additionally, shortened defecation recovery time and a notable improvement in gastrointestinal function were observed.

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INTRODUCTION

After alcohol and cholecystolithiasis, hypertriglyceridemia is the third leading cause of acute pancreatitis (AP), accounting for about 10% of all causes, and its prevalence in the Asian population is higher and increasing[1,2]. In addition, the causes of hypertriglyceridemic AP (HTG-AP) are insidious and are commonly ignored in the early stages. Consequently, it is easy to miss a diagnosis, resulting in a disease that progresses to greater severity[3,4].

Excessive serum triglyceride (TG) levels are necessary for developing HTG-AP, and the severity of pancreatitis increases as TG levels increase[5]. High levels of chylomicrons in plasma increase blood viscosity, impair pancreatic microcirculation, and lead to ischemia[6]. Free fatty acids (FFAs) produced by simultaneous lipolysis of excess TG cause capillary damage and intracellular calcium overload in the pancreas[7]. FFAs can also stimulate the production of inflammatory mediators such as tumor necrosis factor α, interleukin (IL)-6, and IL-10, resulting in an inflammatory cascade that damages the pancreas and other organs[8].

In addition to supportive therapy, as with other causes of AP, HTG-AP treatment includes HTG treatment[9]. Hyperlipidemia is treated with lipid-lowering agents and plasma exchange, which significantly increase the risk of infection[10]. Furthermore, because many traditional Chinese medicines inhibit the inflammatory response and lower blood lipids, many people have attempted to combine traditional Chinese medicine to treat HTG-AP[11]. In treating conventional pancreatitis, Chaiqin Chengqi Decoction (CQCQD)[12], Da-cheng-qi Decoction[13] and Chaihu Guizhi Ganjiang Decoction[14] have demonstrated some curative effects. Rhubarb is included in the above-mentioned decoctions, which have the effects of lowering inflammatory mediators, reducing organ damage, and relieving defecation [15].

To confirm the efficacy of CQCQD in treating HTG-AP, we conducted a retrospective analysis of patients with HTG-AP treated in our hospital from January 2019 to November 2022.

MATERIALS AND METHODS

Patients

The clinical data of 39 patients with HTG-AP admitted to the First Hospital of Fuyang Hangzhou from January 2019 to November 2022 were retrospectively analyzed. All patients had mild-to-moderate pancreatitis and were previously treated with lipid-lowering therapy if tolerated by the gastrointestinal tract. Among them, 19 patients took oral Chinese medicine in the early stages, whereas the remaining 20 patients did not (Figure 1).

Inclusion criteria

Patients who meet all the following criteria will be included: (1) Satisfied two of three of the following diagnostic criteria for AP: Typical symptoms and signs of abdominal pain (acute, sudden, persistent, and severe epigastric pain radiating to the back), elevated serum amylase and lipase levels of at least three times the upper limit of normal, and imaging findings consistent with AP; (2) The serum TG level > 11.30 mmol/L, or the TG level was between 5.65 and 11.30 mmol/L, but the serum was chylous[16]; (3) Other causes of pancreatitis (*e.g.*, bile duct disease, alcohol consumption, trauma, and tumor) were ruled out; and (4) The severity of pancreatitis ranged from mild to moderate.

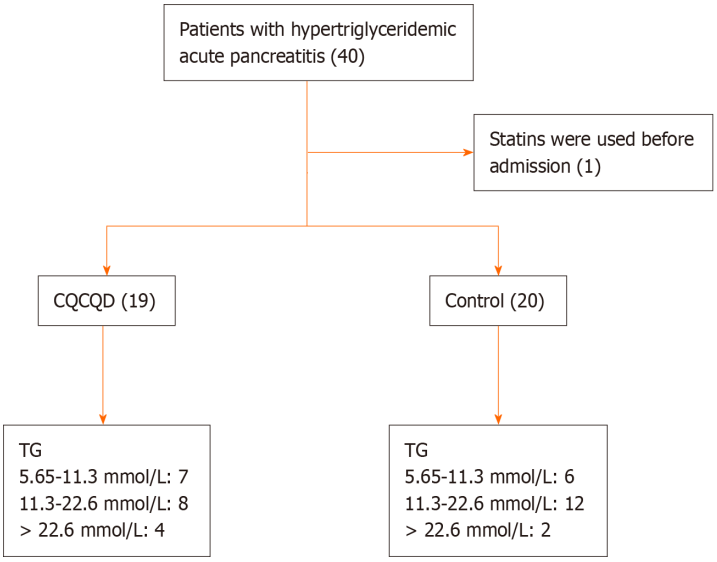

Figure 1 A flowchart depicting the patient selection process. CQCQD: Chaiqin Chengqi Decoction; TG: Triglyceride.

Exclusion criteria

Patients who meet all the following criteria will be excluded: (1) Recurrent episodes of chronic pancreatitis; (2) Known history of duodenum, liver, gallbladder, or bile duct neoplasms; (3) Chronic alcohol abuse; (4) Combined cholecystolithiasis and choledocholithiasis were observed; (5) Combined with gastrointestinal bleeding or mechanical ileus; (6) Had comorbid malignancies and had received radiotherapy, chemotherapy, oral targeted agents, or immunotherapy in the previous half-year; (7) Had taken traditional Chinese medicine in the past six months; (8) Had combined familial hypercholesterolemia or were on long-term oral lipid-lowering medication for various arterial stenoses; and (9) Pregnancy or lactation.

Herbal formulation

Please refer to Table 1 for further details.

Calculation of the assessment scale

The presence or absence of gastrointestinal symptoms such as abdominal pain, abdominal distension, nausea and vomiting, and cessation of defecation was used to calculate the acute gastrointestinal injury (AGI) score[17]. The bedside index for severity of AP was used to evaluate the prognosis of patients based on blood urea nitrogen levels > 25 mg/dL, disturbance of consciousness, systemic inflammatory response syndrome, age, and pleural effusion[18]. The Balthazar computed tomography (CT) severity index was used to assess disease severity, and the prognosis was determined by combining the imaging grade of AP and the degree of pancreatic necrosis[19].

Statistical analysis

All data are presented the mean ± SEM. The IBM SPSS Statistics 23 statistical software was used for statistical analysis. The independent sample *t*-test was used to compare differences between groups, and statistical significance was set at $P < 0.05$. All statistical plots were prepared using GraphPad Prism 7 software.

RESULTS

Clinical characteristics

In the present study, 39 patients (Table 2) were included, with an average age of 40 years. Among them, 76.92% were males, and all patients had a body mass index above the upper limit of normal. Twenty patients were treated with a conventional HTG-AP regimen, and 19 were treated with CQCQD for 3 d. Most participants (84.6%) also had fatty liver disease. At the time of admission, 13 patients in the experimental group and 9 in the control group stopped defecating. After gastrointestinal tolerance was achieved, all patients were treated with oral lipid-lowering agents (fenofibrate or atorvastatin). Serologic parameters were commonly rechecked 3-6 d (mean 4.1 d) after treatment. Abdominal CT was performed upon admission for each patient to evaluate their conditions, and most patients (89.7%) underwent CT re-evaluation 3-5 d after treatment.

Effect of CQCQD on blood lipids

At the time of admission, all patients had higher blood lipid levels [CQCQD group *vs* control group, TG: 14.93 ± 1.87 mmol/L *vs* 15.71 ± 1.72 mmol/L, $P = 0.78$; Cholesterol (CHO): 9.76 ± 0.96 mmol/L *vs* 8.71 ± 0.56 mmol/L, $P = 0.34$]. All

Table 1 Lists the Chinese herbs included in the Chaiqin Chengqi Decoction

Chinese name	English name	Latin name	Scientific name	Weight (g)
Chaihu	Chinese thorowax root	Bupleuri Radix	*Bupleurum chinense DC.*	10
Baishao	White paeony root	Paeoniae Radix Alba	*Paeonia lactiflora Pall*	10
Huangqin	Baical skullcap root	Scutellariae Radix	*Scutellaria baicalensis Georgi*	10
Zhishike	Fructus aurantii immaturus	Aurantii Fructus Immaturus	*Citrus aurantium L.*	10
Jianghoupo	Officinal magnolia bark	Cortex Magnoliae Officinalis	*Magnolia officinalis Rehd et Wils*	10
Dahuang	Rhubarb root and rhizome	Rhei Radix et Rhizoma	*Rheum palmatum L.*	10
Xuanmingfen	Weathered sodium sulfate	Thenardite	Na_2SO_4	10
Jinyinhua	Wild honeysuckle flower	Lonicerae Japonicae Flos	*Lonicera japonica Thunb.*	20
Chonglou	Yunnan manyleaf paris rhizome	Paridis Rhizoma	*P. polyphylla Smith var. chinensis (Franch.) Hara*	9

Table 2 Characteristics of the study population

Parameters	CQCQD	Control	*P* value
Number of patients	19	20	
Number of male patients	15	15	1
Age (yr)	44.00 ± 13.24	41.25 ± 10.19	0.15
Hypertension (*n*)	2	5	0.41
Diabetes (*n*)	8	9	1
Fatty liver (*n*)	18	15	0.18
BMI (kg/m^2)	28.87 ± 4.09	26.78 ± 4.38	0.43
NRS score	2.26 ± 0.28	1.68 ± 0.17	0.07
BISAP score	1.11 ± 0.17	0.65 ± 0.17	0.06
AGI score	1.00 ± 0.00	0.95 ± 0.05	0.32
Balthazar score	2.63 ± 0.22	2.37 ± 0.14	0.32
Biochemical data			
WBC (× 10^9/L)	13.51 ± 1.16	12.21 ± 1.05	0.41
HCT	0.42 ± 0.01	0.42 ± 0.01	0.96
CRP (mg/L)	130.55 ± 19.98	58.42 ± 13.50	0.01[a]
AST (U/L)	29.37 ± 2.85	30.25 ± 5.29	0.87
ALT (U/L)	25.79 ± 4.11	34.40 ± ± 4.99	0.19
CHO (mmol/L)	9.76 ± 0.96	8.71 ± 0.56	0.34
TG (mmol/L)	14.93 ± 1.87	15.71 ± 1.72	0.78
APOE (mg/L)	163.26 ± 23.11	169.94 ± 14.52	0.81
UA (μmmol/L)	363.15 ± 31.70	383.28 ± 22.85	0.61

[a]$P < 0.05$.

CQCQD: Chaiqin Chengqi Decoction; BMI: Body mass index; NRS: Numerical rating scale; BISAP: Bedside index for severity in acute pancreatitis; AGI: Acute gastrointestinal injury; WBC: White blood cell; HCT: Hematocrit; CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CHO: Cholesterol; TG: Triglyceride; APOE: Apolipoprotein E; UA: Uric acid.

patients were started on oral lipid-lowering drugs once the gastrointestinal tract could tolerate them in the early stages. The TG levels of the two groups were significantly lower than those at admission to a safe level during the first reexamination of blood lipids. However, the TG level of the CQCQD group was lower than that of the control group (3.14 ± 0.25 mmol/L *vs* 4.96 ± 0.47 mmol/L, $P < 0.01$) (Figure 2A-C). Meanwhile, APOA1 Levels were significantly lower in the CQCQD group than in the control group (0.64 ± 0.03 g/L *vs* 0.82 ± 0.04 g/L, $P < 0.01$) after treatment (Figure 2D).

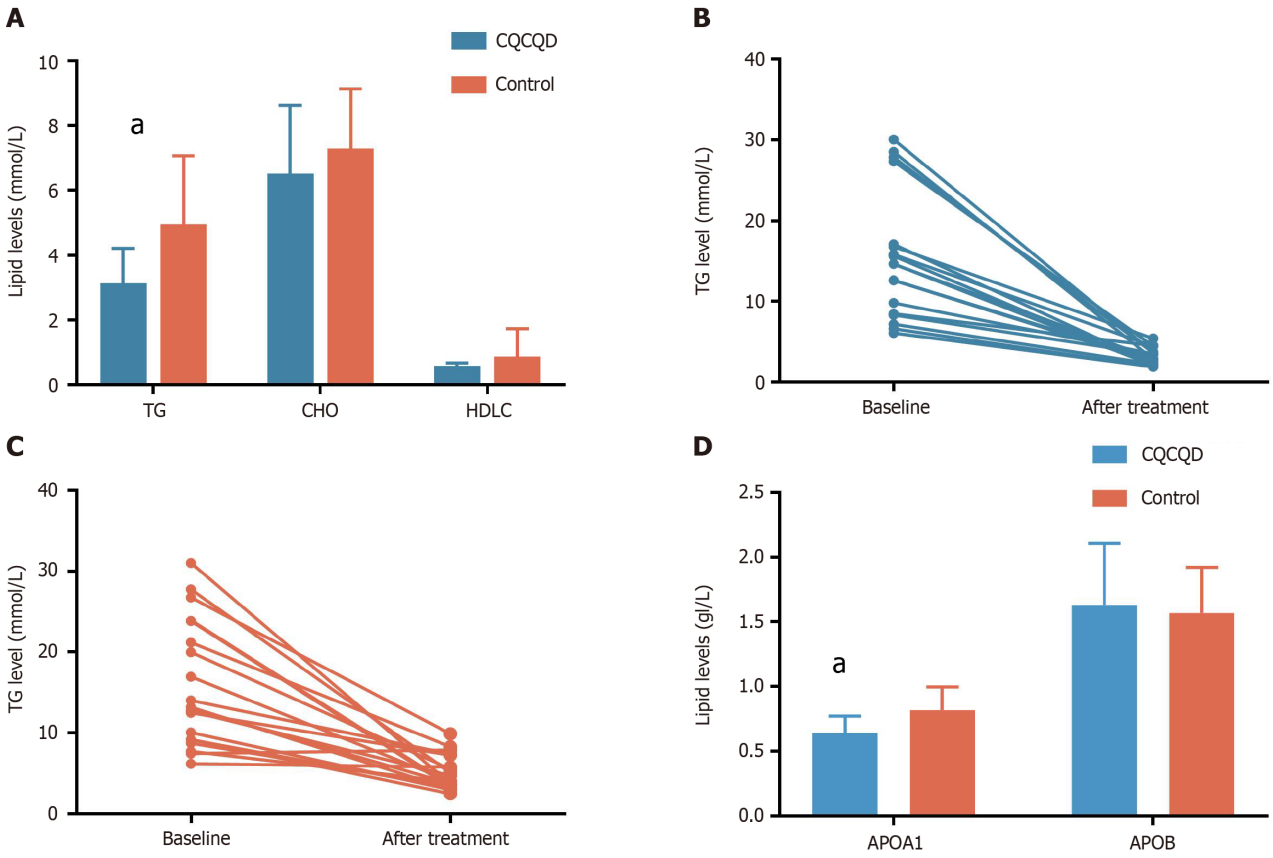

Figure 2 The alterations in lipid levels pre- and post-treatment. A: Changes in triglyceride (TG), cholesterol and high density lipoprotein cholesterol levels before and after treatment; B: Changes in TG levels before and after treatment in the Chaiqin Chengqi Decoction group; C: Changes in TG levels before and after treatment in the control group; D: Changes in apolipoprotein A1 and apolipoprotein B levels before and after treatment. $^{a}P < 0.05$. TG: Triglyceride; CHO: Cholesterol; HDL-C: High density lipoprotein cholesterol; APOA1: Apolipoprotein A1; APOB: Apolipoprotein B; CQCQD: Chaiqin Chengqi Decoction.

However, CHO, HDL-C, and APOB levels were not significantly different between the two groups after treatment (Figure 2A).

Effect of CQCQD on GI symptoms

On admission, 22 patients stopped defecating (13 patients in the CQCQD group), and 35 had varying degrees of upper abdominal pain. Except for one patient in the control group without gastrointestinal symptoms upon admission, all remaining patients had an AGI grade of 1. The time to resume defecation after adding CQCQD was significantly shorter for patients who had stopped defecation at admission than the control group (1.62 ± 0.21 d *vs* 2.40 ± 0.50 d, $P = 0.04$) (Figure 3). After 3 d of treatment, the patients in the CQCQD group had more bowel movements than the control group (2.51 ± 0.25 times *vs* 1.00 ± 0.17 times, $P < 0.01$) (Figure 4A). Simultaneously, two patients in the CQCQD group exhibited a frequency of defecation that exceeded three times per day.

The gastrointestinal function of most patients returned to normal, and AGI was significantly lower than the control group (0.11 ± 0.07 *vs* 0.42 ± 0.11, $P = 0.02$) (Figure 4B). Simultaneously, the defecation recovery time curve revealed that the CQCQD group resumed defecation faster (Hazard ratio: 3.7) (Figure 5). However, in the present study, CQCQD did not prove advantageous in relieving abdominal pain symptoms, which could be attributed to the relatively higher numerical rating scale scores in the experimental group on admission (2.63 ± 1.24 d *vs* 1.53 ± 0.70 d, $P = 0.79$) (Figure 3).

Serological indicators after treatment

Except for hematocrit, the first reexamination of serum biological indicators after treatment revealed no significant difference between CQCQD and control groups (Table 3). The C-reactive protein (CRP) level in the CQCQD group was significantly higher than that in the control group on admission. However, no significant difference was observed in the CRP levels between the two groups in the first review. Furthermore, patients in the CQCQD group had a significant decrease in CRP (86.96 ± 21.62 mg/L *vs* 29.34 ± 12.63 mg/L, $P = 0.03$) (Figure 6).

During treatment, three patients (one in the CQCQD group and two in the control group) had transient alanine aminotransferase/aspartate aminotransferase levels higher than three times the upper limit of the normal range, but all returned to normal levels.

Image changes

The Balthazar score, obtained through imaging, was also used to evaluate pancreatitis progression. There was no statist-

Table 3 The characteristics of serological indicators were examined for the first time after treatment

Parameters	CQCQD	Control	*P* value
Number of patients	19	20	
HCT	0.38 ± 0.01	0.41 ± 0.01	0.04
CRP (mg/L)	43.70 ± 11.06	29.09 ± 6.13	0.25
ALT (U/L)	35.11 ± 6.78	43.70 ± 11.93	0.55
AST (U/L)	31.78 ± 5.53	34.80 ± 7.28	0.75
ALB	36.39 ± 1.11	39.33 ± 0.99	0.06
UA (μmmol/L)	258.83 ± 33.34	341.65 ± 30.15	0.07
CERA	62.61 ± 3.18	68.15 ± 3.26	0.23

CQCQD: Chaiqin Chengqi Decoction; HCT: Hematocrit; CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALB: Albumin; UA: Uric acid; CERA: Creatinine.

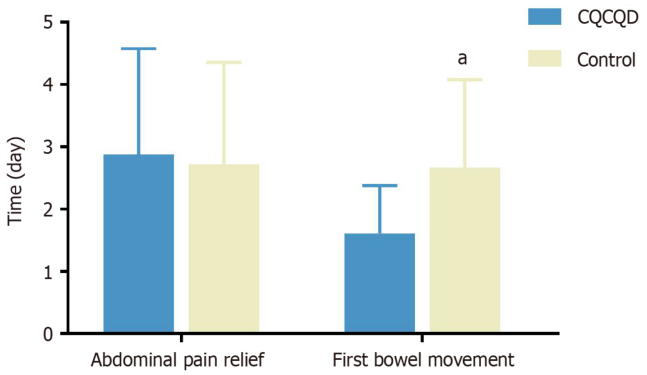

Figure 3 Analysis of bowel recovery and abdominal pain relief. [a]*P* < 0.05. CQCQD: Chaiqin Chengqi Decoction.

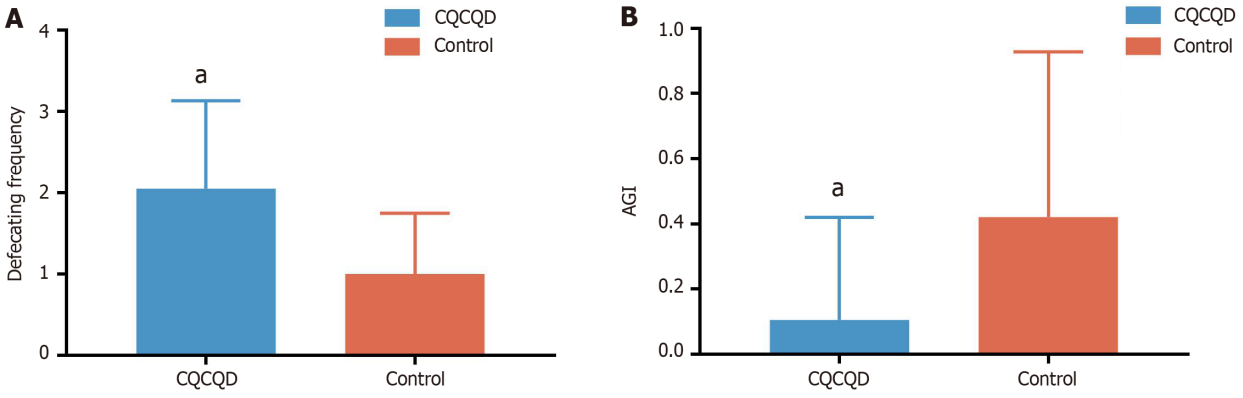

Figure 4 Analysis of acute gastrointestinal injury score and number of bowel movements after treatment. A: Comparison of defecating frequency between the two groups after 3 d of treatment; B: Comparison of acute gastrointestinal injury between the two groups after 3 d of treatment. [a]*P* < 0.05. AGI: Acute gastrointestinal injury; CQCQD: Chaiqin Chengqi Decoction.

ically significant difference in Balthazar scores between the two groups upon admission (CQCQD group *vs* control group: 2.63 ± 0.22 *vs* 2.37 ± 0.14, *P* = 0.32). Subsequent CT examination after 3-5 d of treatment revealed a slight improvement in Balthazar scores for both groups. However, no significant disparity was observed between the two groups (CQCQD group *vs* control group: 2.44 ± 0.70 *vs* 2.29 ± 0.69, *P* = 0.53) (Figure 7).

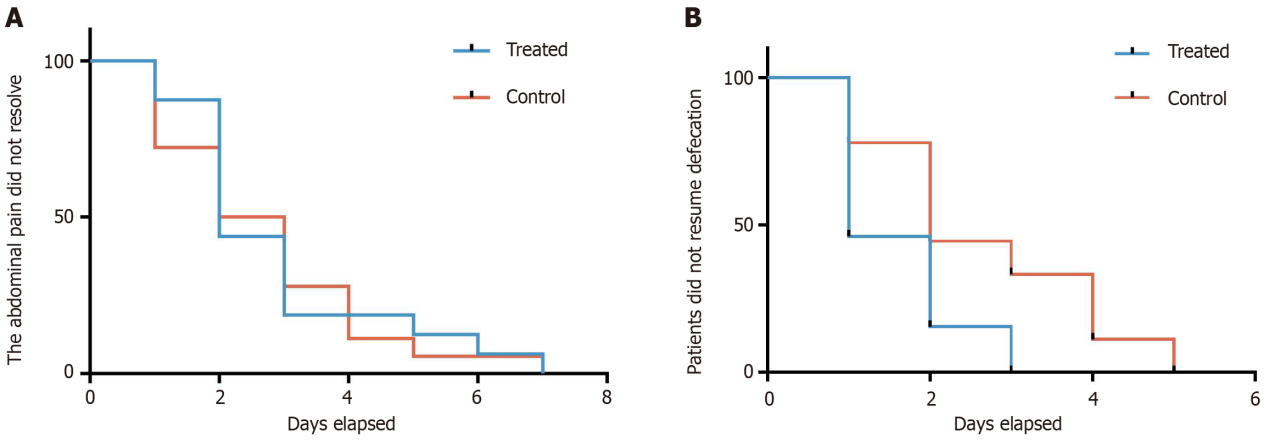

Figure 5 Analysis of duration of symptoms. A: Curves for time without relief from abdominal pain; B: Curves for time without resumption of defecation.

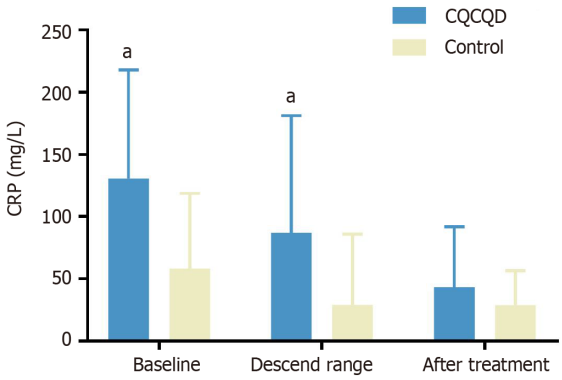

Figure 6 Analysis of the degree of decrease in C-reactive protein. $^{a}P < 0.05$. CRP: C-reactive protein; CQCQD: Chaiqin Chengqi Decoction.

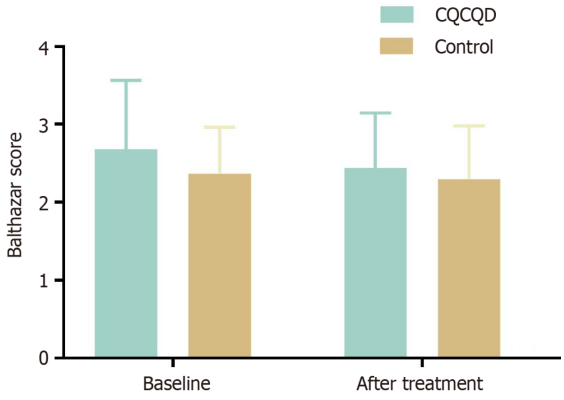

Figure 7 Changes of Balthazar score before and after treatment. CQCQD: Chaiqin Chengqi Decoction.

DISCUSSION

Compared with other causes of pancreatitis, HTG-AP has a longer disease course, is more likely to progress to severe disease, and has a worse prognosis[20]. On the one hand, because of the unique pathogenesis of HTG-AP, chylomicrons prevent pancreatic duct obstruction, while FFAs aggravate systemic inflammatory response[21]. On the other hand, a lack of attention to hyperlipidemia results in lower early diagnosis and intervention rates[22]. Consequently, the primary goal of HTG-AP treatment is to reduce TG levels to a safe level at the earliest. Patients with intestinal function tolerance can be treated with oral lipid-lowering drugs, whereas those who cannot tolerate them may require plasma exchange[23].

Oral lipid-lowering agents such as fenofibrate or atorvastatin are commonly used to treat hyperlipidemia. Fenofibrate accelerates chylomicron and TG degradation through the peroxisome proliferator-activated receptor (PPAR) pathway [24]; whereas atorvastatin reduces cholesterol and TG levels by inhibiting HMG-CoA[25]. In addition to hyperlipidemia,

patients with HTG-AP frequently have fatty liver, diabetes, and other metabolic diseases. In China, CQCQD has a long history of use for treating AP, and some drugs regulate glucose and lipid metabolism. Bupleurum can improve lipid metabolism by upregulating the FGF21 pathway and increasing the expression of *GLUT1* and *PGC-1α*[26]. Bupleuri radix and paeoniae radix alba synergistically reduce lipid production by activating AMP-activated protein kinase α (AMPK α) and inhibiting PPARγ[27]. Through the MAPK/PI3K/Akt signaling pathway, Scutellariae radix can improve insulin resistance and regulate blood lipid and glucose metabolism[28]. Because CQCQD reduces TG levels through a pathway different from that of statin/fibrate, patients with CQCQD in the present study had significantly lower post-treatment TG levels than those in the control group.

AP is frequently complicated by gastrointestinal dysfunction, which manifests as abdominal pain, distension, ileus, and bowel dilatation and plays an important role in disease progression[29]. Intestinal dysfunction promotes the translocation of opportunistic pathogens in the intestine, which can lead to infection and worsen AP[30]. The findings of the present study revealed that patients in the CQCQD group returned to defecation more quickly, with an average of 2.51 ± 0.25 defecation/d after 3-d treatment. CQCQD contains sodium sulfate, which is commonly used as an ionic laxative, as well as antibacterial and defecation-promoting Chinese herbs such as rhubarb and lonicerae japonicae flos. Rhubarb could improve gastrointestinal symptoms in patients with pancreatitis and significantly reduce the duration of abdominal pain and the time to first defecation[31]. Animal studies have revealed that rhubarb can improve gastrointestinal peristalsis function by increasing motion secretion and inhibiting the activity of Na^+-K^+-exchanging ATPase in the small intestinal mucosa[32]. Lonicerae japonicae flos has antibacterial activity against Escherichia coli, Candida albicans, and Klebsiella pneumoniae, which can help prevent infection to a certain extent[33].

Meanwhile, we confirmed that CQCQD was beneficial for gastrointestinal function recovery by comparing AGI grading. AGI grading is helpful in determining the severity of gastrointestinal dysfunction in patients with AP and can be used as an important prognostic indicator[34]. After 3-d treatment, the AGI grade in the CQCQD group was significantly lower than that in the control group.

CRP is the most commonly used and least expensive biomarker for pancreatitis, and CRP level 72 h after onset is an excellent indicator of disease severity[35]. Although the CRP levels in the CQCQD group were higher on admission, they declined more quickly. They were no longer significantly different from those in the control group, indicating that they can inhibit the inflammatory response to some extent. CQCQD treatment reduced plasma lipopolysaccharide (LPS), sCd14, and LPS-binding prot levels by inhibiting the upregulation of p-Sre, p-p85a, and c-Fos, and alleviated LPS and cytokine-mediated inflammatory exudation[36]. Saikosaponin can inhibit NLRP3 activation by downregulating the AMPK/mTOR pathway, improving islet function, preventing pancreatitis progression, and inhibiting pancreatic stellate cell activation by preventing fibrosis[37]. In addition, multiple drugs in CQCQD usually exhibit synergistic effects. Network pharmacology analysis revealed that baicalin in CQCQD reduced pancreatic acinar cell damage, and emodin, rhein, and chrysin reduced the inflammatory response by inhibiting activation of the TLR4/NLRP3 pathway[38]. Consequently, adding CQCQD quickly reduced CRP by inhibiting the inflammatory response.

In this retrospective study, no significant difference was observed in the occurrence of abnormal liver function between CQCQD and control groups. Although traditional Chinese medicine has been implicated as a potential cause of drug-induced liver damage, longer clinical observations are warranted to establish conclusive evidence. Notably, even after three consecutive days of CQCQD administration, two cases still experienced more than three episodes of defecation per day, indicating the need for timely dosage adjustment during clinical application.

CONCLUSION

CQCQD can significantly lower TG and APOA1 Levels, shorten defecation recovery time, improve gastrointestinal function, and inhibit the inflammatory response in patients with HTG-AP.

ARTICLE HIGHLIGHTS

Research background

Hypertriglyceridemia is currently the third leading cause of acute pancreatitis (AP), with its incidence continuing to rise. Moreover, there exists a positive correlation between the severity of pancreatitis and elevated levels of triglycerides (TG). Notably, Chaiqin Chengqi Decoction (CQCQD) has been historically employed in our country for the treatment of AP.

Research motivation

CQCQD has a rich historical background in the management of pancreatitis in China. The lipid-lowering effects of certain Traditional Chinese Medicine components have been observed in previous research. In order to validate its efficacy in treating hypertriglyceridemic AP (HTG-AP) and facilitate its clinical implementation, we conducted a retrospective study.

Research objectives

To assess the impact of CQCQD on blood lipid levels and clinical manifestations in patients with mild, mild/moderately HTG-AP.

Research methods
The clinical data of 39 patients with HTG-AP admitted to our hospital between January 2019 and November 2020 were retrospectively analyzed. We conducted a comparative analysis of changes in blood lipids, gastrointestinal symptoms, and abdominal computed tomography (CT) findings before and after treatment between the two groups.

Research results
Twenty patients were treated with conventional HTG-AP regimen, and 19 patients were additionally treated with CQCQD. After receiving treatment, the TG level of the CQCQD group was lower than that of the CQCQD group (3.14 ± 0.25mmol/L *vs* 4.96 ± 0.47 mmol/L, $P < 0.01$). However, there were no significant differences observed in other lipid parameters, including total cholesterol, high-density lipoprotein cholesterol, and apolipoprotein B, between the two groups. After 3 d of treatment, the patients in the CQCQD group had more bowel movements than the control group (2.51 ± 0.25 times *vs* 1.00 ± 0.17 times, $P = 0.01$). The gastrointestinal function of most patients returned to normal, and AGI was significantly lower than that of the control group (0.11 ± 0.07 *vs* 0.42 ± 0.11, $P < 0.01$). The CT reexamination conducted after 3-5 d of treatment revealed no significant difference in Balthazar score between the two groups (2.44 ± 0.70 *vs* 2.29 ± 0.69, $P = 0.53$).

Research conclusions
In HTG-AP patients, CQCQD can significantly reduce the TG level, shorten the recovery time of defecation, significantly improve the gastrointestinal function.

Research perspectives
More data are required for a more comprehensive analysis in future investigations. Simultaneously, it is imperative to conduct fundamental experiments to elucidate the underlying mechanism of CQCQD.

FOOTNOTES

Co-first authors: Hai-Fu Zhang and Ze-Xuan Su.

Author contributions: Zhang HF and Su ZX contributed equally to this work as co-first authors; Zhang HF and Su ZX carried out data curation; Zhang HF and Xie BY were responsible for designing the research study and writing the paper; Feng YH and Li SJ conducted data analysis and completed the visualization process.

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Institutional review board statement: This study is a retrospective study, and the use of patient clinical data has passed ethical review, ethical review No. 2022-lw (031).

Informed consent statement: The study received approval from the institutional review board of The First People's Hospital of Fuyang, and the requirement for informed consent was waived.

Conflict-of-interest statement: The authors declare that there are no competing interests associated with the manuscript.

Data sharing statement: The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author Bi-Yun Xie upon reasonable request.

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ORIGINAL ARTICLE

Observational Study

COVID-19 pandemic amplified mortality rates among adolescents with bipolar disorder through family-related factors

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Abstract

BACKGROUND

Recently, a growing number of adolescents have been afflicted with mental disorders, with annual morbidity rates on the rise. This trend has been exacerbated by the global coronavirus disease 2019 (COVID-19) pandemic, leading to a surge in suicide and self-harm rates among this demographic.

AIM

To investigate the impact of the COVID-19 pandemic on adolescent bipolar disorder (BD), along with the underlying factors contributing to heightened rates of suicide and self-harm among adolescents.

METHODS

A comprehensive statistical analysis was conducted utilizing clinical interviews and self-reports obtained from patients or their guardians. Diagnostic criteria for BDs were based on the Diagnostic and statistical manual of mental disorders, international classification of diseases-11, and the National institute of mental health research domain criteria. Statistical analyses were performed using SPSS 26.0 software, with significance set at $P < 0.05$.

RESULTS

A cohort of 171 adolescents diagnosed with BD between January 1, 2018, and December 31, 2022, was included in the analysis. The gender distribution was 2.8:1 (female to male), with ages ranging from 11 to 18 years old. Major factors contributing to adolescent BDs included familial influences, academic stress, genetic predisposition and exposure to school-related violence. Notably, a significant increase in suicide attempts and self-harm incidents was observed among adolescents with BD during the COVID-19 pandemic. Statistical analysis indicated that the pandemic exacerbated familial discord and heightened academic stress, thereby amplifying the prevalence of suicidal behavior and self-harm among adolescents.

CONCLUSION

The COVID-19 pandemic has exacerbated familial tensions and intensified the incidence of suicide and self-harm among adolescents diagnosed with BD. This study underscores the urgent need for societal, familial and educational support systems to prioritize the well-being of adolescents and offers valuable insights and guidelines for the prevention, diagnosis and treatment of adolescent BDs.

Key Words: Adolescents; Bipolar disorder; COVID-19; Suicide; Self-harm

Core Tip: More adolescents have suffered from bipolar disorder (BD) since the coronavirus disease 2019 (COVID-19) pandemic outbreak. A total of 171 adolescents with BD were recruited and analyzed from January 1, 2018 to December 31, 2022. Family-related factors and academic stress played significant roles in emergence and exacerbation of adolescent BDs. The COVID-19 pandemic exacerbated family relationships and greatly increased the occurrence of suicide and self-harm among adolescents with BD. This study aimed to focus the attention of society, families and schools to increase care about adolescents and also provide guidance and references for the prevention, diagnosis and treatment of adolescent BDs.

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INTRODUCTION

Bipolar disorder (BD), also known as manic-depressive illness, is a profoundly severe and complex chronic mental disorder characterized by recurrent episodes of significant emotional fluctuation. It manifests in extreme highs and lows in mood, along with altered behavior, cognition, sleep patterns and energy levels[1]. Clinically, BD presents with cognitive impairments, socio-psychological disturbances and persistent manic-depressive mood oscillations[2]. The precise etiology of BD remains elusive, posing ongoing challenges in the identification of consistent and reliable biomarkers for its diagnosis, understanding of its pathogenesis, neurobiology and treatment strategies[3].

BD ranks as a leading cause of disability worldwide, impacting at least 1% of the global population[4,5]. It affects approximately 40 million people, with an age-standardized prevalence of 489.8 *per* 100000 individuals[6]. The 20-year post-diagnosis mortality rate for BD patients exceeds 6%, which is more than 20 times higher than that of the general population[1]. Notably, about one-third to one-half of individuals with BD engage in suicidal behaviors, with up to 20% of these attempts successful[7].

The current authors research is focused on adolescents diagnosed with BD in Huangshi. Findings underscore a significant correlation between the coronavirus disease 2019 (COVID-19) pandemic and increased familial stress, which in turn has contributed to a rise in BD cases among such adolescents. Statistical analysis established a clear connection between the COVID-19 pandemic and a heightened incidence of suicidal and self-harm behaviors in adolescents suffering from BDs, predominantly influenced by family-related factors.

MATERIALS AND METHODS

Participants

A total of 171 mentally disordered adolescents aged ≤ 18 years were recruited from January 1, 2018 to December 31, 2022.

Inclusion and exclusion criteria

The diagnosis of BD was established following the criteria described in the Diagnostic and statistical manual of mental disorders, International classification of diseases-11 and the National Institute of Mental Health Research Domain Criteria

[8,9]. Participants included in the study were individuals under 18 years of age who met these diagnostic standards and had comprehensive medical records. Exclusion criteria encompassed absence of a BD diagnosis, incomplete data, or failure to fulfill the established diagnostic guidelines.

Assessment of causes

The assessment of factors contributing to BD, along with associated abnormal illness behaviors such as suicide or suicide attempts (M8) and self-harm (M9), was based on insights from previous studies[10,11]. These factors included family-related and genetic factors, school violence and academic pressure.

Statistical analysis

Data were statistically processed and analysed using SPSS version 26.0. Statistical significance was set at $P < 0.05$.

The monthly incidence of cases was compared before and during the COVID-19 pandemic employing the Mann-Whitney U test.

Binary logistic regression analysis (Forward LR method) was utilized to evaluate the impact of variables including the COVID-19 pandemic, family-related factors, academic stress and school violence on suicide and self-harm behaviors. A *P*-value larger than 0.10 indicated a lack of significant impact, leading to exclusion of the variable, while a *P*-value ≤ 0.05 signified a significant effect, warranting inclusion of the variable. The 95%CI for both *P*-values and odds ratios (OR) were also calculated.

Univariate logistic regression was employed to explore the relationship between the COVID-19 pandemic and the statistically significant influencing factors identified. Calculation of 95%CIs and ORs helped generate a comprehensive understanding of the relationships and impacts studied.

RESULTS

Case information on BD among adolescents in Huangshi, 2018-2022

This study included 171 adolescents diagnosed with BD. Figure 1A illustrates the temporal distribution of these BD cases. Figure 1B highlights a marked contrast in the incidence of BD cases between the pre-pandemic and during-pandemic periods, broken down by month.

Of the 171 adolescents with BD, 126 were female and 45 were male, resulting in a gender ratio of approximately 2.8:1, as depicted in Figure 1C. The age at onset varied from 11 to 18 years, with an average age of 15.54 ± 1.62 years. The peak incidence was observed in 16-year-olds, as shown in Figure 1C.

Potential risk factors causing BD

A significant proportion of the BD patients surveyed (125 out of 171, or 73.1%) identified family-related issues as a contributing factor to their disorder, as demonstrated in Figure 2A. Academic stress was reported as the second most prevalent cause, affecting 41.52% (71 patients). Genetic predisposition (20 patients, 13.25%) and experiences of school violence (7 patients, 4.27%) were also identified as influential factors in the development of BD, as detailed in Figure 2A.

When examining the distribution of BD cases in relation to potential contributing factors over the years, family-related factors and academic stress emerged as the predominant causes for the onset and aggravation of BD. An annual increase in the number of BD cases attributed to these factors was observed. Nonetheless, the roles of genetic predisposition and school violence in the development of BD should also be recognized, as depicted in Figure 2B.

Within the spectrum of family-related factors, being a 'left-behind' child was identified as a significant contributor in 57.6% of the cases (125 patients), and feeling unrecognized or misunderstood by family members was reported in 56.8% of these cases. Such findings highlight the major impact of family dynamics on adolescent BD, as shown in Figure 2C.

High occurrence of suicide and self-harm among adolescent BD

Abnormal illness behaviors encompass a spectrum of detrimental clinical manifestations arising from mental disorders, with the gravest instances exhibited as suicide and/or suicide attempts (M8), as well as self-harm (M9). Among the 171 cases of BD, 114 individuals reported experiencing suicidal ideation and/or making suicide attempts, while 71 patients engaged in self-harming behaviors, constituting 66.67% and 41.52% of patients, respectively (Figure 2D). Data analysis suggests the upsurge in suicide attempts and self-harm to the repercussions of the COVID-19 pandemic (Figure 2D).

Binary logistic regression analysis (Forward LR) revealed that family-related factors exerted a significant influence on suicide ($P < 0.001$, OR = 5.149, 95%CI: 2.498-10.614) and self-harm ($P < 0.001$, OR = 4.046, 95%CI: 1.803-9.081), whereas academic stress and school violence did not demonstrate statistical significance in their impact and were consequently excluded as causal factors. Subsequent univariate logistic regression analysis revealed a statistically significant effect of the COVID-19 pandemic on family-related factors ($P < 0.001$, OR = 9.507, 95%CI: 2.850-31.711) (Figure 2E).

DISCUSSION

This study included 171 BD patients, with a higher prevalence among females than males, possibly due to emotional sensitivity and hormonal fluctuations. Age analysis revealed a peak in patient numbers at 16 years, coinciding with the high school entrance examinations. The onset age predominantly ranged from 13 to 17 years in the studied cohort, with a

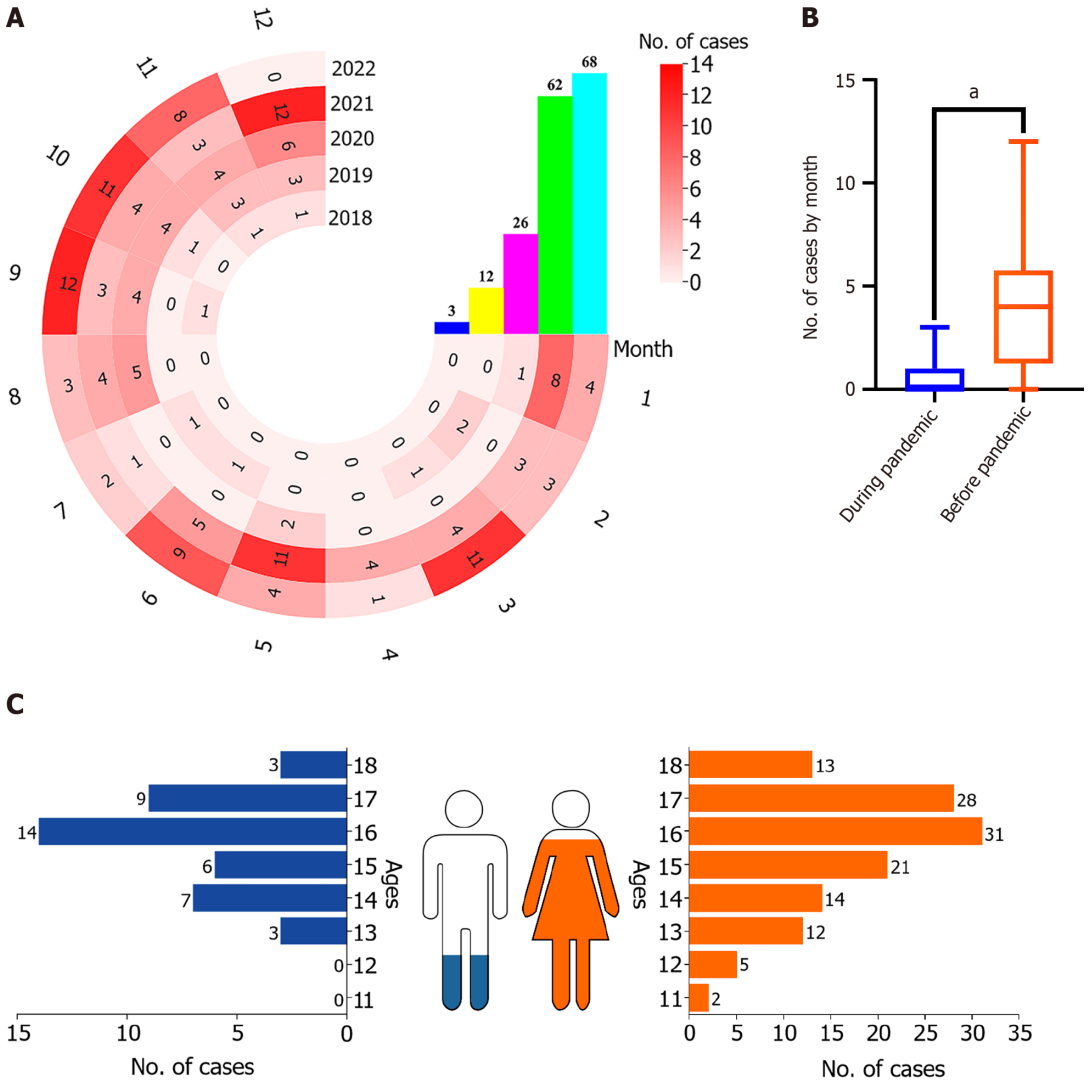


Figure 1 Case information. A: Bipolar disorder case distribution by year and month from January 2018 to December 2022; B: Distribution of case numbers during and before the Coronavirus disease 2019 pandemic ($^aP < 0.001$); C: Age and gender distribution.

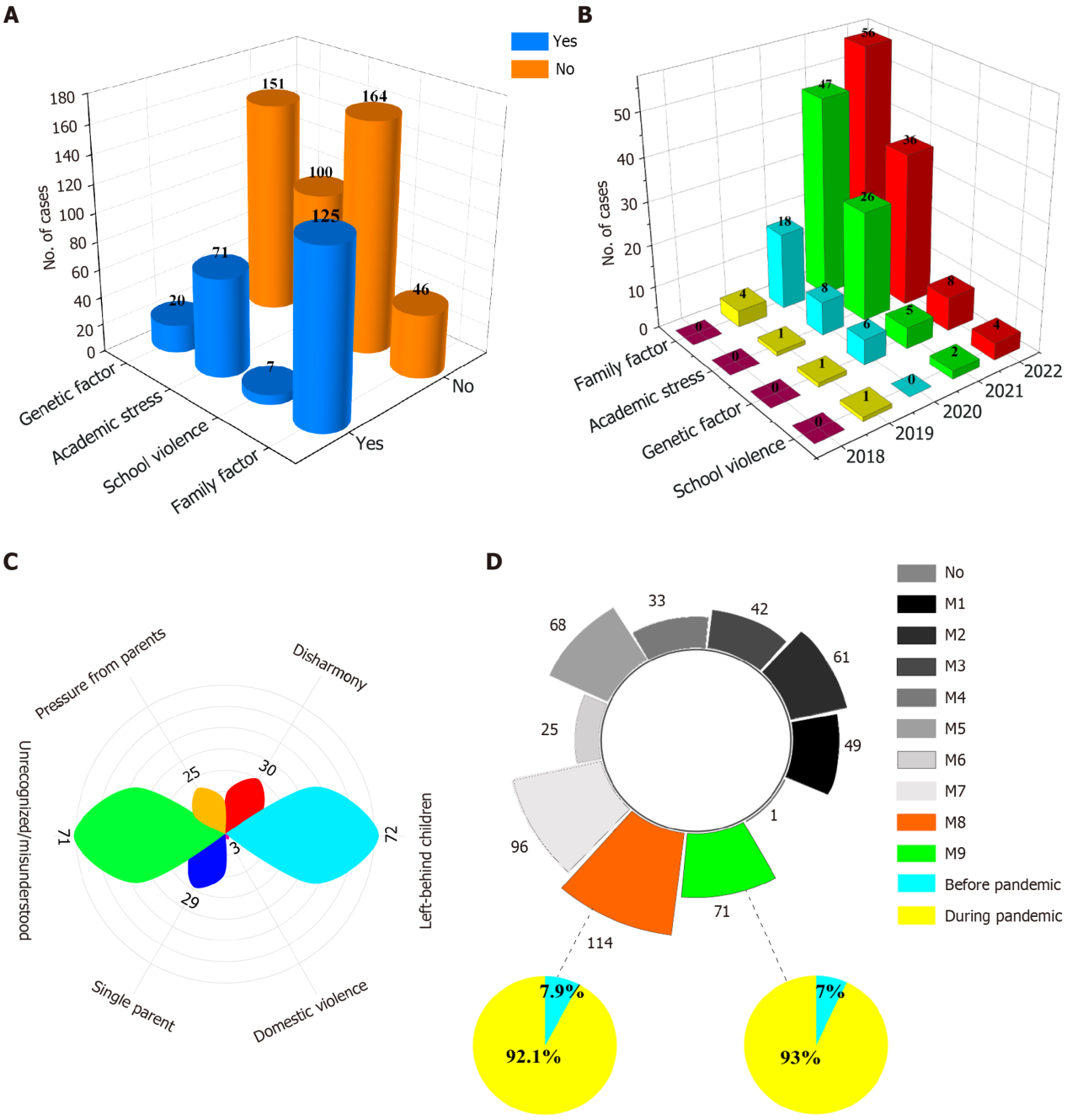
significant number of patients being high school students, underscoring the strong link between academic pressure and BD onset.

BD incidence was linked to multiple factors, including familial dynamics, genetic predispositions, school bullying and academic stress. Academic pressure and family-related factors were significantly associated with BD in adolescents. A notable number of patients had familial ties, especially those who were either left-behind children or felt unrecognized and misunderstood by their families.

The prevalence of suicide and self-harm among adolescents escalated during the COVID-19 pandemic. A marked increase in the incidence of suicides and/or suicide attempts (M8) and self-harm (M9) was observed between the pre-pandemic and pandemic periods. Logistic regression analysis substantiated the profound impact of the COVID-19 pandemic on the rise in suicide and self-harm rates among adolescents with BD, primarily due to family-related stressors.

CONCLUSION

The COVID-19 pandemic has heightened BD morbidity in adolescents, with statistical analysis highlighting a robust association between pandemic-related family stressors and increased rates of suicide and self-harm in this group. Furthermore, the COVID-19 pandemic likely exacerbated family-related factors through enforced isolation and other restrictive measures.



E

Independent variable	Dependent variable	B	SE	Wald	*P*	OR	95%CI
Family factor (1)	Suicide	1.639	0.369	19.725	0.000	5.149	(2.498-10.614)
	Self-harm	1.398	0412	11.482	0.001	4.046	(1.803-9.081)
Pandemic (1)	Family factor	2.252	0.615	13.426	0.000	9.507	(2.850-31.711)

Figure 2 High occurrence of suicide and self-harm among bipolar disorder diagnosed adolescents in Huangshi. A: Possible causes of bipolar disorder; B: Distribution of influencing factors by year; C: Case distribution in different family-related factors; D: Case distribution with different abnormal illness behaviors and suicide (suicidal attempts) (M8) and self-harm (M9) ratio before and during the coronavirus disease 2019 (COVID-19) pandemic; E: Logistic regression analysis exploring the relationship between the COVID-19 pandemic, and family-related factors and the relationship between family-related factors and suicide and self-harm. SE: Systematic error; OR: Odds ratios; B: Regression coefficient.

ARTICLE HIGHLIGHTS

Research background

Recently, there has been an alarming escalation in mental health disorders among adolescents, with annual incidence rates steadily increasing. The onset of the coronavirus disease 2019 (COVID-19) pandemic has particularly seen a surge in cases of bipolar disorder (BD) among this demographic.

Research motivation

This study aimed to examine trends in BD prevalence among adolescents before and during the COVID-19 pandemic. It investigates the escalation in abnormal mental health behaviors and identifies potential risk factors, such as family factors and academic pressures.

Research objectives

The primary goal of this research is to assess the impact of the COVID-19 pandemic on the incidence of BD in adolescents. It also seeks to understand the factors contributing to the increased rates of suicide and self-harm within this group.

Research methods

For this study, data collection was conducted through clinical observations. The diagnosis of BD was based on the criteria given in the Diagnostic and statistical manual of mental disorders, international classification of diseases-11 and the National Institute of Mental Health's Research Domain Criteria.

Research results

The study revealed that family-related factors and academic stress are pivotal in the onset and intensification of BDs in adolescents. The COVID-19 pandemic has further strained familial relationships and led to a significant increase in suicide and self-harm incidents among adolescents diagnosed with BD.

Research conclusions

The study suggests that the rise in suicide and self-harm rates among adolescents with BD may be more closely linked to family-related factors than to the COVID-19 pandemic itself. However, the pandemic has potentially aggravated the family-related factors through enforced social isolation and other restrictive measures.

Research perspectives

The study highlights that social isolation, a preventative measure during a pandemic, is closely associated with challenging household dynamics. Understanding the interplay between family factors and a pandemic is crucial for developing strategies to prevent adverse behaviors in adolescents with BD. Future research, including prospective randomized trials, is required to further elucidate this relationship.

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FOOTNOTES

Co-corresponding authors: Ju-Min Xie and Zu-Cai Xu.

Author contributions: Ye ZF, Xie JM, and Xu ZC conceived the study; Xie JM and Xu ZC supervised the study; Tan MQ and Ye ZF provided the data source; Ye ZF, Hong YH, and Yang JL analyzed the data, performed the statistical analysis and drew the figure; Ye ZF and Xie JM wrote the manuscript; Xie JM revised the manuscript. All authors read and agreed to publish the paper.

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Informed consent statement: All patients in this study had been informed, and they consented to sharing the data. All participants in this study provided written informed consent or parental consent if under the age of 18.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: The processed data was available in the paper, and raw data is freely serviced from first and corresponding

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CASE REPORT

Tricuspid mass-curious case of Li-Fraumeni syndrome: A case report

Tyler Huffaker, Stella Pak, Anum Asif, Prince Otchere

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Abstract

BACKGROUND

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant cancer-predisposing syndrome, which can manifest as a polymorphic spectrum of malignancies. LFS is associated with an early onset in life, with the majority of cases occurring prior to the age of 46. Notwithstanding the infrequency of primary cardiac tumors, it behooves clinicians to remain vigilant in considering the differential diagnosis of such tumors in LFS patients who present with a cardiac mass. This is due to the markedly elevated risk for malignancy in this particular population, far surpassing that of the general populace.

CASE SUMMARY

Herein, we present a case of a 30-year-old female with LFS who was found to have a tricuspid valve leaflet mass.

CONCLUSION

This case exemplifies valuable learning points in the diagnostic approach for this exceptionally rare patient population.

Key Words: Li-Fraumeni syndrome; Cardiac mass; Intracardiac thrombus; Transesophageal echocardiogram; Cardiac magnetic resonance imaging; Case report

Core Tip: Li-Fraumeni syndrome is a rare autosomal dominant cancer-predisposing syndrome, which can manifest as a polymorphic spectrum of malignancies.

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INTRODUCTION

Li-Fraumeni syndrome (LFS) is a rare familial tumor predisposition syndrome caused by an autosomal dominant mutation in a p53 tumor suppressor gene on chromosome 17[1]. LFS manifests itself in various ways across both the genotypic and phenotypic spectra. Despite the broad range of phenotypic expressions, this syndrome is associated with a specific set of cancers, which includes soft-tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumor, adrenocortical carcinoma, leukemia, or bronchoalveolar lung cancer. LFS is also characterized by a predisposition to develop various types of cancers at a relatively young age. Nearly 50% of affected men and women develop an LFS-associated malignancy by 46 for men and by 31 for women[2]. According to the Chompret criteria, a proband is diagnosed with LFS if they meet at least one of the following conditions: (1) Diagnosis of an LFS-associated malignancy before the age of 46; (2) Having one or more first or second-degree relatives who were diagnosed with an LFS-associated malignancy before the age of 56; and (3) Having one or more first or second-degree relatives with multiple tumors, regardless of the age of onset[1]. These criteria are essential for identifying individuals who may have an inherited predisposition to LFS. Diagnosis and genetic testing based on these criteria can help determine the risk of cancer and allow for appropriate medical monitoring and preventive measures for affected individuals and their families.

The incidence of LFS has been reported to range from a mere 0.05% to 0.2% on a global scale, classifying it as an exceedingly rare condition[3]. Consequently, this rarity has contributed to a dearth of comprehensive knowledge concerning LFS within the medical community. Furthermore, specific percentage data regarding the risk of primary cardiac tumor among LFS patients compared to the general population remains conspicuously absent. Nevertheless, it is imperative to emphasize that a well-established association exists between LFS and a significantly heightened overall risk of cancer. In light of this, it stands to reason that individuals afflicted with LFS face a notably elevated susceptibility to various forms of cancer, encompassing the peril of primary cardiac tumor, when juxtaposed against their counterparts lacking this hereditary syndrome. Herein, we present a case of a 30-year-old female with LFS who was found to have a tricuspid valve leaflet mass. This case serves as an illustration of important lessons in the diagnostic approach for an exceptionally rare group of patients, offering valuable insights for learning.

CASE PRESENTATION

Chief complaints

A 30-year-old female was referred to our cardio-oncology clinic due to a cardiac mass in the right ventricle, which was detected during an annual surveillance echocardiography for two atrial septal defects.

History of present illness

Her medical history was notable for LFS and a personal history of various cancers, including breast cancer, ovarian cancer, as well as soft tissue and bone sarcoma.

Physical examination

At the time of evaluation, the patient reported no recent episodes of chest pain, palpitations, exertional dyspnea, orthopnea, or peripheral edema. The physical exam also showed no evidence of a murmur, arrhythmia, jugular venous distention, crackles in the lung field, or leg swelling.

Imaging examinations

The review of the transthoracic echocardiography (TTE) revealed a 1 cm × 1 cm mass arising from the tricuspid valve (Video 1). This mass was not present on the TTE conducted a year prior to this TTE, indicating it is a new finding. Considering the patient's complex medical history, it was decided to pursue a comprehensive approach involving transesophageal echocardiogram (TEE) and cardiovascular magnetic resonance imaging (MRI) to further evaluate her cardiac mass. TEE revealed an echogenic mass attached to the anterior tricuspid valve leaflet, measuring 1.22 cm × 0.735 cm. Cardiac MRI visualized a highly mobile mass in the anterior leaflet of the tricuspid valve (Figure 1).

MULTIDISCIPLINARY EXPERT CONSULTATION

In light of her previous cancer history, the finding of a new cardiac mass raised concerns for possible primary cardiac tumor or metastasis. We had a multi-disciplinary approach including cardio-oncology, multimodal cardiac imaging specialty, cardiothoracic surgery, interventional cardiology, and pediatric and adult oncology. Together, with the patient,

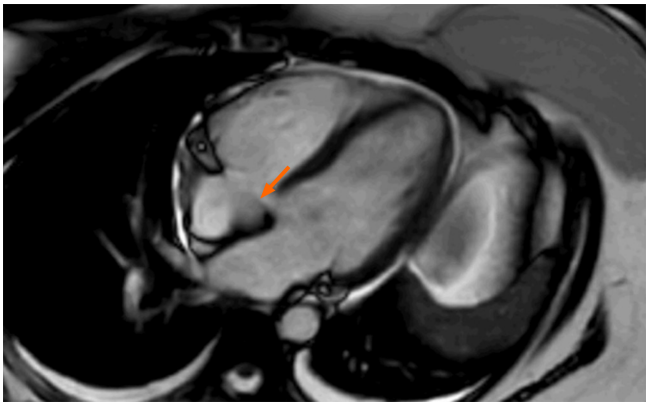

Figure 1 Cardiac magnetic resonance imaging showing an enhancing lesion near the septal leaflet of a tricuspid valve (orange arrow).

the consensus was to surgically remove the mass.

FINAL DIAGNOSIS

Intracardiac thrombus.

TREATMENT

Subsequently, the patient underwent cardiothoracic surgery. Her biopsy showed a 2 cm mass arising from the posterior leaflet of the tricuspid valve with a thin stalk. This mass was excised at the stalk. The specimen was identified as a large, organized thrombus with no evidence of malignancy. Her atrial septal defects were also successfully closed in during the surgery. Her postoperative recovery was uneventful.

OUTCOME AND FOLLOW-UP

The patient experienced no complications at the 1-month follow-up after surgery.

DISCUSSION

Cardiac tumors are uncommon conditions, traditionally diagnosed postmortem, but with the progress in imaging techniques, they are now more frequently encountered in clinical practice. Due to its widespread availability and excellent temporal-spatial resolution, TTE stands as the primary method of investigation for cardiac masses, ensuring accurate assessment of hemodynamic impacts[4]. While some cardiac masses can be easily identified through TTE alone, others may necessitate the integration of more advanced technologies, such as cardiovascular MRI, and TEE for better visualization. Cardiovascular MRI offers robust tissue characterization with high-contrast resolution, enabling precise differentiation between benign and malignant cardiac lesions. Its first pass perfusion enables detection of regions of relative hyper-perfusion, which is typically seen in malignant lesions. Cardiovascular MRI offers a robust tissue characterization with high-contrast resolution, playing a pivotal role in distinguishing between benign and malignant cardiac tumors. With its first-pass perfusion capability, cardiovascular MRI makes it easy to spot regions with relative hyperperfusion—a major indicator commonly linked to malignant lesions[5].

In the case we present, the cardiac mass, which was found to be a thrombus, was shown to have an enhancement on the cardiovascular MRI. However, it should not have exhibited enhancement, as it lacks a vasculature. False enhancement is known to be exceedingly rare with cardiovascular MRI, although the specific rate has not yet been reported due to its scarcity. This case highlights the importance of not solely relying on cardiovascular MRI for the identification of cardiac masses, particularly when suspicion for malignancy is high.

Also, the case exemplifies an efficient approach for managing a cardiac mass in patients at high risk of developing primary cardiac tumors or cardiac metastases. Patients are at high risk for cardiac thrombosis when they exhibit the following characteristics: the presence of cancer in another part of the body, personal history of cancer in the past, LFS, Carney complex, asbestos exposure, or family history of primary cardiac tumor[6-8].

If the cardiovascular MRI showed features more consistent with a thrombus, the preferred approach would have been a catheter-based mechanical thrombectomy. This typically utilizes an angiographic catheter with a suction mechanism.

Thrombolytic agents are not recommended in these cases due to the risk of thrombus fragments traveling from the right side of the heart to the lungs, potentially leading to a pulmonary embolism.

CONCLUSION

The lessons drawn from this case can serve as a stepping stone towards enhancing the overall management of cardiac masses and improving patient prognosis. Furthermore, as medical knowledge evolves, further research in this area has the potential to lead to even more effective strategies for managing cardiac masses in high-risk patient populations.

FOOTNOTES

Author contributions: Huffaker T and Pak S contributed to the manuscript writing and revision; Asif A contributed to the revision and image editing; Otchere P contributed to the supervision revision.

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CASE REPORT

Endovascular treatment of direct carotid cavernous fistula resulting from rupture of intracavernous carotid aneurysm: A case report

Guang Ouyang, Kai-Li Zheng, Kuan Luo, Mu Qiao, Yuan Zhu, De-Rui Pan

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Abstract

BACKGROUND

Direct carotid cavernous fistulas (CCFs) are typically the result of a severe traumatic brain injury. High-flow arteriovenous shunts secondary to rupture of an intracavernous aneurysm, resulting in direct CCFs, are rare. The use of a pipeline embolization device in conjunction with coils and Onyx glue for treatment of direct high-flow CCF resulting from ruptured cavernous carotid artery aneurysm in a clinical setting is not well documented.

CASE SUMMARY

A 58-year-old woman presented to our department with symptoms of blepharoptosis and intracranial bruits for 1 wk. During physical examination, there was right eye exophthalmos and ocular motor palsy. The rest of the neurological examination was clear. Notably, the patient had no history of head injury. The patient was treated with a pipeline embolization device in the ipsilateral internal carotid artery across the fistula. Coils and Onyx were placed through the femoral venous route, followed by placement of the pipeline embolization device with assistance from a balloon-coiling technique. No intraoperative or perioperative complications occurred. Preoperative symptoms of bulbar hyperemia and bruits subsided immediately after the operation.

CONCLUSION

Pipeline embolization device in conjunction with coiling and Onyx may be a safe and effective approach for direct CCFs.

Key Words: Intravascular therapy; Carotid cavernous fistulas; Intracavernous carotid aneurysms; Case report

Core Tip: A patient with direct carotid cavernous fistula was treated with a pipeline embolization device in the ipsilateral internal carotid artery across the fistula. Additionally, coils and Onyx were placed through the femoral venous route, followed by placement of the pipeline embolization device with assistance from a balloon-coiling technique. No intraoperative or perioperative complications occurred. Preoperative symptoms of bulbar hyperemia and bruits subsided immediately after the operation.

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INTRODUCTION

Direct carotid cavernous fistulas (CCFs) are abnormal vessel connections between the cavernous sinus and the internal carotid artery (ICA)[1]. Direct CCF is typically the result of a severe traumatic brain injury. Laceration of the cavernous segment of the ICA wall or avulsion of the cavernous ICA wall by trauma may lead to direct CCF. Spontaneous carotid cavernous sinus fistula is rare. High-flow arteriovenous shunts secondary to a ruptured intracavernous aneurysm resulting in a direct CCF are also rare. Indirect CCF is also known as cavernous sinus dural arteriovenous fistula and compression of the carotid artery may spontaneously resolve it. However, direct CCF and most indirect CCFs require surgical treatment.

Endovascular intervention of these lesions is usually the main treatment. In the past, CCF was treated with a balloon that occluded the ICA at the expense of sacrificing it[2]. In recent decades, there has been a significant development of endovascular techniques in the treatment of these challenging lesions, such as CCF. Treatments include a detachable balloon that obliterates the fistula, cavernous sinus filled with coils and liquid embolic agent to eliminate the shunt, and covered stent placement to obliterate direct CCF. Detachable balloons, coils, liquid embolic agents, and covered stents are now commonly used in endovascular therapy[3,4]. The development of flow-diversion devices has provided further options for treatment.

For small-caliber fistulas, coil embolization can be used alone, but larger shunts tend to require utilizing adjunct devices such as nondetachable balloons or stents to ensure the patency of the ICA. A pipeline endovascular device (PED) can be used for this purpose.

Cavernous sinus surrounding structures such as cranial nerves III, IV, V, and VI can be affected on the ipsilateral side of the cavernous sinus congestion. Clinical presentation can also include abducens palsy, exophthalmos, epistaxis, chemosis, and bruits. The ideal outcome of CCF treatment is complete occlusion of the fistula while maintaining the patency of the carotid artery and preserving the integrity of the cranial nerves. A model treatment of CCF secondary to rupture of intracavernous aneurysm is absolute occlusion of the shunt, to avoid recurrent rupture of the aneurysm and to treat the paralysis caused by the aneurysmal pressure against the cerebral nerves.

CASE PRESENTATION

Chief complaints

Blepharoptosis with intracranial murmur for 1 wk.

History of present illness

A 58-year-old woman presented with ptosis of the left eyelid accompanied by pulsatile tinnitus. According to the patient's self-report, these symptoms suddenly appeared 1 wk previously and gradually worsened, resulting in limited vision and hearing discomfort.

History of past illness

The patient was in good health before. She had no history of infectious disease, food or drug allergy, or surgery. She also denied having a history of head trauma or other related diseases, as well as diseases in other systems.

Personal and family history

The patient's parents are both alive.

Physical examination

During physical examination, there was right eye exophthalmos and ocular motor palsy. The remaining neurological examination was normal.

Laboratory examinations

No obvious abnormality was found.

Imaging examinations

Magnetic resonance imaging revealed a right-sided aneurysm (Figure 1), with tortuous and increased vascular shadow in the posterior space of the right eye.

FINAL DIAGNOSIS

The final diagnosis was direct CCF.

TREATMENT

We decided to perform endovascular treatment of the CCF and the aneurysm using a combined transarterial and transvenous approach. Preoperatively, the patient was pretreated with 100 mg aspirin and 75 mg clopidogrel for several days. Clopidogrel was substituted with ticagrelor after the thromboelastography test showed a low platelet inhibition rate. Intraoperatively, right ICA angiography demonstrated a ruptured giant cavernous carotid aneurysm with a fistulous outflow *via* the ipsilateral subpetrosal sinus and the ipsilateral superior ophthalmic vein (Figure 2). A PED was deployed in the ICA across the aneurysmal neck *via* a transfemoral approach and the procedures were performed under general anesthesia. Under Traxcess-14 micro-guidewire guidance, an Eechelon-10 microcatheter was inserted *via* the femoral vein, across the subpetrosal sinus, then through the right-side cavernous sinus, and into the aneurysmal sac. We withdrew the micro-guidewire and filled the aneurysmal sac with several coils through the Eechelon-10 microcatheter. Onyx glue was injected through the microcatheter slowly and intermittently under the protection of the Scepter balloon. Immediate postoperative angiography showed normal patency of the parent ICA and a marked reduction in arteriovenous shunting (Figure 3). As for the residual shunting, the surgeon thought that it would disappear with thrombus formation (Figure 4). Postoperatively, dual antiplatelet therapy with ticagrelor (90 mg/d) and aspirin (100 mg/d) was continued. The day after the operation, aspirin was discontinued due to hematuria. The patient received single antiplatelet therapy with ticagrelor 90 mg twice daily, which was maintained for 3 mo.

OUTCOME AND FOLLOW-UP

The patient's symptoms of right eye hyperemia and bruits immediately disappeared after surgery. Digital subtraction angiography (DSA) demonstrated only minimal residual fistulous flow, consistent with the patient's gradual recovery from thrombosis. After 3 mo of follow-up, the patient had no neurological defects, and the right eye proptosis and chemosis disappeared. DSA confirmed total obliteration of the fistula with stable occlusion of the aneurysm, concurrent with complete resolution of the symptoms.

DISCUSSION

PED is a brief but unique versatile device composed of cobalt–chromium and platinum that provides 30%–35% metal surface area coverage and is self-expandable[5]. Many cerebrovascular pathologies that are considered untreatable by conventional techniques have been treated after the introduction of flow-diverting stent technology. As for anatomically complex aneurysms, PED is a superior choice to surgical clipping and endovascular coiling.

Although PED was approved by the United States FDA only for wide-neck ICA aneurysms, it has gained wide acceptance as a treatment approach for unruptured intracranial aneurysms, including small aneurysms and other types of aneurysms, with techniques and indications for PED use still evolving.

Distal aneurysms are those located beyond the circle of Willis. PEDs can be used to treat distal aneurysms located at or beyond the A2 segment of the anterior cerebral artery and the P2 segment of the posterior cerebral artery. The M2 segment of the middle cerebral artery may incur a high rate of occlusion and ischemic events, but PED is a feasible option for aneurysms in the pericallosal artery and those that are not manageable with simple coiling. The main challenges of PED treatment for distal aneurysms lie in the fact that its release system is harder than that of conventional stents, and PED release requires a larger diameter catheter[6]. The treatment of wide-necked bifurcation aneurysm *via* PED is easier than by unassisted or assisted coiling. The complication rate of ischemic events and occlusion after bifurcation aneurysms treated by flow diversion devices (FDD) is high, so this approach is only suggested when the surgical and other endovascular approaches are unfeasible. The main concern of PED therapy for bifurcated aneurysms is perioperative or

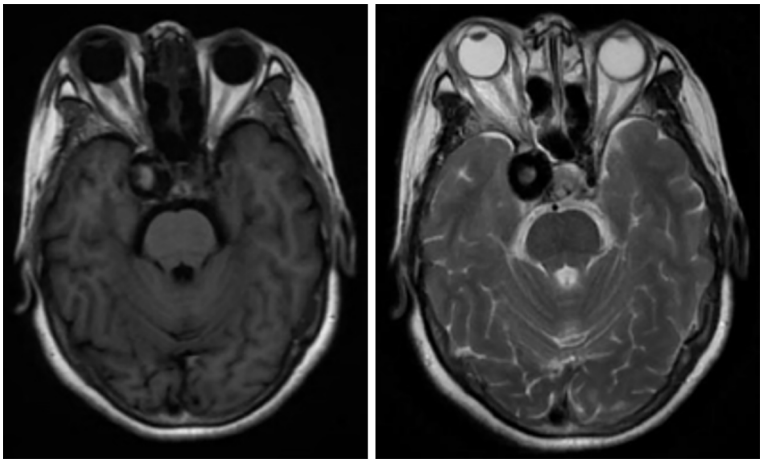

Figure 1 Brain magnetic resonance imaging revealed a right-sided aneurysm, with tortuous and increased vascular shadow in the posterior space of the right eye.

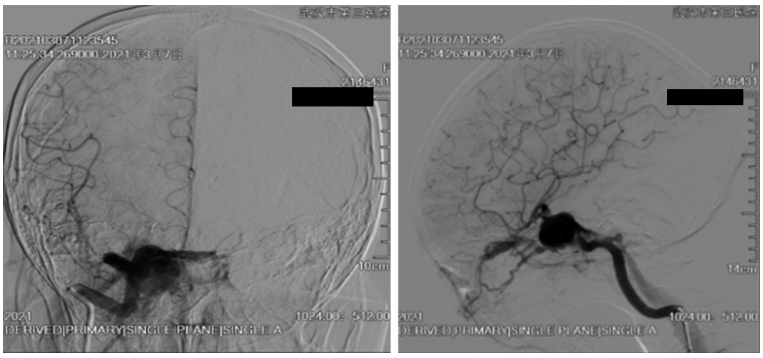

Figure 2 Digital subtraction angiography confirmed the presence of a high-flow carotid cavernous fistula.

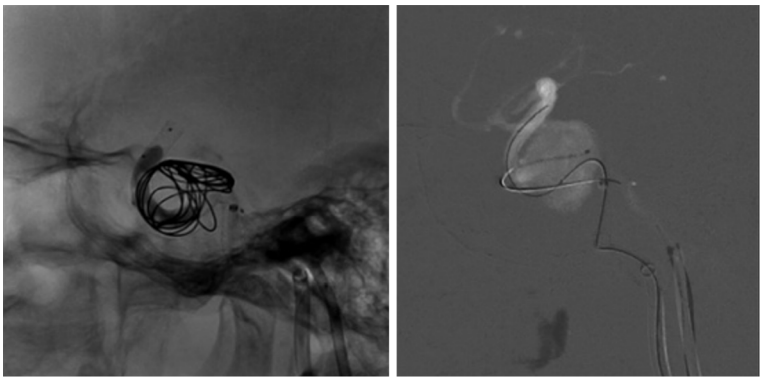

Figure 3 Several coils were filled to the aneurysmal sac using the Eechelon-10 microcatheter.

late thromboembolic events of PED-covered branches and perforating vessels[7].

FDD can also be applied to small aneurysms with lower ischemic complication rates[8]. PED is also suitable for complex ruptured small aneurysms that cannot be treated by other methods, especially for blood-blister-like aneurysms [9]. For aneurysm recurrence after endovascular treatment or previously clipped aneurysm, flow diversion is also a reasonable option. For recurrent aneurysms with previously stent-assisted embolization, compared with those without stent-assisted embolization, FDD treatment has a poor outcome and an increased incidence of adverse events. The presence of a previous stent will result in the PED apposition to the vessel wall and incomplete opening, triggering ischemic events. Nine anterior communicating aneurysms postsurgical clipping have been reported, with a complete occlusion rate of 83% and no perioperative complications[10].

It is still controversial whether PEDs for large or giant aneurysms should be combined with coiling. It is generally believed that PED in conjunction with coiling would be more effective. However, recent studies have shown that PED

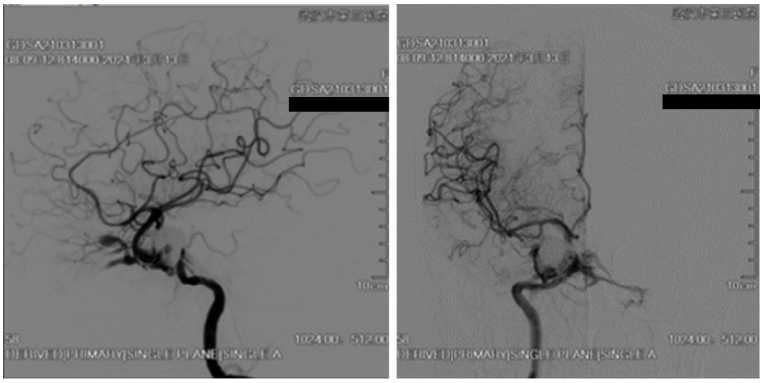

Figure 4 Immediate postoperative angiography showed normal patency of the parent internal carotid artery and a marked reduction in arteriovenous shunting.

combined with coiling treatment of intracranial aneurysm reduces the probability of aneurysm rupture and has an obstructive effect on aneurysms, causing them to shrink or disappear.

Compared with conventional endovascular therapy, PED cannot effectively treat lesions immediately and may delay the healing process. Also, the stent may prolapse without support[11]. The use of coils in conjunction with pipelines can resolve this problem. Coils in the aneurysmal sac can act as a scaffold to avoid the stent protruding into the aneurysm. Coils can reduce the incidence of postoperative aneurysm rupture and hemorrhage through the embologenic and mechanical support effect of coiling, and can also reduce the incidence of aneurysmal rupture and recurrence caused by PED shortening or postoperative displacement.

Coiling may cause the PED to open badly or cause incomplete stent apposition. Studies have shown that the incidence of early ischemic events after PED combined with coil embolization is significantly higher than that after PED alone. Lin *et al* reported that, among 104 patients with complex aneurysms, 29 were treated with PED and coils, and 75 were treated with PED alone. It was concluded that complete aneurysmal occlusion was achieved in a higher proportion of cases treated with the pipeline plus coils compared with pipeline only and reduced the need for retreatment. There was no significant difference in periprocedural and delayed complications between the two groups[12].

Although PEDs are mainly used for treatment of particular internal carotid aneurysms, recent reports describe their off-label use for CCF treatment. Concerning CCFs, Baranoski *et al*[13] described a case of traumatic CCF that was treated in a multisession approach, initially deploying two PEDs across the fistulous site to provide double coverage, followed by transvenous coiling of the inferior ophthalmic vein and cavernous sinus. DSA demonstrated complete obliteration of the fistula with no residual shunting. For the low-flow types A and B CCFs, one single PED may be sufficient due to a low-pressure gradient. PED can induce thrombosis by reducing flow, providing a permanent closure by endothelization of the CCF[14].

The sole use of multiple overlapping PEDs has also been described in the treatment of CCF. Without embolic agents into the cavernous sinus, multiple PEDs can also efficiently reduce high-flow fistula and avoid cranial nerve injury during a dense coil mass within the cavernous sinus[15,16].

The current literature shows that using PED for treatment of CCF is likely to be safe and effective[17]. First, PED can reduce the use of coil or embolization materials, thereby reducing the mass effect in the aneurysmal sac or cavernous sinus, as wells as cranial nerve complications due to the mass effect. Second, PED as a barrier can reduce the risk of embolization material such as coils and liquid penetrating into the ICA, increase the safety of liquid embolization agent occlusion of the fistula through venous approach, and improve the cure rate. Compared with balloon occlusion, PED can reduce the risk of ischemia rate. Third, PEDs can promote the formation of thrombosis at the fistula by reducing the flow. Many reviews suggest that flow diversion may be a useful tool in the treatment of CCF.

Most CCF patients with residual shunting on angiography after PED deployment were found to be occluded at later follow-up. This shows that PEDs can affect flow rate and promote thrombosis.

The role of PED is based on the two mechanisms of blood flow guidance and promotion of the cervical endoderm to promote aneurysmal healing. Compared with the traditional stent, a PED can better reshape the parent artery at the neck of the aneurysm[14,18]. Aneurysmal diameter and morphology, parent artery diameter ratio, cervical ratio, collateral artery, and gender are risk factors for postoperative occlusion of aneurysms. PEDs have been shown to have good safety and efficacy for the treatment of complex internal carotid aneurysms. Follow-up appointments confirmed that 86.8% and 95.2% of aneurysms had complete occlusion at 1–5 years postoperatively.

The main drawback of PED treatment for CCF is the time that it takes for the fistula to become occluded, which may delay symptomatic improvement. In addition, PED is expensive and requires dual antiplatelet therapy, but this method is simple and reduces the risk of cranial nerve damage[19,20].

The complications of flow diversion mainly include ischemic stroke and cerebral hemorrhage, which are the mass effects of giant aneurysms. The occurrence of ischemic stroke is mainly caused by the stent adhering to the vessel wall or poor opening of the stent. Multiple PEDs or stenting of the parent artery may lead to inadequate stent opening. Also, parent artery stenosis or side branch artery occlusion may cause ischemic stroke. Mechanical compression or detachment of the thrombosis can occlude the branch vessel. Cerebral hemorrhage includes delayed aneurysmal rupture and delayed

lobar cerebral hemorrhage. Delayed aneurysmal rupture is caused by continuous blood flow in the aneurysm after FDD treatment and continuous enlargement of thrombosis leading to aneurysmal rupture. Delayed cerebral hemorrhage is associated with vascular wall damage during FDD treatment, especially with dual antiplatelet therapy. In addition, cerebral hemorrhage may be associated with increased postoperative blood flow[21]. There is a risk of further postoperative aggravation due to the mass effect of a large aneurysm.

CONCLUSION

We believe that the use of PED in conjunction with coils and/or liquid embolic agents for the treatment of CCF secondary to a rupture of an intracavernous aneurysm may be a safe and effective strategy. PED can protect the parent vessel during transvenous coiling or liquid embolization infusion. For the aneurysm with residual shunting, PED-induced alterations in flow contribute to thrombosis. Dual antiplatelet therapy may lead to bleeding complications and its dose should be adjusted when needed.

FOOTNOTES

Author contributions: Ouyang G and Zheng K were responsible for manuscript writing and data curation; Luo K and Qiao M were responsible for data curation; Zhu Y was responsible for methodology and resources; Pan D was responsible for manuscript writing, reviewing, and editing, and project administration.

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CASE REPORT

Concomitant treatment of ureteral calculi and ipsilateral pelvic sciatic nerve schwannoma with transperitoneal laparoscopic approach: A case report

Yang Xiong, Jin Li, Han-Jie Yang

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Abstract

BACKGROUND

Schwannomas are rare peripheral neural myelin sheath tumors that originate from Schwann cells. Of the different types of schwannomas, pelvic sciatic nerve schwannoma is extremely rare. Definite preoperative diagnosis of pelvic schwannomas is difficult, and surgical resection is the gold standard for its definite diagnosis and treatment.

CASE SUMMARY

We present a case of pelvic schwannoma arising from the sciatic nerve that was detected in a 40-year-old man who underwent computed tomography for intermittent right lower back pain caused exclusively by a right ureteral calculus. Subsequently, successful transperitoneal laparoscopic surgery was performed for the intact removal of the stone and *en bloc* resection of the schwannoma. The total operative time was 125 min, and the estimated blood loss was inconspicuous. The surgical procedure was uneventful. The patient was discharged on postoperative day 5 with the simultaneous removal of the urinary catheter. However, the patient presented with motor and sensory disorders of the right lower limb, caused by partial damage to the right sciatic nerve. No tumor recurrence was observed at the postoperative appointment.

CONCLUSION

Histopathological examination of the specimen confirmed the diagnosis of a schwannoma. Thus, laparoscopic surgery is safe and feasible for concomitant extirpation of pelvic schwannomas and other pelvic and abdominal diseases that require surgical treatment.

Key Words: Schwannoma; Sciatic nerve; Laparoscopy; Ureteral calculi; Pelvic neoplasms; Case report

Core Tip: Schwannomas are rare peripheral neural myelin sheath tumors originating from Schwann cells. Pelvic sciatic nerve schwannoma is extremely rare. The clinical manifestations of pelvic schwannomas may be asymptomatic, viscerally oppressive, or neurological due to compression or invasion of the original nerves. Definite preoperative diagnosis of pelvic schwannomas is difficult, and surgical resection is the gold standard for definite diagnosis and treatment. We present a case of pelvic schwannoma arising from the sciatic nerve that was detected in a 40-year-old man who underwent computed tomography for intermittent right lower back pain caused exclusively by a right ureteral calculus. Subsequently, successful transperitoneal laparoscopic surgery was performed for the intact removal of the stone and *en bloc* resection of the schwannoma. Laparoscopic surgery is safe and feasible for concomitant extirpation of pelvic schwannomas and other pelvic and abdominal diseases that require surgical treatment.

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INTRODUCTION

Schwannoma, also known as neurilemmoma, is a rare peripheral neural myelin sheath tumor originating from Schwann cells that provide proper nutrition and mechanical protection for axons and promote rapid saltatory excitation propagation[1]. Tumors may occur in any organ or nerve stem but are more common in the head, neck, and extremities [2]. Pelvic schwannomas arising mostly from the sacral nerve or hypogastric plexus is of rare occurrence[3]. Schwannoma of the sciatic nerve, which passes through the inferior piriformis foramen out of the pelvis and then generally divides into the tibial nerve and the common peroneal nerve at the top of the popliteal fossa, is a neurogenic tumor originating from the sacral plexus and can be grouped as a pelvic or extrapelvic schwannoma according to its location.

When pelvic schwannomas are small, they are usually asymptomatic, and most are found incidentally, such as when patients are examined for checkups or other unrelated diseases. Symptomatic pelvic schwannomas normally signify large volumes of tumors with compression of the surrounding vital tissues or apparatuses, such as the nerves, iliac vessels, urinary bladder, ureter, and intestines. Therefore, the clinical presentations of pelvic schwannomas are highly nonspecific and vary depending on tumor location and size[4]. The variability of symptoms leads to a clinically delayed diagnosis or misdiagnosis of urological or gynecological diseases. Although it is difficult to completely remove a pelvic schwannoma because of its deep location and complex relationship with its surrounding tissues, the preferred first choice of treatment is complete surgical resection[5]. The preoperative diagnosis and surgical treatment of pelvic schwannomas remains a challenge for the urologists, gynecologists, and general surgeons.

CASE PRESENTATION

Chief complaints

A 40-year-old man presented with an intermittent dull right lower back pain over the past three months.

History of present illness

The patient had experienced intermittent dull right lower backache with frequent urination and urgency 3 months prior to presentation. Therefore, he sought medical attention at a local hospital. A urological computed tomography (CT) was performed, and the scan revealed a right upper ureteral stone and a low-density mass in the right pelvic space. Due to uncertainty about the right pelvic mass, local doctors referred the patient to our department for concomitant surgical resection of the right upper ureteral stone and ipsilateral pelvic mass.

History of past illness

The patient claimed that he was in good health, denied having any history of basic diseases such as hypertension, diabetes, coronary heart disease and cerebrovascular disease; infectious diseases such as hepatitis and tuberculosis; trauma and surgery; and drug and food allergy.

Personal and family history

The patient was born and raised in the original place; had no history of contact with schistosomiasis water, infectious diseases, bad habits such as smoking and alcohol consumption, contact with toxic and radioactive substances, sexually transmitted diseases; and had no family history of hereditary diseases. His wife and children were healthy.

Physical examination

No tenderness or pain on percussion was observed in either of the renal region. The entire abdomen was soft with no palpable mass. No abnormalities were observed in the external genitalia. A digital rectal examination revealed no obvious findings.

Laboratory examinations

Dry chemistry urinalysis revealed 108 leukocytes/μL and 173 red blood cells/μL. Repeat urine cultures were sterile. No significant abnormalities were observed in routine biochemical and hematological tests.

Imaging examinations

Chest radiography and electrocardiographic findings were normal. CT urography (CTU) showed a 2-cm right upper ureteral calculus with ipsilateral hydronephrosis, which was eventually found to be the main cause of the symptoms (Figure 1A and B). Simultaneously, a well-demarcated 5-cm homogeneous oval solid mass was observed in the right pelvic space without manifestations of any infiltration in the bladder, ureter, rectum, or other surrounding tissues (Figure 1B and C). In the arterial phase, branches of the internal iliac vessels were found in the anterior, medial, and posterior parts of the mass, and the boundary between the posterior part of the mass and the piriformis muscle was blurred (Figure 1C). In the excretion phase, the collection system above the stone was obviously dilated, and the ureter beneath the stone was still obviously dilated compared with the contralateral ureter; however, no obvious contrast agent was excreted (Figure 1D). Magnetic resonance imaging (MRI) and fine-needle aspiration (FNA) biopsy were not performed.

FINAL DIAGNOSIS

The preoperative tentative diagnosis was pelvic schwannoma based on the CTU characteristics of the tumor.

TREATMENT

The patient was counseled about all available treatment options, such as upper ureteral calculi, which could be removed through percutaneous nephrolithotomy, laparoscopic ureterolithotomy, or flexible ureteroscopic techniques, and the solid mass could be resected either laparoscopically or through robotic surgery. The patient eventually elected to undergo transperitoneal laparoscopic surgery for concomitant treatment of ureteral calculi and pelvic schwannoma. Following urethral catheterization and endotracheal intubation under general anesthesia, the patient was placed in a 45° left lateral decubitus position with a 15° Tredelenburg position, and a 4-trocar configuration was used. After the pneumoperitoneum was established using the Veress technique, a 10-mm trocar was placed through a 1.5-cm umbilical incision for a 30° endoscope (Karl Storz, Germany) and peritoneal insufflation with carbon dioxide. The pneumoperitoneum pressure was maintained at 12-14 mmHg. Another 10-mm trocar was inserted 3 cm from the right costal margin at the homolateral midclavicular line (MCL). A 10-mm trocar was inserted at the intersection of the right MCL and the horizontal line of the homolateral iliac crest, and a 5-mm trocar was inserted between the umbilicus and pubic symphysis. Following the mobilization of the right colon, a partial Kocher maneuver was performed to expose the upper segment of the right ureter and renal pelvis. The ureter was dissected until a stone was identified as a bulge. The ureter was incised longitudinally over the stone using a laparoscopic scalpel, and the stone was extracted using an endoscopic grasper. The ureter was implanted with a double-J stent (Cook Urological, United States) and successively sutured using interrupted 3-0 absorbable Vicryl sutures (Ethicon, United States). During exploration, the middle-upper ureter between the stone and mass was obviously dilated and hydrous, indicating compression of the pelvic mass on the surrounding ureter. The tumor was found beneath the right external iliac vessels and was dissected smoothly, except on the bottom side, which adhered firmly to the piriformis. In addition to the narrow space of the lateral pelvic wall, the tumor was difficult to dissect completely and was reluctantly incised. After removing the spilled myxoid material (Antoni B), which appeared as a hypodense shadow in the CT scan image, *en bloc* resection of the tumor was completed without visible injury to the surrounding tissues. Finally, a drain is placed in the Douglas pouch. The total operative time was 125 min, and the estimated blood loss was inconspicuous. The surgical procedure was uneventful.

OUTCOME AND FOLLOW-UP

The drain was withdrawn on postoperative day 2. The patient was discharged on postoperative day 5 with the simultaneous removal of the urinary catheter. The double-J stent was removed three weeks postoperatively. However, the patient presented with numbness in the anterior region of the right crus and dorsum of the right foot on the first postoperative day. Right foot drop, and thus difficulty in ambulation, was later observed. A subsequent neurophysiological examination, which consisted of motor and sensory nerve conduction of the common peroneal nerves and motor nerve conduction of the tibial nerves, reported no positive wave induced by the motor action potential of the right common peroneal nerve and decreased amplitude and conduction velocity of the motor action potential of the right tibial

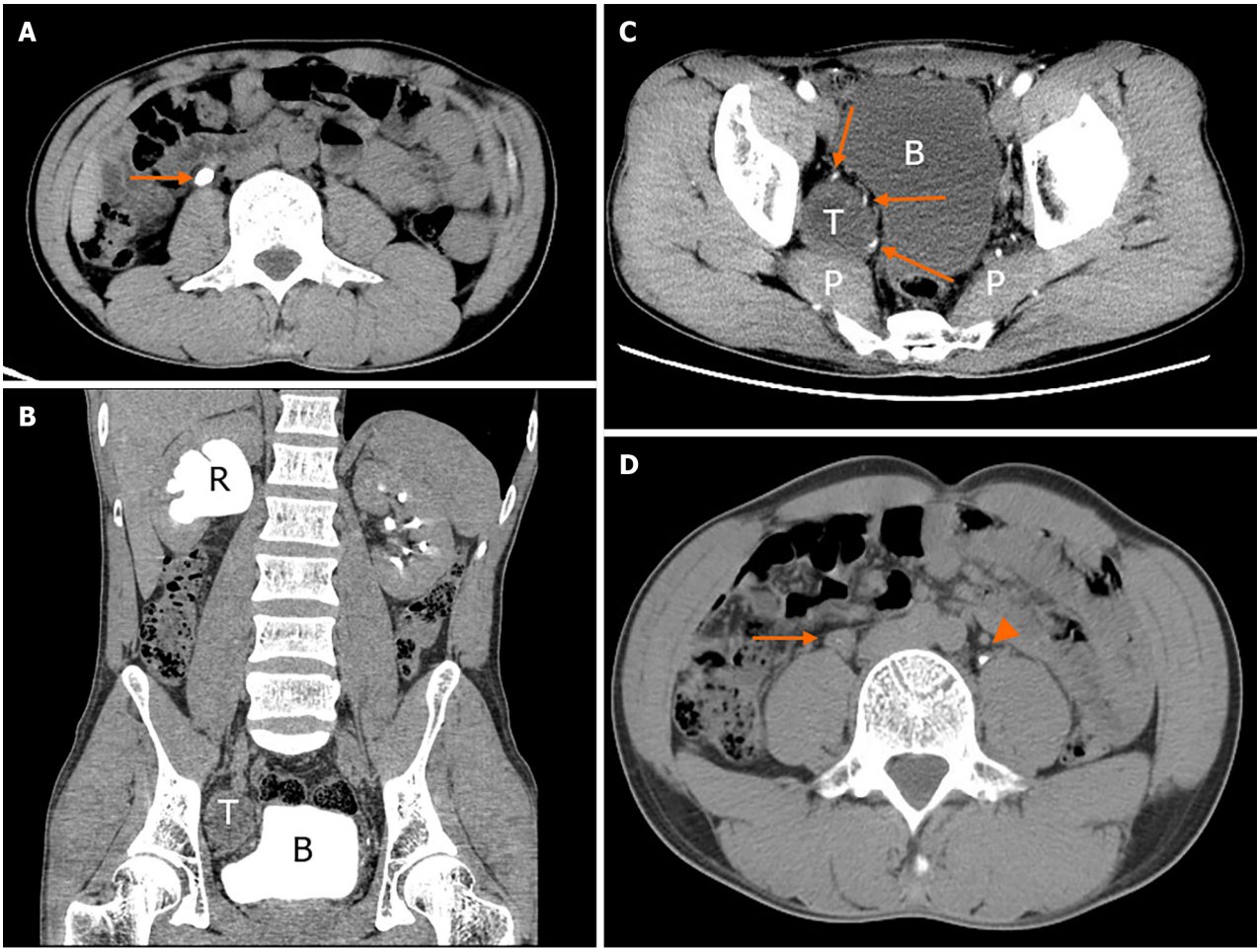

Figure 1 Abdominal and pelvic computed tomography scan. A: Abdominal non-contrast axial computed tomography (CT) scan showed a 2-cm right upper ureteral calculi at the lumbar 3 level (arrow); B: The excretion phase of coronal CT urography (CTU) showed the dilated hydronephrotic renal pelvis caused by right ureteral stone obstruction and the deformed bladder caused by pelvic tumor compression; C: Contrast axial CT scan showed the anatomical location of pelvic tumor with blurred boundary between the posterior part of the mass and the piriformis muscle and abundant arterial supply at the anterior, medial and posterior part of the mass (arrows); D: The excretion phase of axial CTU showed the ureter (arrow) beneath the stone was still obviously dilated compared with the contralateral ureter (arrowhead). R: Renal pelvis; T: Pelvic tumor; P: Piriformis muscle; B: Bladder.

nerve and sensory action potential of the right common peroneal nerve. The histopathology of the specimen demonstrated typical characteristics of an alternating hypocellular myxoid matrix (Antoni B) and hypercellular components (Antoni A), with spindle tumor cells arranged in a palisade or whorl pattern (Figure 2A). Hematoxylin and eosin staining revealed rare cell atypia and mitosis. Immunohistochemical analysis revealed diffuse, strong S100 expression, and sporadic Ki-67 expression (Figure 2B and C). Smooth muscle actin, cytokeratin, CD117, and Dog-1 tests were immunohistochemically negative. Although the numbness and dyskinesia of the right lower limb improved and no CT evidence of recurrence was observed at the year follow-up appointment, the patient still walked with a limp and underwent rehabilitation training.

DISCUSSION

Schwannomas are generally well-circumscribed, slow-growing, solitary benign tumors, whereas multiple or malignant schwannomas are usually observed in patients with von Recklinghausen disease (neurofibromatosis) or schwannomatosis. The clinical manifestations of pelvic schwannomas may be asymptomatic, viscera-oppressive, or neurologic due to compression or invasion of the original nerves, often leading to a delayed diagnosis. Apart from clinical manifestations that lack preoperative diagnostic specificity, the radiological characteristics of schwannomas are insufficient to make a definite diagnosis because of their enormous variability. There are two main reasons for this significant radiological heterogeneity, the first is the different proportions of Antoni A and Antoni B components in schwannoma, and the second is usually because of the degenerative changes, such as tumor cystic transformation, calcification, hemorrhage, and hyalinization[6]. Alterations in these elements lead to changes in schwannomas on CT and MRI scans. However, radiological modalities are not all helpful and contribute to displaying tumor size, location, and relationships with the surrounding structures[7]. In the present case, abdominal CT revealed a low-density mass in the right lateral pelvic wall. Delayed marginal enhancement did not occur until the CTU excretion phase was achieved. One of the most important

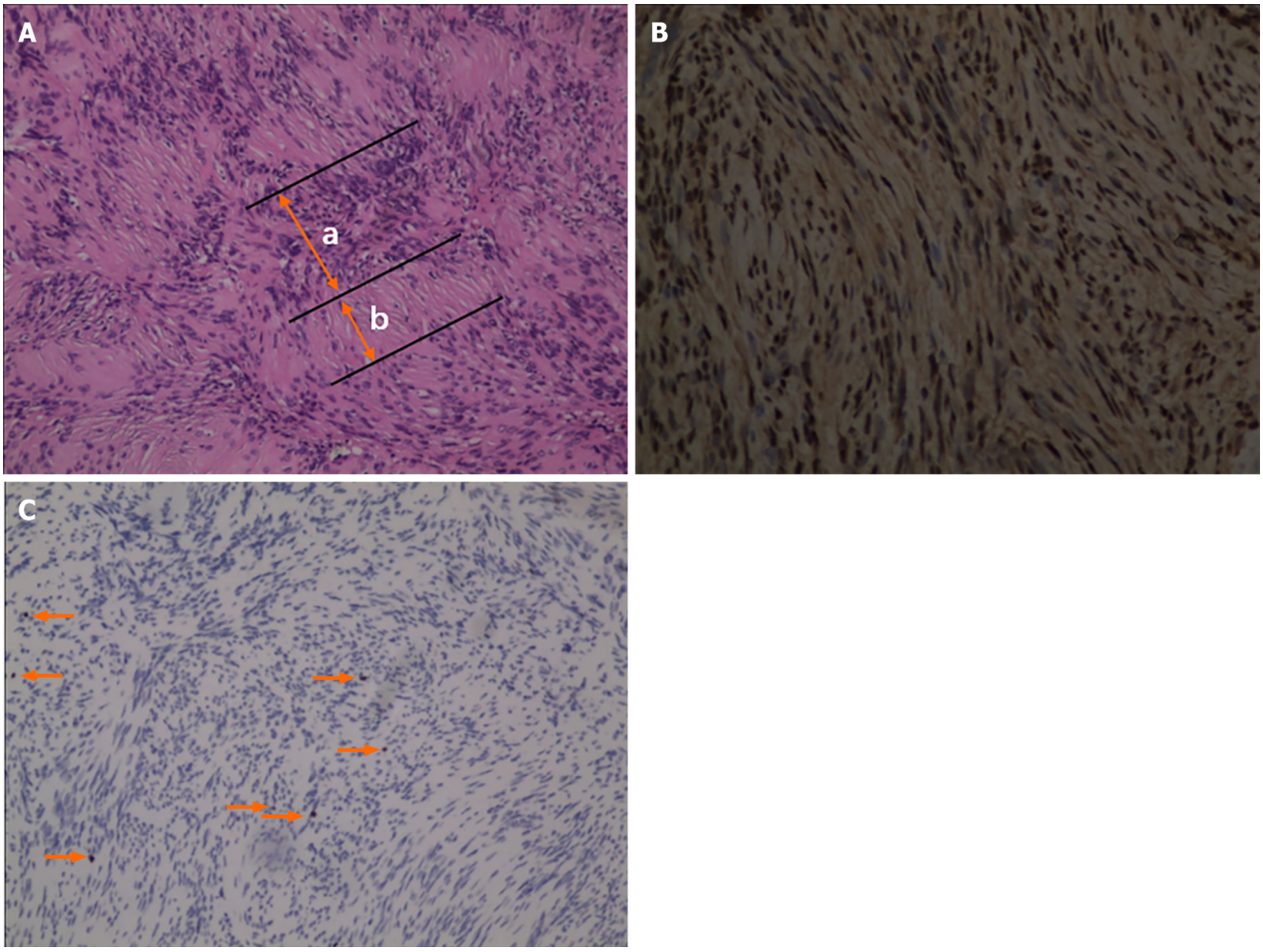

Figure 2 Immunohistochemical staining and evaluation. A: The histopathological section from pelvic tumor showed typical characteristics of alternating Antoni B and Antoni A with spindle tumor cells arranged in palisade or whorl pattern (hematoxylin and eosin, × 100); B and C: Immunohistochemical detection showed diffuse strong S100 expression and sporadic Ki-67 expression (arrows) (× 100). a: Antoni A; b: Antoni B.

radiological findings is the abundance of blood supply to the mass, which is a critical indicator of strict bleeding control and a clear surgical field.

Radiological modalities guided by FNA were not performed in our case to avoid biopsy-related bleeding and intestinal injuries resulting from the intractable anatomical characteristics of the tumor. Although previous and recent studies have recommended FNA biopsy for a definite preoperative diagnosis[8,9], most studies have concluded that FNA is of limited value[3,6,10]. They do not recommend routine preoperative FNA biopsy for the following reasons: (1) Cellular pleomorphism may mislead the interpretation of microscopic results; (2) The manipulation may complicate bleeding, infection and tumor seeding; and (3) FNA specimens cannot be embedded in paraffin or immunohistochemically stained. Therefore, *en bloc* resection is the gold standard for definite diagnosis and treatment of schwannomas.

En bloc resection of pelvic schwannomas can be performed using open, laparoscopic, or robot-assisted approaches. The goal of schwannoma resection using any approach is to eradicate the tumor while preserving pelvic organ function whenever possible. With the rapidly increasing application of endoscopic techniques in surgery, the acceptance of (robot-assisted) laparoscopic resection as an alternative to open resection for pelvic schwannomas is increasing. Konstantinidis *et al*[11] reported that laparoscopy is a safe and efficient option for treating pelvic schwannomas and may offer the advantage of better exposure owing to the magnification of the laparoscopic view, especially in narrow anatomic pelvic spaces. Ningshu *et al*[12] also commented that laparoscopic extirpation of pelvic schwannomas is superior to open surgery in terms of postoperative rehabilitation, pain, hospital stay, and oncological results. However, four of the six enrolled patients in their study developed different degrees of neurological deficits. Robotic surgical systems have been gradually developed to reduce the incidence of neurological complications because of their hand-eye coordination, high-definition 3D view of the surgical field, and seven degrees of freedom[13]. These advantages are particularly important for robotic surgical systems for separating delicate and vulnerable anatomical structures in a narrow operating space. In our case, the patient finally underwent laparoscopic surgery because of subjective aspiration for concomitant removal of the ureteral calculi and ipsilateral pelvic tumor. Our laparoscopic resection of the schwannoma was uneventful, with excellent one-year postoperative oncological results. However, the patient presented with motor and sensory disorders of the right lower limb, and subsequent electrophysiological analysis suggested that it was caused by partial damage to the right sciatic nerve. According to the postoperative condition analysis conducted by our surgical team, the dissection of the tumor root was probably too difficult to protect the sciatic nerve branches because of the narrow lateral pelvic spaces,

abundant blood supply to the tumor root, and tight adhesion with the sciatic nerve. Wang *et al*[14] also reported a similar successful resection of intrapelvic sciatic schwannoma through laparoscopic surgery, in which the patient experienced a transient numbness in the right heel after surgery. They concluded that the laparoscopic approach used for treating intrapelvic schwannomas of the sciatic nerve was safe and feasible under the guarantee of comprehensive preoperative preparation because of the patient's condition and sufficient experience from the surgeon with regard to laparoscopic surgery on pelvic tumors. In the past, our center has carried out approximately 40 laparoscopic radical prostatectomies and 25 laparoscopic radical cystectomies annually. Since the introduction of the Da Vinci robotic system, approximately 35 robotic radical prostatectomies and 20 robotic radical cystectomies have been performed annually. Based on these findings, laparoscopic or robotic surgery is feasible for patients for the simultaneous treatment of ureteral stones and ipsilateral intrapelvic sciatic nerve schwannomas. Woo *et al*[15] published an interesting case of sciatica, and subsequent surgical results confirmed that sciatica was caused by an intrapelvic sciatic notch schwannoma. Successful excision was achieved *via* a transgluteal subpiriformis approach. This approach was not adopted in our patient, mainly due to concerns about the need for a large skin incision and unfamiliarity of anatomical pathways.

In our case, combined with literature reviews, we firstly proposed an analysis method to achieve ideal schwannoma resections, called the "trifecta", which were free of radiological recurrence, early complications and neurological damages. To achieve this goal, our suggestions for pelvic schwannoma resection are as follows: (1) Adjuvant use of intraoperative electrophysiological monitoring may decrease the incidence of neurological damage; (2) Preoperative multidisciplinary treatment (MDT) involving urology, obstetrics and gynecology, neurosurgery, and general surgery is strongly recommended to achieve the trifecta goal; and (3) Strict hemostatic techniques may avoid unnecessary side injuries.

CONCLUSION

The preoperative diagnosis of schwannoma is difficult; most are suspected diagnoses, and the final definite diagnosis still requires surgical removal of the gross specimens. The trifecta goal can be achieved using laparoscopic surgery for pelvic schwannoma resection, especially when patients have other urological, general, or gynecological diseases that require surgical removal. MDT cooperation, intraoperative electrophysiological monitoring, and strict hemostatic techniques will further compensate for the limitations of laparoscopic surgery. To conclude, laparoscopic surgery is safe and feasible for concomitant extirpation of pelvic schwannomas and other pelvic and abdominal diseases that require surgical treatment.

FOOTNOTES

Author contributions: Xiong Y contributed to manuscript writing and editing; Li J contributed to data collection and data analysis; Yang HJ contributed to conceptualization and supervision. All authors have read and approved the final manuscript

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CASE REPORT

Safety and efficacy of transcatheter arterial embolization in autosomal dominant polycystic kidney patients with gross hematuria: Six case reports

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Abstract

BACKGROUND

To retrospectively report the safety and efficacy of renal transcatheter arterial embolization for treating autosomal dominant polycystic kidney disease (ADPKD) patients with gross hematuria.

CASE SUMMARY

The purpose of this study is to retrospectively report the safety and efficacy of renal transcatheter arterial embolization for treating ADPKD patients with gross hematuria. Materials and methods: During the period from January 2018 to December 2019, renal transcatheter arterial embolization was carried out on 6 patients with polycystic kidneys and gross hematuria. Renal arteriography was performed first, and then we determined the location of the hemorrhage and performed embolization under digital subtraction angiography monitoring. Improvements in routine blood test results, routine urine test results, urine color and postoperative reactions were observed and analyzed. Results: Renal transcatheter arterial embolization was successfully conducted in 6 patients. The indices of 5 patients and the color of gross hematuria improved after surgery compared with before surgery. No severe complication reactions occurred.

CONCLUSION

For autosomal dominant polycystic kidney syndrome patients with gross hematuria, transcatheter arterial embolization was safe and effective.

Key Words: Renal artery; Autosomal dominant polycystic kidney disease; Gross hematuria; Interventional radiology; Embolization; Case report

Core Tip: In this manuscript, we report the retrospective analysis to evaluate efficiency and safety of transcatheter arterial embolization in autosomal dominant polycystic kidney patients with gross hematuria in the Chinese population and currently there is no relevant article published.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder caused by mutations in *PKD1* and *PKD2*[1,2]. Its pathological characteristic is a bilateral progressive enlarged kidney filled with multiple renal cysts. With the development of disease, early renal dysfunction changes to end-stage renal disease (ESRD). ADPKD is also associated with external manifestations, such as hypertension, hepatic cysts, pain, infection and intracranial aneurysms[3].

Dialysis is recommended as the first-line renal replacement therapy in ESRD patients with ADPKD[4]. However, kidneys with cysts continue to enlarge during the dialysis period, leading to significant complications[5,6], including dyspnea, abdominal pain, lumbago and persistent hematuria. To treat these problems, nephrectomy and renal transplantation could be performed. However, its drawbacks, namely, high invasiveness, poor prognosis and relatively low efficacy, restrict its application[7,8].

Transcatheter renal artery embolization (renal TAE) is a minimally invasive therapeutic option that is used for relieving the symptoms and reducing kidney volume[9-11], and it is regarded as an alternative to surgery before renal transplantation. However, no previous studies have focused on the treatment of ADPKD patients with gross hematuria. The aim of this study was first to retrospectively assess the safety and efficacy of renal TAE in ADPKD patients with gross hematuria.

CASE PRESENTATION

Chief complaints

Assess the safety and efficacy of renal TAE in ADPKD patients with gross hematuria.

History of present illness

ADPKD patients with gross hematuria. The study population was composed of ADPKD patients who had undergone hemodialysis regularly at Zhenjiang First People's Hospital. All patients underwent routine blood tests, routine urine tests and abdominal no-contrast computed tomography (CT) scans before and after renal TAE.

History of past illness

Kidneys with cysts continue to enlarge during the dialysis period, leading to significant complications, including dyspnea, abdominal pain, lumbago and persistent hematuria.

Personal and family history

ADPKD is a genetic disorder caused by mutations in *PKD1* and *PKD2*.

Physical examination

The pathological characteristic of ADPKD is a bilateral progressive enlarged kidney filled with multiple renal cysts.

Laboratory examinations

All patients underwent routine blood tests and routine urine tests. All 6 patients who suffered from gross hematuria had ESRD. The hemoglobin and erythrocyte levels of all patients were obviously decreased. The levels of erythrocytes in the urine of the 2 included patients were obviously increased.

Imaging examinations

All patients underwent abdominal no-contrast CT scans. An abdominal no-contrast CT scan showed bilateral enlarged kidneys full of cysts of uniform size. Acute hemorrhage was found in the cysts (Figure 1).

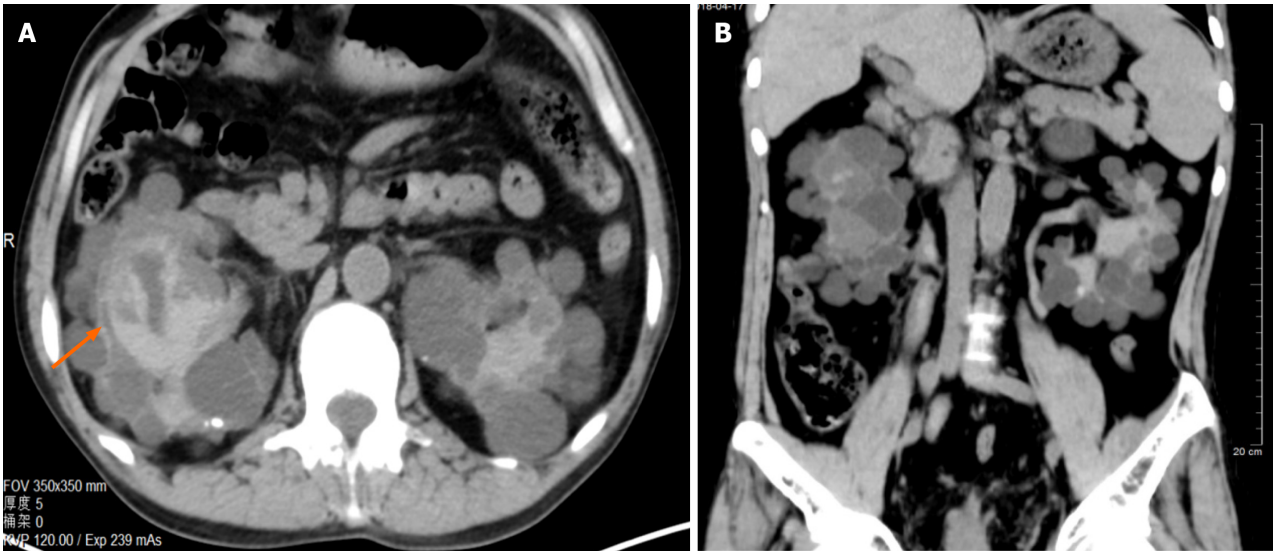

Figure 1 51-year-old male patient with autosomal dominant polycystic kidney disease had gross hematuria for 1 wk. He regularly conducts hemodialysis in hospital. The abdominal no-contrast computerized tomography scan showed bilateral enlarged kidneys which were full of cysts of uniform size. Acute hemorrhage was found in the cysts (orange arrow).

FINAL DIAGNOSIS

Based on the laboratory and Imaging examinations. All 6 patients were diagnosed as ADPKD patients with gross hematuria.

TREATMENT

All 6 ADPKD patients underwent renal TAE successfully. Renal arteriography showed enlarged bilateral kidneys with thin arteries. Selective renal angiography revealed definite hemorrhagic positions in branches of the renal arteries (Figure 2A). For these patients, the branches of the renal vascular bed were embolized with microspheres from the gelatin sponge particle (GSP) in 3 patients (Figure 3A), and the bilateral main renal arteries and branches of the renal vascular bed were embolized with microcoils and microspheres from the GSP in 1 patient. Microcoils were found in the bilateral main renal arteries of 2 patients (Figure 2B). For these patients, embolization of branches of the renal vascular bed were performed with microspheres from the polyvinyl alcohol (PVA) or GSP, and embolization of the bilateral main renal arteries were performed again with microcoils (Figure 3B).

OUTCOME AND FOLLOW-UP

The 1st day after embolization, the gross hematuria in all 6 patients clearly faded. On the 3rd day after embolization, the erythrocyte levels in the urine of 2 patients decreased. Four patients refused routine urine tests. The hemoglobin and erythrocyte levels of all patients were increased (Table 1).

No severe complications occurred from the beginning of embolization to discharge. Two included patients had fever (grade 1) without symptoms of shivering or chills. The highest temperature was 38.8 °C, and the temperature ultimately decreased to normal before discharge. Three patients had lumbago (grade 2), and the highest numerical rating scale was 4. Nonsteroidal anti-inflammatory drugs were used to relieve pain. No complications occurred in 1 patient.

DISCUSSION

Our results showed that renal TAE was safe and effective for ADPKD patients with gross hematuria. The color of the urine faded on the 1st day after embolization and did not recur during the duration of hospitalization. Five patients' blood tests and routine urine test results improved on the 3rd day after embolization. No severe complications occurred in any of the patients. Fever and lumbago after embolization were grade 1-2 without the need for surgical, endoscopic, or radiologic interventions[12]. Ischemia, necrosis and swelling occur in organizations due to embolization of branches of the renal vascular bed; these conditions are called postembolization syndrome. Fever and lumbago are common complications after embolization in ADPKD patients with postembolization syndrome[13].

Table 1 Characteristics of 6 patients including indices, embolic agents and complications

Case	Sex	Age	Hemoglobin in blood in G/L		Erythrocyte in blood as 10^{12}/L		Erythrocyte in urine as U/L		Embolic agents	Complications
			Pre-operation	Post operation	Pre-operation	Post operation	Pre-operation	Post operation		
1	Male	51	65	86	2.4	3.23	/		Microspheres of GSP+ microcoils	Fever
2	Male	51	67	85	2.49	3.16	/		Microspheres of GSP	Fever
3	Female	44	72	76	2.6	2.8	/		Microspheres of GSP	Pain
4	Male	48	56	71	2.03	2.57	/		Microspheres of GSP	Pain
5	Male	64	88	93	2.97	3.11	24376.2	8338	Microspheres of GSP+ microcoils	Pain
6	Male	64	73	81	2.56	2.73	42455.3	3855.5	Microspheres of PVA+ microcoils	None

GSP: Gelatin sponge particle; PVA: Polyvinyl alcohol.

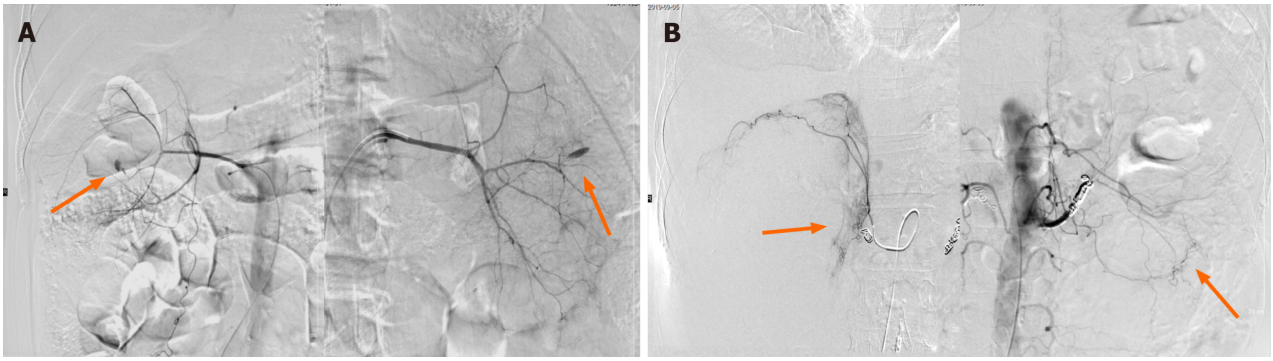

Figure 2 Bilateral renal arteriography. A: Bilateral renal arteriography showed bilateral enlarged kidneys and slender branches of renal arteries with contrast-medium leaking indicating acute hemorrhage (orange arrows); B: Bilateral renal arteriography showed bilateral enlarged kidneys with microcoils positioned at the main renal arterials and contrast-medium leaking indicating acute hemorrhage (orange arrows).

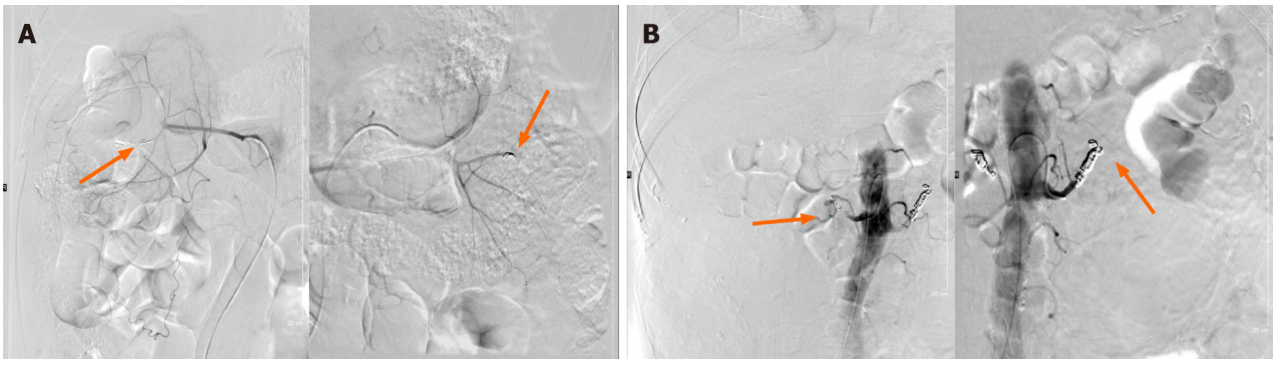

Figure 3 Autosomal dominant polycystic kidney disease patients. Bilateral renoarteriography showed that microcoils positioned at the renal arterial branches and no contrast-medium leaking indicating the success of hemostasis (orange arrows). A: Conducted transcatheter renal artery embolization with microspheres of polyvinyl alcohol (diameter, 350 μm-560 μm) in branches of renal arteries and microcoils; B: Conducted transcatheter renal artery embolization with microspheres of polyvinyl alcohol (diameter, 350 μm-560 μm) in branches of renal arteries and microcoils in main renal arteries.

Gross hematuria is a common complication in ADPKD patients and can occur due to cyst bleeding, urinary tract infection or tumors[14,15]. Gross hematuria is limited and can be alleviated within 1 wk by using etamsylate. Moreover, renal TAE and nephrectomy are the recommended methods for treating this disease. Renal TAE has been gradually recognized in Asia as an option for patients with ADPKD who are not suitable for surgery[16,17]. Previous research confirmed that nephrectomy led to persistent hypotension and aggravated renal anemia[18], which may further increase

the risk for ADPKD patients undergoing dialysis. However, renal TAE rather than surgery is not widely accepted in Western countries because of the higher rate of kidney transplantation in the West[11].

The materials and extent of embolization are considered significant factors for ensuring the safety and efficiency of renal TAE. Owing to the self-specifications of microcoils, which are common mechanical embolic materials, they are usually placed in main renal arteries to reduce the blood flow to the kidneys. Previous studies[19,20] have demonstrated that although microcoils lead to temporary vessel occlusion of renal arteries, later revascularization can lead to renal failure after surgery *via* microcoils alone. Renal TAE was also confirmed in 2 patients in our study. Since revascularization is the main cause of failure, embolization of the renal arterial bed by microspheres or liquid embolic materials is necessary [10,19,21].

With regard to embolization of the renal arterial bed, previous studies[12,19,21] confirmed that the use of liquid embolic materials (anhydrous alcohol) and microspheres of the PVA was safe and efficient. The use of microspheres from the PVA and GSP during embolization was also demonstrated to be effective in our study. Embolization of the renal arterial bed with anhydrous alcohol and microspheres could effectively restrain late revascularization through damaging endothelial tissue, coagulating proteins and inducing microvascular thrombosis and necrosis of perivascular areas[22]. In addition, serious complications linked to anhydrous alcohol and microspheres, such as ectopic embolism, were reported after renal TAE[23]. Such serious complications can be avoided by superselective arterial embolization and detection of nontarget arteries. Because anhydrous alcohol and microspheres are nonradiopaque embolic agents, we emulsified them with radiopaque material, such as contrast media, to monitor the direction of embolic agents. Previous research also suggested that nonradiopaque embolic agents could be mixed with iodized oil and that temporary balloon occlusion catheters could be placed in main renal arteries to prevent backflows of embolic agents[21].

CONCLUSION

For autosomal dominant polycystic kidney syndrome patients with gross hematuria, transcatheter arterial embolization was safe and effective.

FOOTNOTES

Author contributions: Fu JH and Shao WB designed the research study; Fu JH, Li JY, Sui WF and Duan YX performed the research; Sui WF analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

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CASE REPORT

Neurosyphilis complicated by anti-γ-aminobutyric acid-B receptor encephalitis: A case report

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Abstract

BACKGROUND

Syphilis is an infectious disease caused by *Treponema pallidum* that can invade the central nervous system, causing encephalitis. Few cases of anti-N-methyl-D-aspartate receptor autoimmune encephalitis (AE) secondary to neurosyphilis have been reported. We report a neurosyphilis patient with anti-γ-aminobutyric acid-B receptor ($GABA_BR$) AE.

CASE SUMMARY

A young man in his 30s who presented with acute epileptic status was admitted to a local hospital. He was diagnosed with neurosyphilis, according to serum and cerebrospinal fluid (CSF) tests for syphilis. After 14 d of antiepileptic treatment and anti-*Treponema pallidum* therapy with penicillin, epilepsy was controlled but serious cognitive impairment, behavioral, and serious psychiatric symptoms were observed. He was then transferred to our hospital. The Mini-Mental State Examination (MMSE) crude test results showed only 2 points. Cranial magnetic resonance imaging revealed significant cerebral atrophy and multiple fluid-attenuated inversion recovery high signals in the white matter surrounding both lateral ventricles, left amygdala and bilateral thalami. Anti-$GABA_BR$ antibodies were discovered in CSF (1:3.2) and serum (1:100). The patient was diagnosed with neurosyphilis complicated by anti-$GABA_BR$ AE, and received methylprednisolone and penicillin. Following treatment, his mental symptoms were alleviated. Cognitive impairment was significantly improved, with a MMSE of 8 points. Serum anti-$GABA_BR$ antibody titer decreased to 1:32. The patient received methyl-prednisolone and penicillin after discharge. Three months later, the patient's condition was stable, but the serum anti-$GABA_BR$ antibody titer was 1:100.

CONCLUSION
This patient with neurosyphilis combined with anti-GABA$_B$R encephalitis benefited from immunotherapy.

Key Words: Anti-γ-aminobutyric acid-B receptor; GABA$_B$R; Neurosyphilis; Tissue-based assay; Magnetic resonance imaging; Mini-mental state examination; Case report

Core Tip: In this report, we investigated the complex interplay between neurosyphilis and autoimmune encephalitis (AE), specifically anti-γ-aminobutyric acid-B receptor AE. Our findings shed light on the intricate connections between syphilis-related neurological complications and autoimmune responses, highlighting the potential significance of targeted immunotherapies in managing such cases. This investigation contributes valuable insights into the understanding and treatment of neurosyphilis, emphasizing the relevance of considering autoimmune mechanisms in its pathogenesis.

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INTRODUCTION

Neurosyphilis is one of the systemic complications of syphilis caused by *Treponema pallidum*. The prognosis of neurosyphilis varies considerably based on specific populations and disease stages[1-3]. Widespread inflammation has been observed in the brain following neurosyphilis infection. There have been reported cases of syphilis combined with autoimmune encephalitis (AE), such as antibodies against N-methyl-D-aspartate receptor (anti-NMDAR) AE[4-7], or demyelinating diseases, such as antibodies against aquaporin-4 (anti-AQP4) neuromyelitis optica spectrum disorder (NMOSD) in which immunotherapy, including methylprednisolone or immunoglobulin treatment, has shown benefits in the prognosis of neurosyphilis patients[8-10]. In this report, we present a case of neurosyphilis complicated by anti-γ-aminobutyric acid-B receptor (GABA$_B$R) AE.

CASE PRESENTATION

Chief complaints

A young man in his 30 s was admitted to our hospital with complaints of recurrent seizures accompanied by behavioral and psychiatric changes, such as not recognizing family members, inability to communicate, and excited for more than 17 d.

History of present illness

The patient suddenly developed epileptic seizures and was confused for intermittent periods 17 d previously. He was taken to a local hospital and was considered to have an "epileptic status", and was given symptomatic treatment such as "propofol, midazolam, and sodium valproate". Neurosyphilis was considered as the patient's serum (1:16) and cerebrospinal fluid (CSF, 1:4) TRUST titer test was positive. After 14 d of penicillin treatment, the patient developed psychiatric and behavior disorders and was unable to communicate effectively. He was treated with "valproate 0.4 g bid and olanzapine 5 mg bid". His symptoms did not significantly improve, and he was referred to our hospital.

History of past illness

He denied a history of infection, diarrhea, fever, or other previous medical history.

Personal and family history

He had no history of drinking, smoking or drug use. His parents were both in good health.

Physical examination

Neurological examination revealed slow response, difficulty in language expression, personality change, attention and short-term memory impairments, unstable mood, and impulsive behavior. The patient had no other pathological signs.

Laboratory examinations

There were no significant abnormalities in routine blood tests, including biochemistry and coagulation. Tumor markers

were in the normal range. The test results for other infections [herpes simplex viruses (HSV), varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, *etc.*] were negative, and syphilis titers were re-examined on admission, and the TRUST titer was 1:4 in serum and 1:1 in CSF. Pleocytosis (white blood cells of 12 × 10^6/L) and increased protein concentration (0.50 g/L) were found in CSF. Oligoclonal protein electrophoresis was positive in CSF. In addition, the patient's tissue-based assay (TBA) results were compared with TBA-negative examples (Figure 1A and B). TBA of the CSF sample revealed positive neuronal immunoreaction (Figure 1C-F), and a cell-based assay (CBA) for known autoantigens of AE in the serum and CSF samples were screened and compared with GABA$_B$R-negative examples (Figure 1G). GABABR autoantibody was identified in serum (1:100) and CSF (1:3.2) (Figure 1H and I). The test results for other autoantibodies (NMDAR, AQP4, Hu, Yo, Ri, *etc.*) were negative. After 2 weeks, serum-GABA$_B$R was positive (1:32) (Figure 1J). After 3 months, CSF-GABA$_B$R was positive (1:10) (Figure 1K), and serum-GABA$_B$R was positive (1:100) (Figure 1L). A Mini-Mental State Examination (MMSE) score of 2/30 was confirmed.

Imaging examinations

Brain magnetic resonance imaging (MRI) showed significant cerebral atrophy and multiple fluid-attenuated inversion recovery (FLAIR) high signals in the white matter surrounding both lateral ventricles, left amygdala and bilateral thalami (Figure 2). The patient's chest computed tomography (CT) scan showed no significant abnormalities.

FINAL DIAGNOSIS

Based on the clinical examinations and results of TRUST titer and anti-GABA$_B$R antibodies in CSF, the patient was diagnosed with neurosyphilis complicated by anti-GABA$_B$R AE.

TREATMENT

According to the patient's weight, he received intravenous methylprednisolone 1 g QD for 3 d, 0.5 g QD for 3 d, 0.25 g QD for 3 d, and 0.125 g QD for 3 d. Twelve d after methylprednisolone therapy, his psychiatric and behavioral disorders disappeared and his cognitive impairment improved, with the MMSE score increasing from 2/30 to 8/30. The serum TRUST titer decreased to 1:4, and serum GABA$_B$R antibody titer decreased to 1:32 (Figure 1J). The venereal disease research laboratory test (VDRL) and GABA$_B$R antibody detection were not tested due to a lack of CSF samples.

OUTCOME AND FOLLOW-UP

After discharge, the patient was given intramuscular injections of 2.4 million units of penicillin once a week for three weeks. He continued to take methylprednisolone orally at a dose of 60 mg/d, and the dosage was then gradually tapered by one-third every week until the drug was completely withdrawn. His condition remained stable without further aggravation. Three months later, repeat serum TRUST titer was still 1:4, CSF VDRL was negative, but *Treponema pallidum* hemagglutination assay was still positive, and serum and CSF GABA$_B$R antibody titer were 1:100 and 1:10, respectively (Figure 1L and K), the MMSE score was 8/30, and cranial MRI showed that the FLAIR high signals in the white matter surrounding both lateral ventricles, left amygdala and bilateral thalami, and brain atrophy was the same as before (Figure 2). Intravenous methylprednisolone shock therapy was given again for 9 d (0.5 g QD for 3 d, 0.25 g QD for 3 d, 0.125 g QD for 3 d), and the MMSE score increased to 11 points.

DISCUSSION

In the present report, we described a case of neurosyphilis complicated by anti-GABA$_B$R AE, which is to our knowledge, the first reported case. GABA$_B$R is widely expressed in the brain, including the limbic system (such as amygdala), thalamus, and cerebellum. It is involved in the activity of dopaminergic and other monoaminergic neurons by binding to the inhibitory neurotransmitter GABA[11]. Most of the patients with anti-GABA$_B$R AE are middle-aged and elderly men, who usually have acute or subacute onset. The main clinical manifestations include epilepsy, mental disorders, and memory loss. Approximately half of the patients with anti-GABA$_B$R AE have abnormal cranial MRI of the medial temporal lobe. One-third of patients present with small-cell lung cancer[12]. However, this patient's tumor markers were within the normal range, and chest CT showed no significant abnormalities. There was no evidence of tumor.

Our case had typical acute onset manifestations. His electroencephalogram showed a diffuse slow wave, cranial MRI showed significant cerebral atrophy and multiple FLAIR high signals in the white matter surrounding both lateral ventricles, left amygdala and bilateral thalami. Why did the acute course of disease cause significant brain atrophy? We think it is unlikely that such significant brain atrophy occurred as a short-term consequence of brain damage and the brain atrophy in this patient might reflect long-standing progression. Patients with asymptomatic neurosyphilis can show brain atrophy, despite showing no symptoms. Approximately 75% of patients with neurosyphilis have been reported to show normal or nonspecific brain atrophy on cranial MRI, which may reflect a quiescent and prolonged course of

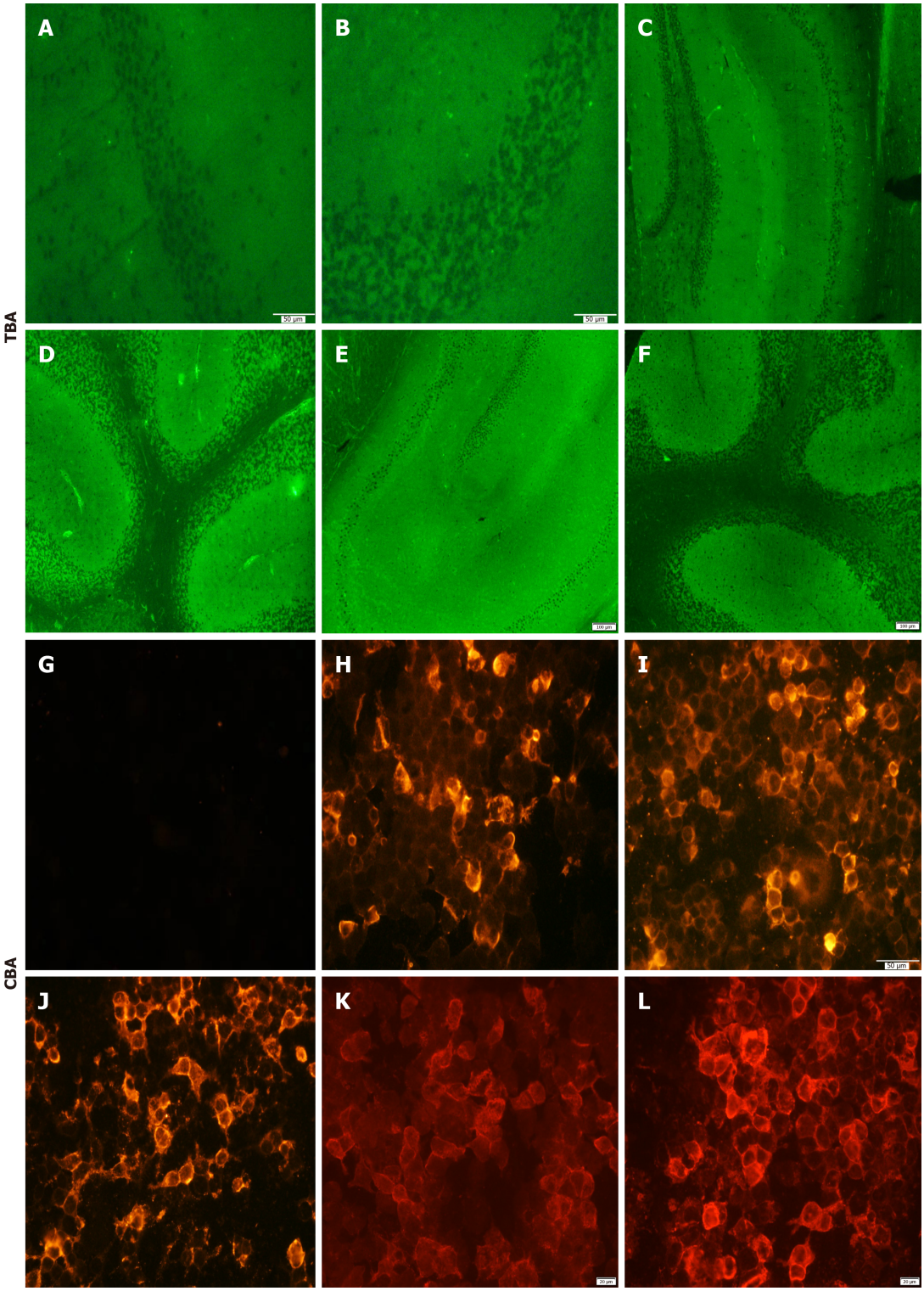

Figure 1 Tissue-based assay and γ-aminobutyric acid-B receptor titer before and after treatment. A and B: Tissue-based assay (TBA)-negative case example; C and D: TBA-positive on admission; E and F: TBA positive after three months; G: Anti-γ-aminobutyric acid-B receptor (GABA$_B$R)-negative case example; H: Cerebrospinal fluid (CSF)-GABA$_B$R positive on admission (1:3.2); I: Serum-GABA$_B$R positive on admission (1:100); J: Serum-GABA$_B$R positive after two weeks (1:32); K: CSF-GABA$_B$R positive after three months (1:10); L: Serum-GABA$_B$R positive after three months (1:100). TBA: Tissue-based assay; CBA: Cell-based assay.

syphilis, whereas parenchymal lesions in the temporal lobe and thalami can be seen in both early and late stages of neurosyphilis[13,14]. Patients with neurosyphilis have varying clinical and neuroimaging features, including cerebral infarction or hemorrhage, atrophy, demyelination, arteritis, encephalitis, and hippocampal sclerosis[15]. Therefore, this patient's brain atrophy may be related to years of latent syphilis infection, reflecting the long-term progression of the disease. The hyperintense lesions in the medial temporal region and white matter (such as splenium of corpus callosum *etc.*) on the patient's cranial MRI were associated with the development of seizures, cognitive deficits, and psychobehavioral abnormalities, and all of these imaging abnormalities, especially lesions of the limbic system, are typical of

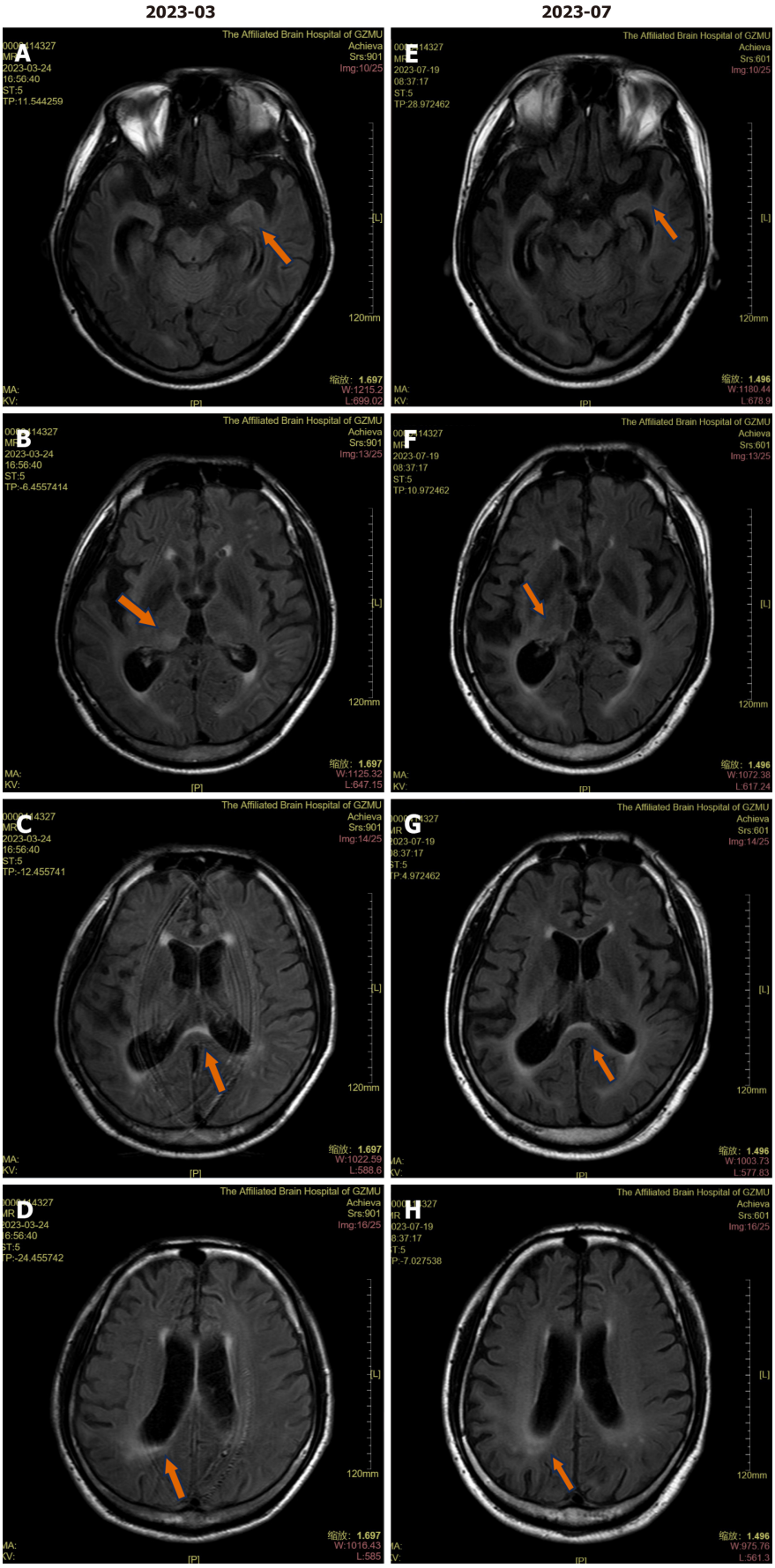

Figure 2 Brain magnetic resonance imaging scan on admission and after three months. A and E: T2 fluid-attenuated inversion recovery (FLAIR) image shows the high signal of the left amygdala; B and F: T2 FLAIR image shows the high signal of the right thalamus; C and G: T2 FLAIR image shows the high signal of the corpus callosum; D and H: T2 FLAIR image shows the high signal in the white matter surrounding the posterior part of the lateral ventricular body.

neurosyphilis and anti-GABA$_B$R encephalitis.

Infection is a risk factor for AE, and AE has been reported following HSV, severe acute respiratory syndrome coronavirus 2 infection *etc.*[16,17]. Syphilis, also known as "the great imitator", and neurosyphilis are both widely known to share clinical features with many diseases. Recently, AE triggered by syphilis has been increasingly recognized[4,18,19]. The cause of secondary AE following syphilis may be due to syphilis directly injuring brain tissue, releasing neuronal proteins capable of inducing autoantibody production and central nervous system damage. There have been several reported cases of anti-NMDAR AE complicated by syphilis[5,6], in which immunotherapy has improved the outcome of patients and is recommended in complicated cases. In the present case, penicillin and antiepileptic treatment only improved seizures but not cognitive impairment and mental abnormalities. Following methylprednisolone shock therapy, the patient's psychiatric and behavioral disorders disappeared and his cognitive impairment improved, accompanied by a decrease in the anti-GABA$_B$R titer (1:100 to 1:32) and an increase in the MMSE score from 2 to 8. Although the patient continued to take methylprednisolone orally for one month, three months later the patient's cognitive impairment did not continue to improve, and the MMSE remained at about 8/30 points. Thus, we reviewed the patient's CSF syphilis titer and GABA$_B$R titer and found that the VDRL was negative, but the anti-GABA$_B$R antibody titer in serum and CSF had increased again. After another round of methylprednisolone treatment, the patient's MMSE score increased to 11/30. These data indicate that the cognitive damage caused by syphilis may be partially worsened by anti-GABA$_B$R AE, and immunotherapy intervention is necessary.

Therefore, for infectious diseases of the central nervous system, if symptoms do not significantly improve after targeted anti-infective treatment, antibody testing is of crucial clinical significance. It plays an important role in disease warning, guiding diagnosis and treatment, and evaluating prognosis. It is also worth noting that AE cannot be ruled out based solely on a negative antibody test result. The most commonly used methods for antibody testing in clinical settings are CBA and TBA, both of which are indirect immunofluorescence techniques[20,21], CBA can only detect about 30 known antibodies, leaving many unknown antibodies undiscovered. Therefore, when CBA is negative but the patient's clinical manifestations meet the criteria for AE, TBA results should be considered. TBA-positivity indicates the presence of antigen-antibody reactions but does not specify the type of antibody (it could be a known or unknown antibody), and it can provide information on the different brain regions and subcellular localization of the antibodies. Our team previously conducted a retrospective analysis of 81 patients diagnosed with neurosyphilis and found that TBA positive staining was significantly correlated with head MRI abnormalities ($P < 0.001$ for parenchymal abnormalities and $P = 0.013$ for white matter lesions). The cognitive prognosis of TBA-positive neurosyphilis patients was significantly worse than that of TBA-negative patients ($P < 0.001$)[22].

Our patient with syphilis complicated by anti-GABA$_B$R AE was timely diagnosed and immunotherapy in addition to anti-syphilis treatment was beneficial in this patient.

CONCLUSION

Syphilis in combination with AE (*e.g.* anti-NMDAR AE) or demyelinating disease (*e.g.* anti-AQP4 NMOSD) has been previously reported. However, to date, cases of neurosyphilis combined with anti-GABA$_B$R AE have rarely been reported. If the characteristics of neurosyphilis combined with anti-GABA$_B$R AE are defined, we will be able to identify, diagnose, and treat these patients earlier.

FOOTNOTES

Author contributions: Hu YF, Zheng D and Fang YX designed the study and drafted the manuscript; Fang YX and Zhou XM took care of the index patient and were responsible for the collection of clinical data; Liu GH conducted most of the experiments and obtained the TBA and CBA images. All authors have read and approved the final manuscript.

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CASE REPORT

Long-term complete response to anti-programmed-death-1 monotherapy in a patient with relapsed and refractory ovarian adenocarcinoma: A case report

Guang-Di Zhou, Qin Li

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Abstract

BACKGROUND

Ovarian cancer is the most common malignant tumor of the female reproductive system, and the survival rate of patients with relapsed and refractory ovarian cancer is very low.

CASE SUMMARY

Here, we report a case of high-grade serous papillary adenocarcinoma of the ovary that was successfully treated with immunotherapy. Radical surgery and adjuvant chemotherapy for the 56-year-old patient were successful; however, her tumor relapsed. Subsequent second-line chemotherapy, targeted agents, and other treatments were ineffective, as the tumor continued to recur and metastasize. Anti-programmed cell death-1 (PD-1) monotherapy (tislelizumab) completely alleviated the tumor, and the multiple metastatic tumors disappeared. To date, the patient has used anti-PD-1 for 32 months, experiencing no disease progression and maintaining good health without additional treatment.

CONCLUSION

This case suggests that anti-PD-1 immunotherapy may have long-term positive effects on outcomes in some refractory recurrent solid tumors. Further research is needed to identify patients most likely to respond to anti-PD-1 therapy.

Key Words: Anti-programmed cell death-1; Tislelizumab; Ovarian cancer; Relapsed cancer treatment; Immunotherapy; Case report

Core Tip: When chemotherapy, poly adenosine diphosphate ribose polymerase inhibitors, and other treatments are ineffective for relapsed refractory ovarian cancer, anti-programmed death 1 immunotherapy may be the last resort.

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INTRODUCTION

Ovarian cancer has the highest mortality among all gynecological cancers. Over 200000 new cases of ovarian cancer and 150000 deaths are recorded annually worldwide[1]. As few symptoms occur at the initial stage, nearly 70% of patients are diagnosed at an advanced stage, with few receiving early treatment. Primary epithelial ovarian cancer is the most common pathological type of ovarian cancer, accounting for over 85% of ovarian cancers, with ovarian serous adenocarcinoma accounting for approximately three-quarters of primary ovarian cancers[2]. Following the treatment guidelines of the National Comprehensive Cancer Network (NCCN) for ovarian cancer, the first-line treatment plan for epithelial ovarian cancer is surgery with platinum and paclitaxel-based chemotherapy[3-5]. However, some patients experience tumor recurrence and multiple metastases after various therapies, posing significant challenges to continued treatment. Immunotherapy has been applied to various cancers in recent years. Programmed cell death-1 (PD-1) and its receptor programmed cell death ligand-1 (PD-L1) constitute a signaling pathway involved in tumor immune escape and are common targets for cancer immunotherapy. Anti-PD-1 and anti-PD-L1 antibodies have demonstrated obvious curative efficacy in clinical trials for melanoma, bladder cancer, lung cancer, leukemia, breast cancer, and other malignant tumors [6-8]. They have also proven effective in the adjuvant treatment of ovarian cancer[9-12]. Here, we report our experience with a patient with high-grade serous papillary adenocarcinoma of the ovary, who experienced disease progression and metastasis under multiple therapies. The patient ultimately exhibited a good response to anti-PD-1 monotherapy (tislelizumab) and achieved long-term complete response, with rapid disappearance of the multiple metastatic tumors.

CASE PRESENTATION

Chief complaints

At the age of 46, she visited the hospital after a physical examination revealed a pelvic mass without any complaints of discomfort.

History of present illness

The patient was born in 1968, got married at the age of 23, and, after giving birth to a daughter naturally, used a birth control ring to prevent pregnancy. In 2014, at age 46, she visited the hospital after a physical examination revealed a pelvic mass.

History of past illness

No abnormalities.

Personal and family history

The patient had a family history of cancer; her mother had died of lung cancer at 53 years, and her brother had died of bowel cancer at 45 years.

Physical examination

Pelvic examination suggested that both bilateral adnexal areas can be palpated with a mass that extends approximately 6 cm without tenderness.

Laboratory examinations

The patient's carbohydrate antigen 125 (CA125) level was 239.9 U/mL.

Imaging examinations

Pelvic contrast-enhanced computed tomography (CT) indicated multiple cystic masses (largest 9.0 cm × 8.7 cm × 7.4 cm) with solid papillary nodules on both ovaries, suggesting a high probability of serous cystadenocarcinoma. Chest CT detected no abnormalities. To rule out the possibility of ovarian Krukenberg tumor, we performed a biopsy of a gastroscopy specimen, which indicated mild chronic inflammation of the gastric mucosa. And colonoscopy detected no abnormalities.

FINAL DIAGNOSIS

The high-grade serous papillary ovarian adenocarcinoma stage IIB (referring to FIGO 2014).

TREATMENT

In June 2014, the patient underwent a successful radical resection of ovarian cancer, reaching the R_0 level. Pathological examination of the surgical specimen revealed high-grade serous papillary adenocarcinoma of both ovaries, involving the right ovarian fallopian tube. We identified cancer cells in the ascites, but the pelvic lymph nodes, greater omentum, and appendix were negative. The ovarian cancer pathological stage was IIB (referring to FIGO 2014). The patient subsequently received six cycles of first-line chemotherapy with paclitaxel and carboplatin, achieving complete remission. In July 2017, the patient's CA125 began to increase slightly. The first progression-free survival lasted for 2 years. In January 2018, abdominal ultrasonography indicated abdominal lymphadenopathy as well as peripancreatic and hilar solid nodules (maximum size 5.6 cm × 3.1 cm). Following this, she received six courses of second-line chemotherapy with carboplatin and doxorubicin hydrochloride liposome, and her CA125 levels returned to normal. Immediately after six courses of second-line chemotherapy, the patient was treated with oral olaparib as maintenance therapy following the NCCN guideline. A genetic test indicated no BRCA1/2 (Breast Cancer 1/2 mutation) mutations in this patient, the homologous recombination deficiency test is also negative by postoperative genetic testing in August 2018. In July 2019, the patient's CA125 increased again. The second progression-free survival lasted for 17 months, and she discontinued olaparib in August 2019 (olaparib continued treatment for 1 year from August 2018 to August 2019). Subsequently, she received three courses of carboplatin + paclitaxel from September to November 2019, but her CA125 continued to increase. Therefore, she was switched to three courses of carboplatin + doxorubicin hydrochloride liposome from December 2019 to February 2020. However, her CA125 rose to 2000 U/mL. In March 2020, she presented with multiple nodules in the liver and lungs and multiple enlarged lymph nodes in the neck, mediastinum, and retroperitoneum, indicating multiple metastases.

Because surgery, chemotherapy, and targeted drugs (olaparib) failed to control tumor progression, immunotherapy was employed as a last resort. The patient commenced anti-PD-1 monotherapy (tislelizumab, BeiGene Ltd, China, 200 mg intravenous drip every 3–4 wk) in April 2020. The CA125 levels rapidly decreased to normal after three courses of PD1 treatment (Figure 1), the liver and lung metastases disappeared (Figure 2), and the lymph nodes were no longer enlarged, achieving complete remission. She regained good physical condition with no discomfort, and her quality of life returned to normal. Her Eastern Cooperative Oncology Group performance status score was 1. In December 2022, owing to a slight elevation in blood creatinine (reach to 76 umol/L), Tislelizumab monotherapy was discontinued. To date, the third progression-free survival has reached 42 months, with 32 months of PD-1 treatment (April 2020-December 2022) (Treatment process refers to Table 1).

OUTCOME AND FOLLOW-UP

The patient is in good health and has normal renal function. Without any complaints of discomfort. She is still being followed up without any treatment.

DISCUSSION

Ovarian cancer has no obvious symptoms at the early stage; therefore, 80% of patients are diagnosed with advanced disease. The recurrence rate after standard treatment is 80%, and the 5-year survival rate is less than 45%[13,14]. For many patients with refractory ovarian cancer, including ours, effective methods to continue treatment after the failures of surgery, first- and second-line chemotherapy, targeted agents, and other treatment methods are limited. In patients who experience therapy failure repeatedly, the 5-year survival rate is less than 25%[15]. Therefore, immunotherapy represents an important novel treatment option for these patients. However, this procedure is usually expensive. Notably, our patient was treated with tislelizumab, which has a much lower cost than other anti-PD-1 drugs. In China, tislelizumab costs about $200 a dose, translating to approximately $133 per week for the patient. Conversely, nivolumab costs $1250 weekly, and pembrolizumab costs about $1667 weekly. The relatively low price of tislelizumab reduces the financial burden on patients, increasing their likelihood of affording long-term treatment.

Tumors evade the host immune system *via* different mechanisms, with the immune checkpoint PD-1/PD-L1 playing a crucial role[16]. Anti-PD-1 is often used as an adjunct therapy to chemotherapy and targeted agents. Ovarian cancer cells express higher levels of PD-L1 than control cells, and high PD-L1 expression is an independent risk factor for the prognosis of patients with ovarian cancer[17], suggesting adverse clinical outcomes. Moreover, high expression of PD-L1 in the ascites or circulating monocytes of patients with ovarian cancer is associated with adverse outcomes[18]. Additionally, clinical trial data suggest that anti-PD-1/PD-L1 antibodies benefit patients with ovarian cancer[19]. However, unlike Hodgkin lymphoma, melanoma, and lung cancer, research on the application of anti-PD-1 therapy in treating ovarian cancer is limited. In a clinical trial involving avelumab (anti-PD-L1) in 124 patients with recurrent ovarian cancer, the drug was effective in 9.7% of patients, and 44.4% of patients had stable disease[19]. Compared with

Table 1 Treatment process

Date (year, month)	Treatment methods	Duration
June 2014	Operation	/
July 2014-January 2015	TC chemotherapy	6 months
January 2018-June 2018	CD chemotherapy	6 months
August 2018-August 2019	Targeting drug (olaparib)	1 year
September 2019-November 2019	TC chemotherapy	3 months
December 2019-February 2020	CD chemotherapy	3 months
April 2020-December 2022	Anti-PD-1 therapy (tislelizumab)	32 months
December 2022-January 2024	Without any treatment.	13 months

TC: Paclitaxel and carboplatin; CD: Carboplatin and doxorubicin hydrochloride liposome; PD-1: Programmed cell death-1.

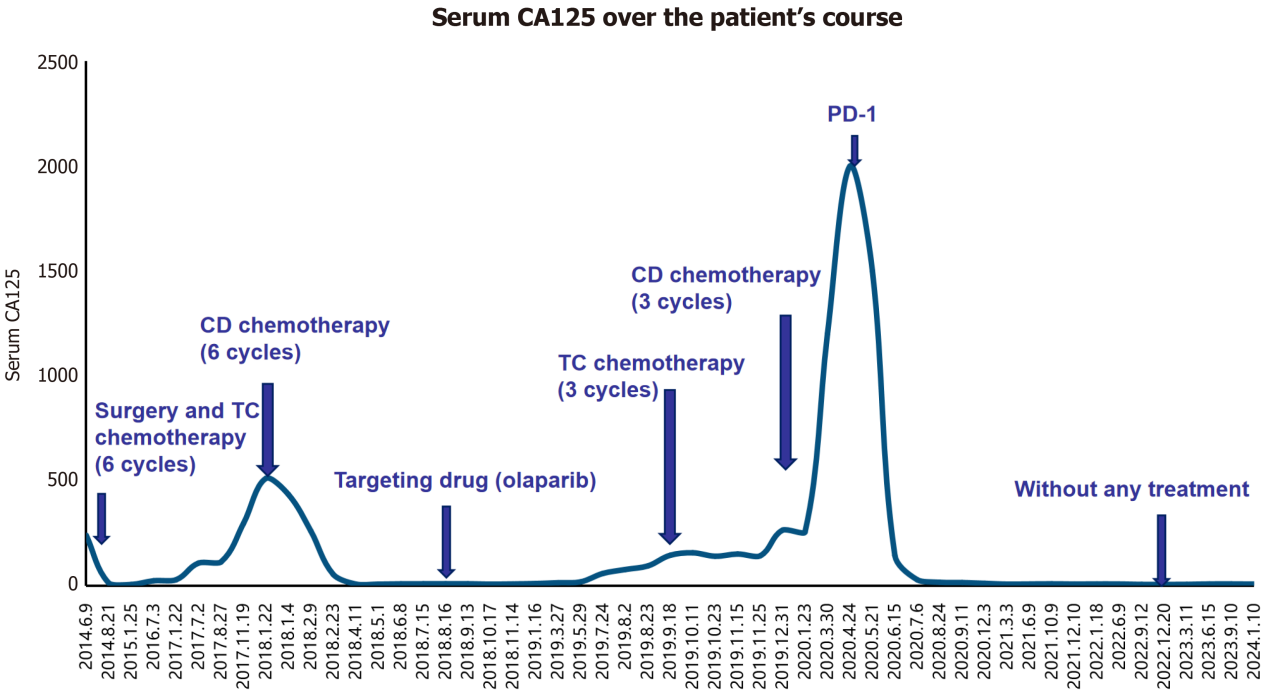

Figure 1 Serum carbohydrate antigen 125 over the patient's treatment course. After three courses of anti-programmed cell death-1 treatment, the patient's carbohydrate antigen 125 decreased from 2000 U/mL to 27.7 U/mL, which was within the normal range. C125: Carbohydrate antigen 125; CD: Carboplatin and doxorubicin hydrochloride liposome; TC: Paclitaxel and carboplatin.

traditional PD-1 inhibitors, tislelizumab eliminates the ability to bind to Fc receptors on the surface of macrophages by modifying the Fc segment, resulting in minimal effects of antibody-dependent cellular phagocytosis, antibody-dependent cell-mediated cytotoxicity, and complement-dependent cytotoxicity, avoiding T cell consumption, and exerting stronger anti-tumor effects than other PD-1 inhibitors. Moreover, no serious adverse reactions occur during use (for example the treatment of this case should be stopped immediately if abnormal renal function is detected), and the tolerance is good. More clinical studies and case reports of anti-PD-1/PD-L1 therapy for ovarian cancer are warranted.

To our knowledge, this is the first publicly reported case of advanced, refractory ovarian cancer achieving long-term complete response to anti-PD-1 monotherapy for 32 months. The progression-free survival time has reached 42 months or more. We posit that the heightened sensitivity to anti-PD1 therapy may be related to the patient's family history of cancer. Our clinical experience suggests that although ovarian clear cell carcinoma is unresponsive to anti-PD1 therapy, ovarian cancer with a family history of cancer, such as Lynch syndrome, is more likely to respond to anti-PD1 therapy. In some cases, anti-PD-1 induces treatment-related adverse events, such as thyroid dysfunction, pneumonia, hip joint pain, pituitary inflammation[20], and lupus erythematosus[21]. Fortunately, our patient developed no adverse events associated with long-term anti-PD-1 therapy for 32 months until a slight rise in serum creatinine prompted cessation. Subsequently, a follow-up was conducted every 3 months. Conventionally, anti-PD1 therapy is used only as an adjunct to chemotherapy or targeted agents when treating ovarian cancer[3,9-12]. However, in our case, complete remission was

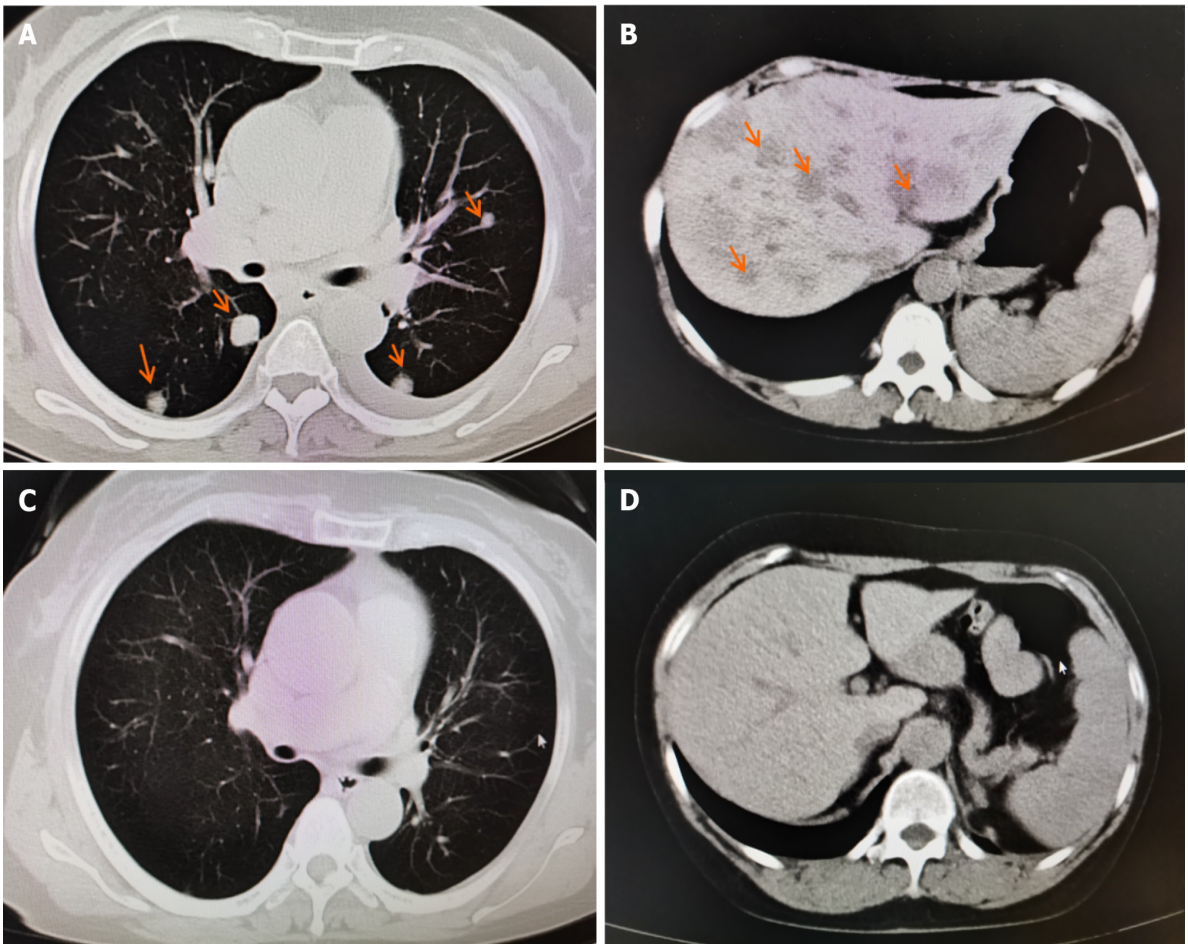

Figure 2 Contrast of the patient's chest computed tomography. A and B: Chest computed tomography (CT) in April 2020 before administration of anti-programmed cell death-1 (PD-1) therapy. The orange arrows indicate metastases; C and D: Chest CT in January 2021, 9 months after initiation of anti-PD-1 therapy. The metastases have disappeared.

achieved solely with anti-PD1 monotherapy, which may play a vital role in treating ovarian cancer. Nevertheless, further research is needed to determine which types of patients are more likely to respond to anti-PD1 therapy.

CONCLUSION

This is the first publicly reported case of advanced, refractory ovarian cancer achieving long-term complete response to anti-PD-1 monotherapy for 32 months. The progression-free survival time has reached 42 months or more. We posit that the heightened sensitivity to anti-PD1 therapy may be related to the patient's family history of cancer.

FOOTNOTES

Author contributions: Li Q designed and performed the research; Both of Li Q and Zhou GD analyzed the data and wrote the paper.

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CASE REPORT

Nd:YAG water mist laser treatment for giant gestational gingival tumor: A case report

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Abstract

BACKGROUND

This case of gestational gingival tumor is huge and extremely rare in clinical practice. As the growth location of this gingival tumor is in the upper anterior tooth area, it seriously affects the pregnant woman's speech and food, causing great pain to the patient. The use of Nd:YGA water mist laser to remove the gingival tumor resulted in minimal intraoperative bleeding, minimal adverse reactions, and good postoperative healing, which is worthy of clinical promotion and application.

CASE SUMMARY

The patient, a pregnant woman, reported a large lump in her mouth on the first day of postpartum treatment. Based on medical history and clinical examination, the diagnosis was diagnosed as gestational gingival tumor. Postoperative pathological biopsy also confirmed this diagnosis. The use of Nd:YAG water mist laser to remove the tumor resulted in minimal intraoperative bleeding, clear surgical field of view, short surgical time, and good postoperative healing.

CONCLUSION

In comparison to traditional surgery, Nd:YAG water mist laser surgery is minimally invasive, minimizes cell damage, reduces bleeding, ensures a clear field of vision, and virtually eliminates postoperative edema, carbonization, and the risk of cross infection. It has unique advantages in oral soft tissue surgery for pregnant patients. Therefore, the clinical application of Nd:YAG water mist laser for the treatment of gestational gingival tumors is an ideal choice.

Key Words: Gestational gingival tumor; Nd:YAG water mist laser; Granulomatous gingival tumor; Minimally invasive dentistry; Pregnancy related diseases; Oral soft tissue surgery; Case report

Core Tip: Pregnant gingival tumors are more common in clinical practice, usually smaller than 1 cm, but gestational gingival tumors with a size of nearly 4 cm are relatively rare. There have been reports of using semiconductor lasers to treat gestational gingival tumors in clinical practice, but the tumors are relatively small and have less bleeding. In this case, Nd:YAG water mist laser was used to remove large tumors. The intraoperative bleeding was minimal, the field of vision was clear, and there was water mist cooling without carbonization. The postoperative effect was ideal.

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INTRODUCTION

Gingival tumors during pregnancy are usually non-malignant lesions[1]. On the basis of gingivitis and chronic periodontitis, the tumor-like lesions are caused by increased levels of sex hormones leading to gingival papillary hyperplasia and enlargement are often seen as single lesions[2,3]. Pregnant gingival tumors belong to the class of granulomatous gingival tumors[4], with abundant blood vessels in the tumor body, generally with diameters less than 2 cm, and have little impact on daily life. However, in severe cases, the tumors may hinder eating, speaking, or even be accidentally bitten, leading to repeated bleeding and secondary infections, thereby endangering the health of mother and child[5]. A case of clinically rare gestational giant gingival tumor was admitted to Ningbo University Affiliated Women and Children's Hospital. On the first postpartum day, Nd:YAG water mist laser resection was performed. The report details our findings.

CASE PRESENTATION

Chief complaints

A 28-year-old female patient developed redness, swelling, and congestion of the gums during the third month of pregnancy. By the seventh month, it was discovered that the upper front teeth had swollen gums on the lip side, about the size of fava beans. Fearful of aggravating the condition while brushing her teeth, she occasionally experienced bleeding while eating. There was no obvious pain initially, but it gradually increased and affected the palatal side. Although it seriously affected food intake and daily activities, she refused surgery due to concerns about the fetus during pregnancy. She came to our department for treatment on the first day after delivery.

History of present illness

By the seventh month, it was discovered that the upper front teeth had swollen gums on the lip side, about the size of fava beans.

Physical examination

There is a huge lump in the front tooth area, and the patient is afraid to close her mouth forcefully. The tumor is dumbbell-shaped and affects the lips and palate on the 11th and 21st teeth. Its dimensions measured approximately 1.9 cm × 1.4 cm × 0.8 cm on the lip side, with a palatal size of approximately 3.2 cm × 2.5 cm × 1.2 cm in size, with a clitoris on the lip side, soft textured, and had a dark purple red color. The surface appeared smooth, with an ulcer approximately 0.6 cm × 0.3 cm × 0.1 cm in size on the labial mass near the cutting end of the tooth. The ulcer surface has slightly white edges and a slightly tough texture. The gap between teeth 11 and 21 has widened to 3 mm, with lip displacement and no looseness of teeth (Figure 1). Poor oral hygiene, along with redness, swelling, and congestion of other gingival papillae and the presence of dental calculus, were also observed.

Laboratory examinations

No abnormalities in the coagulation function test and infectious markers were observed in the elevated white blood cells and neutrophils.

FINAL DIAGNOSIS

Gestational gingival tumors involving teeth 11 and 21, along with chronic periodontitis.

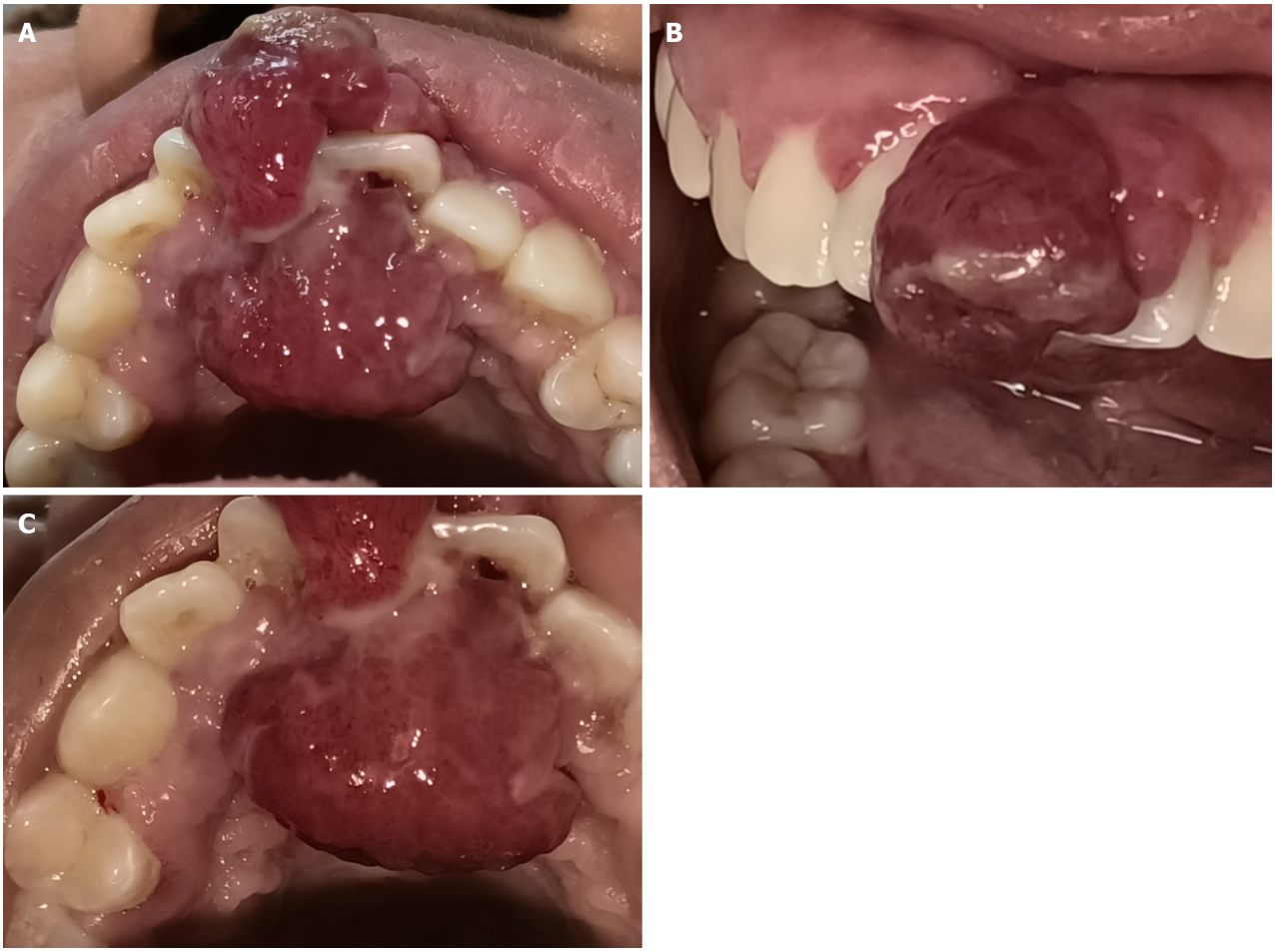

Figure 1 Preoperative. A: Occlusal image; B: Labial image; C: Palatal image.

TREATMENT

Prior to surgery, an informed consent form was signed, and local infiltration anesthesia with articaine and epinephrine Injection was performed. Routine disinfection and drape were used. During the surgery, an incision was made along the normal tissue 0.2 cm around the tumor. The Nd:YAG water mist laser (Wisdom, China) was used in gingival tumor cutting mode, with settings of activated fiber, energy at 140 mJ, frequency at 60 Hz, and water 1, gas 3; this completely removed the tumor tissues associated with teeth 11 and 21. Hemostasis mode (activated fiber, energy of 35 mJ, without water vapor) was then employed to seal and stop bleeding on the surgical site (Figure 2). Due to the patient's weak body and absence of loose teeth on the first day after delivery, no X-rays or further periodontal treatment were taken. Post-surgery instructions included rinsing the mouth with Chlorhexidine mouthwash three times a day, carefully cleaning the teeth every day, and refraining from consuming hard or overheated foods for three days after surgery. After the surgery, the tumor was removed and sent for biopsy. The pathological results showed that it was consistent with granulomatous gingival tumor, with proliferative blood vessels accompanied by a large amount of inflammatory cell infiltration.

OUTCOME AND FOLLOW-UP

One week after surgery, the wound healed well, and there was no recurrence. The interdental space has become smaller, now about 1mm in size, and the inflammation of the entire gums has improved (Figure 3).

DISCUSSION

Gestational gingival tumors are common in clinical practice[6], with the reason for their occurrence being twofold. Firstly, during pregnancy, there is a significant increase in the types of subgingival bacteria, especially the detection rate of periodontal pathogens, which leads to the occurrence of gingivitis and periodontitis[7]. Secondly, there are progesterone and estrogen receptors in gingival, periodontal ligament fibroblasts, and osteoblasts[8]. Elevated levels of sex hormones during pregnancy, combined with continuous inflammatory stimulation, lead to local hyperplasia and swelling of the

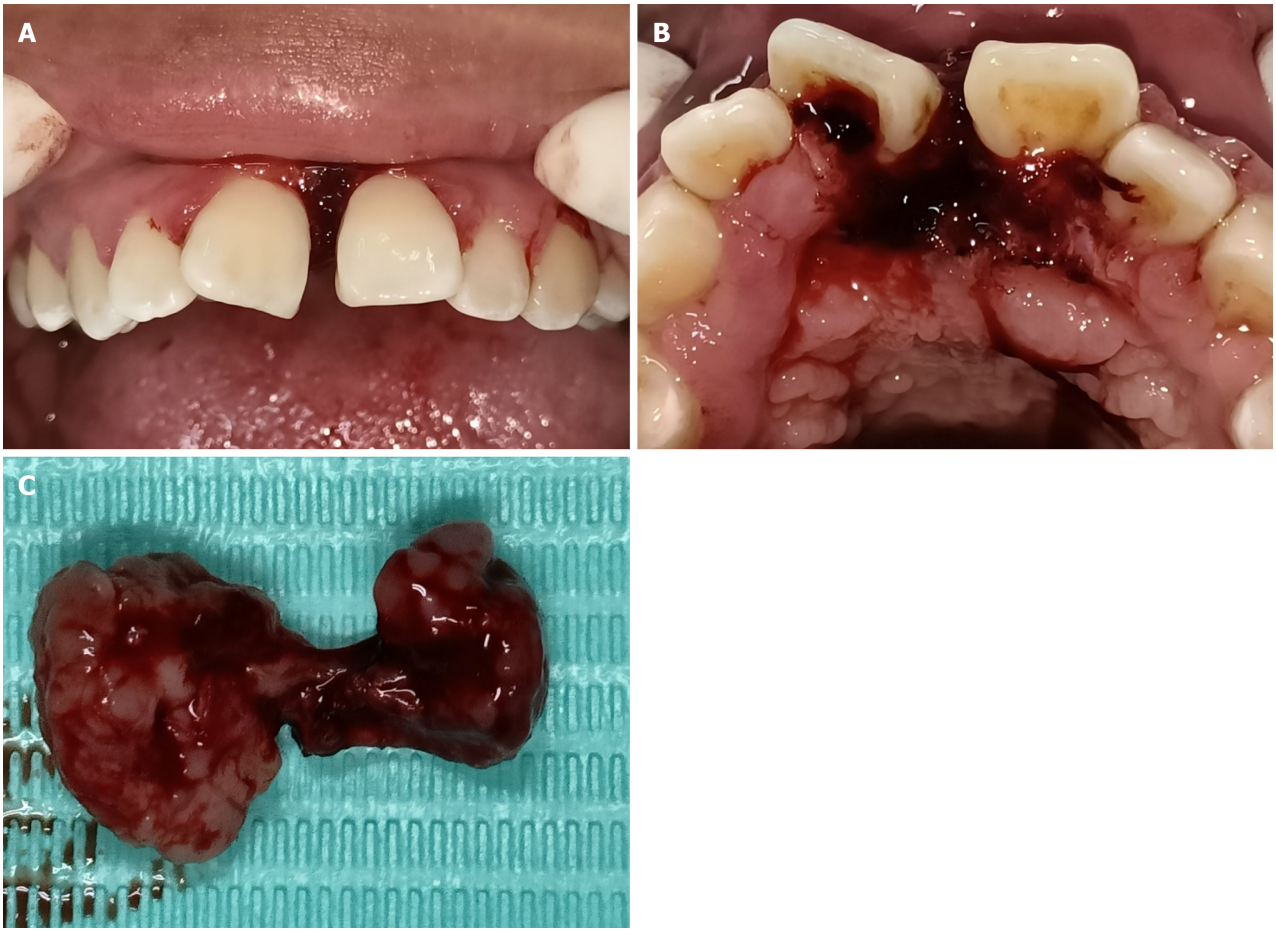

Figure 2 Immediately after surgery. A: Labial image; B: Palatal image; C: Gingival tumor.

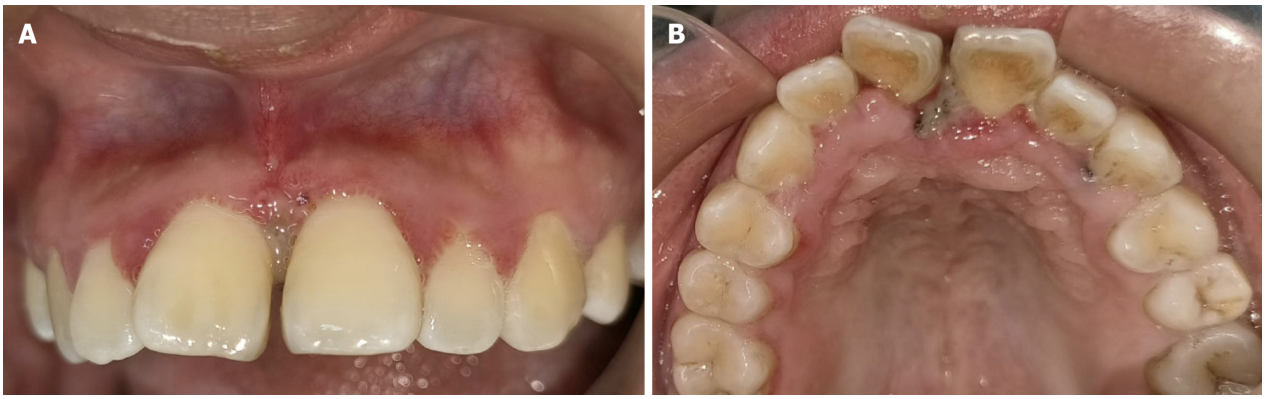

Figure 3 One week after surgery. A: Labial image; B: Palatal image.

gums, resulting in the formation of gingival tumors. Therefore, local plaque and sex hormones are the main causes of gestational gingival tumors. Hence, for the treatment of gingival tumors in pregnant women presenting with small tumors that do not affect oral function and daily life, basic periodontal treatment can be carried out as soon as possible after delivery when the hormone levels return to normal. The gingival tumors may disappear, thus avoiding surgery for patients[9].

Gestational gingival tumors are often accompanied by massive bleeding and can interfere with chewing, affect eating, and thus have adverse effects on the mother's nutrient intake. As the disease progresses, gingival tumors can also damage the alveolar bone, leading to tooth loosening and displacement. In this case, the upper central incisor lip is displaced, and a 3 mm gap appears between teeth 11 and 21, yet fortunately, tooth loosening has not yet occurred. The main treatment method for larger gingival tumors is conventional surgery combined with periodontal scraping to remove irritant factors. Traditional surgery requires gingival tumor resection, extraction of relevant affected teeth, scraping of periodontal ligaments and periosteum, and removal of adjacent bone tissue to prevent recurrence. However, sacrificing the affected

teeth and surrounding alveolar bone may have a negative impact on the patient's postoperative quality of life[10]. Alternatively, a non-surgical treatment method of injecting a mixture of Pingyangmycin and dexamethasone into the tumor cavity has achieved certain results[11], but may not be suitable for pregnant patients.

Gingival tumors are not true tumors, and those with a diameter greater than 2.5 cm are relatively rare[12]. The gingival tumor, in this case, is huge, with a size exceeding 4 cm, which seriously affects the patient's eating, speaking, and daily life. As a result, the patient urgently requests surgery to remove the gingival tumor on the first day after giving birth. The Wisdom Nd:YAG water mist Laser, a neodymium laser that uses crystal material Nd:YAG to generate 1064 nm wavelength, was employed[13]. After being activated by a triggered fiber, it forms an extremely fine beam under the protection of the water mist effect. The high temperature generated vaporizes the tissue to achieve a cutting effect. In addition, by utilizing the absorption characteristics of hemoglobin by Nd:YAG laser, tissue can be quickly vaporized, and capillaries and lymphatic vessels inside the tissue can be sealed, hence reducing intraoperative bleeding and postoperative water reactions. This case achieved good results in the removal of giant gingival tumors using Nd:YAG water mist laser characterized by minimal intraoperative bleeding, clear field of vision, and small wound size. The postoperative reaction is mild, the recovery is fast, and there are no systemic side effects. Therefore, using Nd:YAG water mist laser can reduce intraoperative bleeding, lower suture requirements, shorten surgical time, and promote wound healing. Previous reports have found that the smoke released by ordinary lasers in soft tissue cutting may affect soft tissue healing[14,15]. However, Nd:YAG lasers have a water mist function, which perfectly utilizes the advantages of lasers while avoiding the drawbacks of smoke release, resulting in better surgical results.

CONCLUSION

In comparison to traditional surgery, Nd:YAG water mist laser surgery is minimally invasive, minimizes cell damage, reduces bleeding, ensures a clear field of vision, and virtually eliminates postoperative edema, carbonization, and the risk of cross infection. It has unique advantages in oral soft tissue surgery for pregnant patients. Therefore, the clinical application of Nd:YAG water mist laser for the treatment of gestational gingival tumors is an ideal choice.

FOOTNOTES

Co-first authors: Hong-Yu Chen and Jun-Ji Xu.

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CASE REPORT

Hematochezia due to rectal invasion by an internal iliac artery aneurysm: A case report

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Abstract

BACKGROUND

This case report presents the rare occurrence of hematochezia due to an internal iliac artery aneurysm leading to an arterioenteric fistula, expanding the differential diagnosis for gastrointestinal bleeding. It emphasizes the importance of considering vascular origins in cases of atypical hematochezia, particularly in the absence of common gastrointestinal causes, and highlights the role of imaging and multidisciplinary management in diagnosing and treating such unusual presentations.

CASE SUMMARY

A 75-year-old man with a history of hypertension presented with 12 d of hematochezia, experiencing bloody stools 7-8 times per day. Initial computed tomography (CT) scans revealed an aneurysmal rupture near the right internal iliac artery with suspected hematoma development. Hemoglobin levels progressively decreased to 7 g/dL. Emergency arterial angiography and iliac artery-covered stent placement were performed, followed by balloon angioplasty. Despite initial stabilization, minor rectal bleeding and abdominal pain persisted, leading to further diagnostic colonoscopy. This identified a neoplasm and potential perforation at the proximal rectum. An exploratory laparotomy confirmed the presence of a hematoma and an aneurysm invading the rectal wall, necessitating partial rectal resection, intestinal anastomosis, and ileostomy. Postoperative recovery was successful, with no further bleeding incidents and normal follow-up CT and colonoscopy results after six months.

CONCLUSION

In cases of unusual gastrointestinal bleeding, it is necessary to consider vascular causes for effective diagnosis and intervention.

Key Words: Iliac artery aneurysm; Hematoma; Rectum; Hematochezia; Case report

Core Tip: Lower gastrointestinal bleeding (LGIB) is one of the primary causes of morbidity and mortality in middle-aged and elderly individuals. Hematochezia is a primary manifestation of LGIB and is often associated with ulcers, tumors, and vascular malformations. Here, we report a very rare etiology, which can be attributed to an internal iliac artery aneurysm invading the proximal rectum causing an arterial fistula to the rectum, resulting in massive hematochezia. We hope that this case serves as a reminder that hematochezia may stem from less common causes.

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INTRODUCTION

Lower gastrointestinal bleeding (LGIB) is one of the primary causes of morbidity and mortality in middle-aged and elderly individuals[1]. Hematochezia is a primary manifestation of LGIB and is often associated with ulcers, tumors, and vascular malformations. The terminologies "pseudoaneurysm", "false aneurysm", and "pulsating hematoma" are synonymous, each referring to a specific vascular anomaly characterized by a defect in the vascular wall[2]. This defect culminates in the formation of an extravascular hematoma, which maintains open communication with the intravascular space[3]. An internal iliac artery (IIA) aneurysm is the result of localized dilation of the iliac artery. This may be caused by structural weakness in the arterial wall, typically due to atherosclerosis[4]. The aneurysm may be asymptomatic but can cause serious complications upon enlargement or rupture. Isolated internal iliac artery aneurysm (IAAs) are rare, and rectal bleeding as the primary symptom is even more uncommon. Here, we present an unusual etiology of massive hematochezia attributable to an internal IAA, leading to an arterial fistula to the rectum.

CASE PRESENTATION

Chief complaints

The patient had hematochezia for 12 d and slight abdominal pain.

History of present illness

A 75-year-old man with hematochezia presented to the emergency room in October 2022 due to a 12-d history of hematochezia. The patient's stool was bloody and dark red. He produced bloody stools approximately 7-8 times per day, approximately 100 mL each time, with no accompanying symptoms of fever, vomiting, or abdominal distension. After visiting a local clinic and receiving antibiotic treatment, there was no significant improvement. Since the patient's onset, these symptoms have recurred repeatedly. Three hours prior, the patient experienced an increase in the frequency of bloody stools, accompanied by abdominal pain.

History of past illness

The patient was diagnosed with hypertension 8 years ago. Initially, the condition was identified during a routine health check-up, during which the patient presented with persistently elevated blood pressure readings, averaging 160/95 mmHg. His medical history indicated a gradual increase in blood pressure over the years despite the initiation of antihypertensive therapy. The patient had been on a combination of levoamlodipine besylate and hydrochlorothiazide for the past 8 years, and his blood pressure was partially controlled. He says he usually takes his medication as directed, but sometimes he does not follow the recommended diet and exercise guidelines.

Personal and family history

He had no personal or family history of artery aneurysm or any specific disease.

Physical examination

Upon arrival, his blood pressure was 165/107 mmHg, and his heart rate was 109 beats per minute. Abdominal examination revealed slight abdominal distension and a relatively soft abdomen. Tenderness was present in the lower abdomen, with no rebound tenderness or muscle rigidity. Vascular examination revealed normal arterial pulsations in both lower extremities, with no edema or muscle atrophy present. Digital rectal examination revealed normal anal

sphincter function, with the rectal mucosa being soft and smooth. Insertion of the finger was unobstructed, and no narrowing or palpable masses were detected. Upon withdrawal, the glove was stained with blood.

Laboratory examinations

Laboratory tests revealed a decrease in hemoglobin (Hb) (7 g/dL), an elevated white blood cell count (12.6 × 10^9/L), an increased percentage of neutrophils (88.2%), and an increased CRP level (22.7 mg/dL). There was no evidence of hematuria, with 0-4 red blood cells per high-power field observed under the microscope.

Imaging examinations

The chest X-ray, electrocardiogram, and cardiac ultrasound examination revealed no abnormalities. The patient underwent an enhanced computed tomography (CT) of the entire abdomen and pelvis. CT (Figure 1A-C) revealed an oval-shaped mixed-density mass on the medial side of the right IIA measuring approximately 9.5 cm × 8.5 cm × 7.0 cm. An enhanced scan revealed contrast agent entry inside, closely related to the right IIA, suggesting the possibility of aneurysm rupture and hematoma formation. Imaging also showed signs of hemoperitoneum and peritonitis. An illustration (Figure 1D) shows that the rectal wall was invaded by the right internal IAA, which led to rectal bleeding.

FINAL DIAGNOSIS

The patient was ultimately diagnosed with an internal IAA rupture and rectal perforation. Pathological examination of the aneurysm wall revealed hemorrhage and fibrous exudation (Figure 2A). Rectal pathologic examination revealed ulceration with perforation, mucosal edema, submucosal and serosal purulent inflammation with bleeding and necrosis, consistent with changes related to intestinal perforation. Ulceration was noted at one end of the rectum, while the other end was free of disease (Figure 2B). Additionally, reactive hyperplasia of the perienteric lymph nodes (17 in total) was observed.

TREATMENT

After reviewing the enhanced CT results, the emergency department physician consulted with a vascular surgeon. Following a thorough assessment of the patient's condition, the vascular surgeon decided to perform arterial angiography, place a covered stent into the iliac artery and perform a balloon angioplasty operation under local anesthesia (Figure 3). Two days after the operation, the patient's vital signs were stable, but he reported minor rectal bleeding and mild abdominal pain. For a more definitive diagnosis, the patient was subjected to a colonoscopic examination. Colonoscopy revealed a large neoplasm invading the pelvic cavity approximately 16 cm from the anus, covered with a turbid coating, blood clots, and purulent secretions, with bubbles visible on the surface, suggesting the possibility of a rectal neoplasm with perforation (Figure 4A). After the patient was transferred to the gastroenterological surgery department, an exploratory laparotomy was performed. During the surgery, a hematoma formed by the rupture of the internal IAA was found in the pelvic cavity on the right side of the rectum. The hematoma, approximately the size of an apple, contained a large amount of abscess and stool, giving off an intense malodorous smell. The tumor originated laterally from the right internal IAA and invaded the wall of the rectum on the medial side, communicating with the intestinal lumen. After successful removal of the hematoma and resection of the aneurysm, intraoperative colonoscopy was conducted and revealed a perforation of 0.8 cm in the rectum located 15 cm from the anus and surrounded by neoplastic growth and purulent secretions (Figure 4B). Combined with the intraoperative observations, it is clear that the perforation was located at the site where the hematoma invaded the rectum. During the operation, we decided to perform partial resection of the rectum, followed by intestinal anastomosis and prophylactic ileostomy (the extent of surgical excision is shown in Figure 5). The excised rectal specimen is shown in Figure 6. The surgery was successful, and the patient was discharged from the hospital 7 d later.

OUTCOME AND FOLLOW-UP

After being discharged, the patient recovered well and did not experience any additional episodes of hematochezia. Six months after discharge, he underwent follow-up enhanced CT of the entire abdomen. This investigation revealed no significant abnormalities, corroborating the absence of recurrent or residual vascular disease. Moreover, during the same follow-up period, a thorough colonoscopic examination was performed, which revealed a normal anastomotic site, with no intestinal stenosis, ulceration, or mass formation (Figure 7).

DISCUSSION

IAAs represent a distinct subset of vascular abnormalities characterized by localized dilatation of the iliac artery. The pathogenesis of IAAs typically involves degenerative changes in the arterial wall, often associated with atherosclerosis,

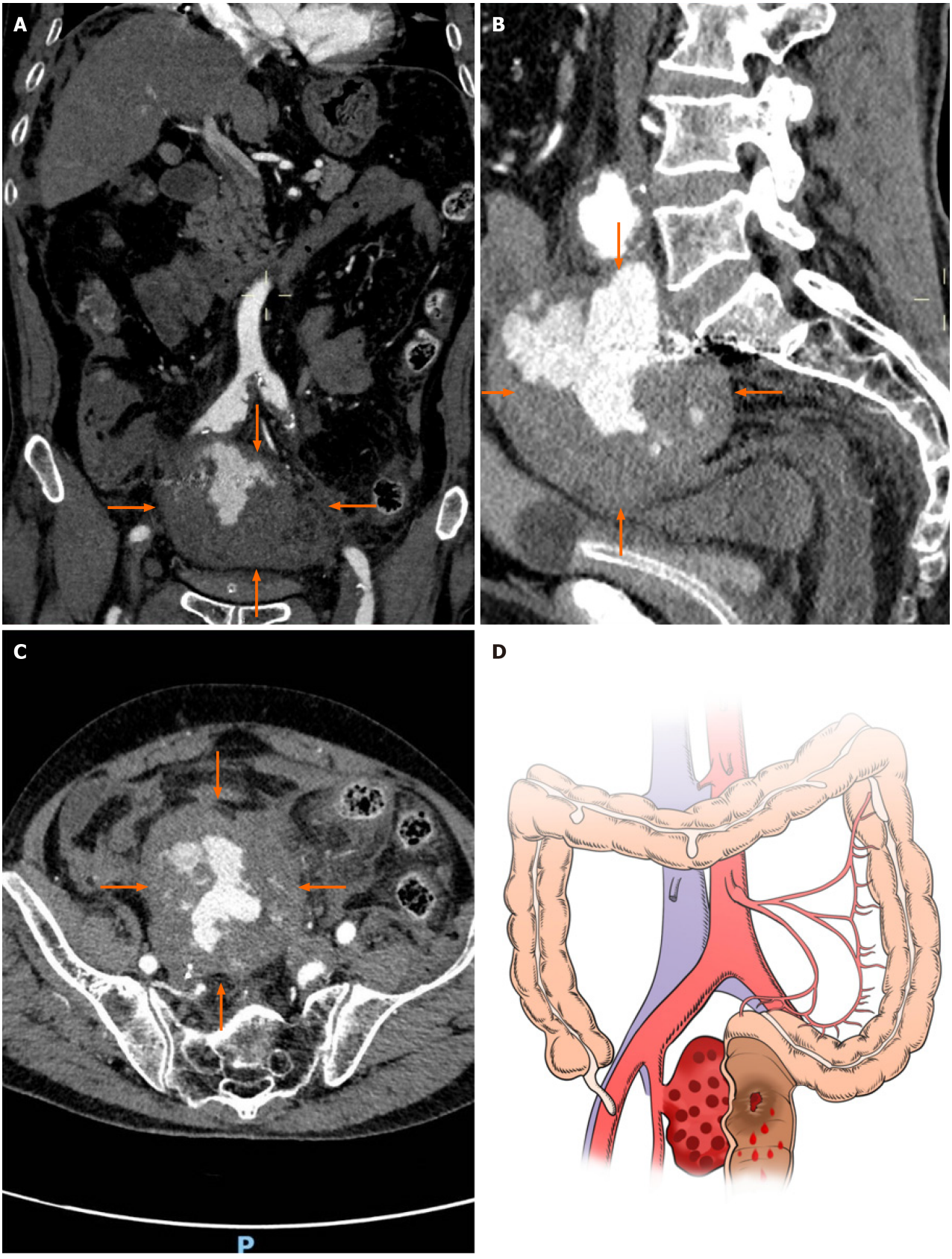

Figure 1 Computed tomography images of the abdomen and pelvis. A: Coronal computed tomography (CT) image showing an oval-shaped mass with mixed high and low densities near the bifurcation of the right internal iliac artery (orange arrow); B: Coronal CT image showing an internal iliac aneurysm occupying the intrapelvic space, with a vertical diameter of approximately 7 centimeters, and suspected to be communicating with the rectum; C: Axial CT image showing that the internal iliac artery aneurysm had transverse and anteroposterior diameters of approximately 9.5 cm and 8.5 cm, respectively, suggesting the possibility of aneurysm rupture and hematoma formation; D: The illustration shows that the rectal wall was invaded by the right internal iliac artery aneurysm, which led to rectal bleeding.

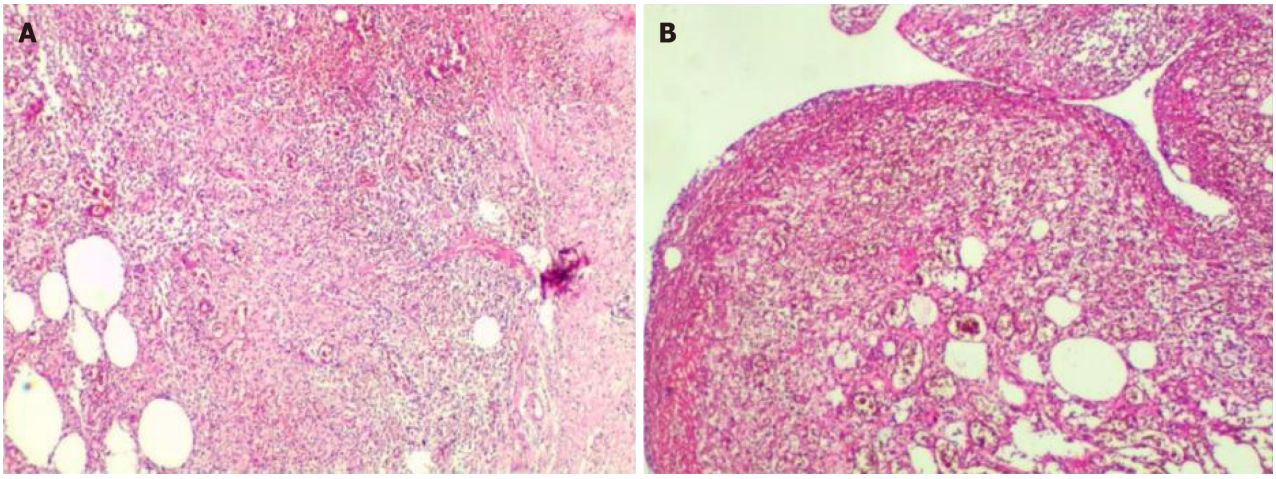

Figure 2 Pathological diagnosis (magnification 10 × 10). A: Pathological examination of the aneurysm wall revealed hemorrhage and fibrous exudation; B: Rectal pathologic examination showed ulceration with perforation, mucosal edema, submucosal and serosal purulent inflammation with bleeding and necrosis, consistent with changes related to intestinal perforation. Ulceration was noted at one end of the rectum, while the other end was free of disease. Additionally, reactive hyperplasia of perienteric lymph nodes (17 in total) was observed.

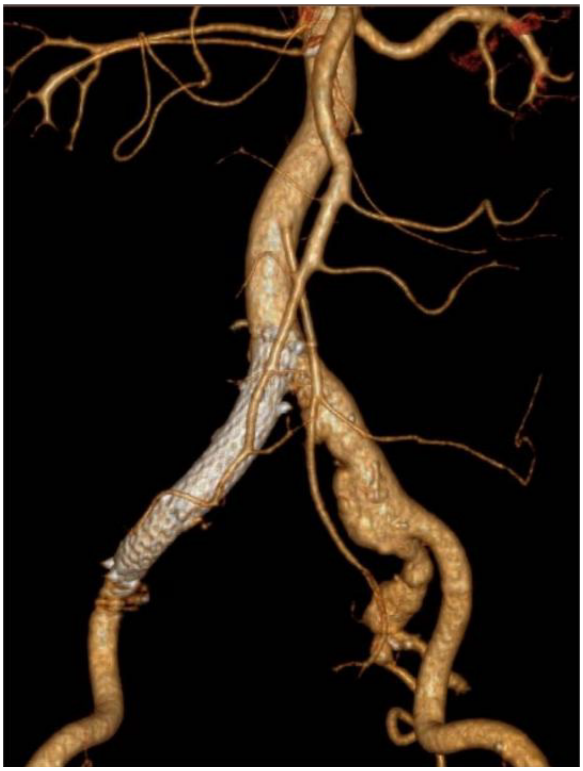

Figure 3 Computed tomography angiography images showing the stent placement site. Postoperative computed tomography angiography suggested that the covered stent deployed in the iliac artery was fixed in its predetermined location and that the pelvic hematoma had decreased in size when compared to its previous size.

leading to weakening and subsequent dilatation[5]. IAAs are markedly more prevalent in older populations, predominantly affecting males older than 60[6]. The exact incidence of IAAs is challenging to ascertain due to their relative rarity compared to aortic aneurysms. Studies suggest that IAAs constitute approximately 2%-6% of all abdominal arterial aneurysms[7]. Specifically, the common iliac artery is most commonly involved in approximately 70% of these aneurysms, while the IIA is involved in approximately 25% of case[8]. IAAs often coexist with other vascular abnormalities, especially abdominal aortic aneurysms. Approximately 10%-25% of patients with abdominal aortic aneurysms also present with IAAs[9].

Unruptured IAAs have a high risk of rupture and are associated with high mortality rates. The literature indicates that the mortality rate for patients with ruptured untreated IAAs can reach 80%, underscoring the importance of early detection and intervention[10]. In addition to the risk of rupture, IAAs are prone to thrombus formation and embolism,

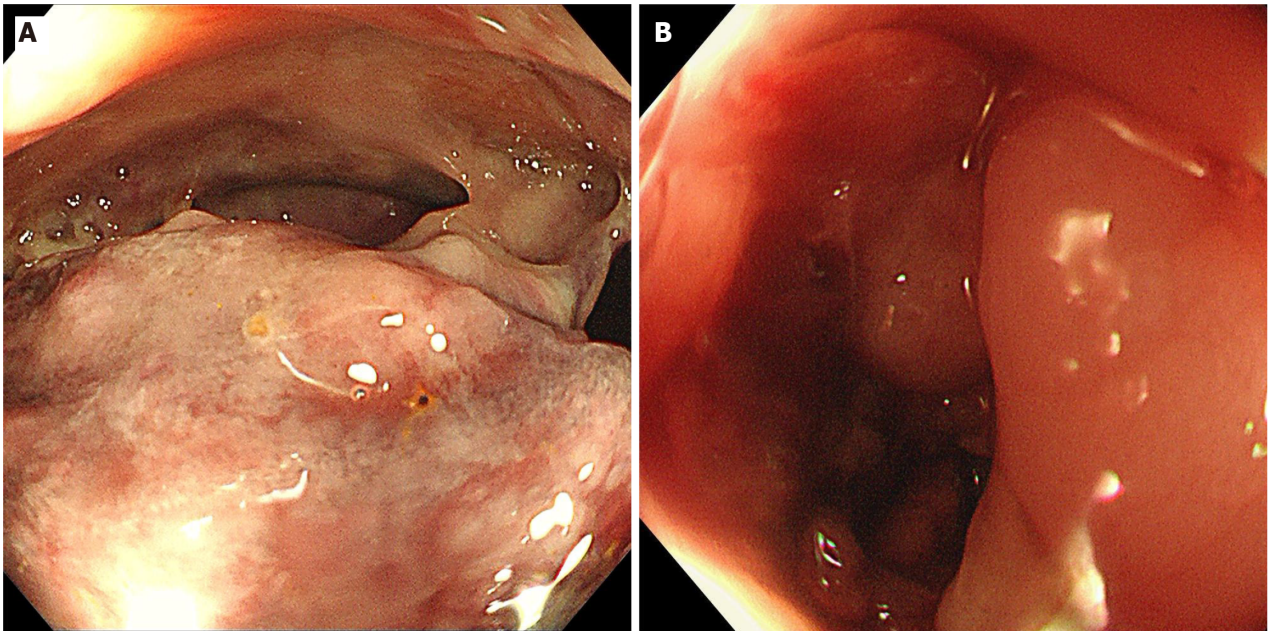

Figure 4 Colonoscopic images. A: Preoperative colonoscopy revealed a large neoplasm invading the pelvic cavity approximately 16 cm from the anus and covered with a turbid coating, blood clots, and purulent secretions, with bubbles visible on the surface, suggesting the possibility of a rectal neoplasm with perforation; B: Intraoperative colonoscopy revealed a perforation 0.8 cm in the rectum located 15 cm from the anus and surrounded by neoplastic growth and purulent secretions.

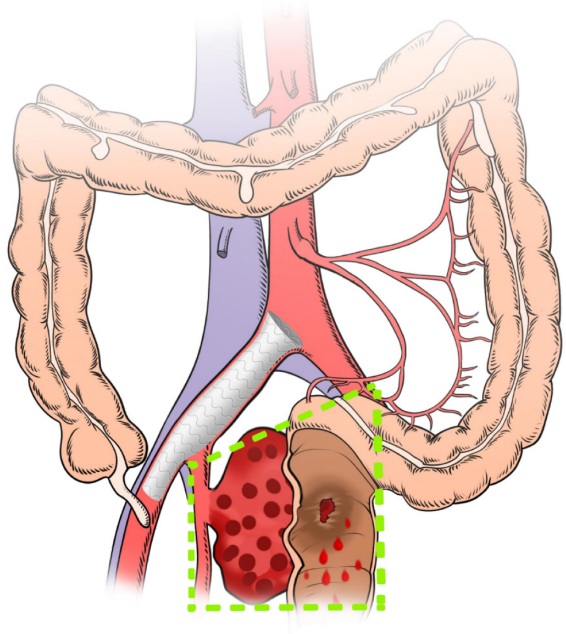

Figure 5 A hand-drawn drawing of the scope of the surgical resection. Illustration showing the extent of surgical excision: Hematoma evacuation, aneurysm resection, resection of the diseased part of the rectum, intestinal anastomosis, and prophylactic ileostomy (as shown within the area marked by the green line).

further increasing the mortality risk[11]. The risk factors for IAAs mirror those for atherosclerotic diseases and include hypertension, smoking, and hyperlipidemia[12,13]. If left untreated, IAAs are likely to rupture, which can lead to life-threatening hemorrhage or, in rare instances, adjacent organ invasion[14,15], as noted in the current case involving rectal bleeding.

Very little is known about the occurrence of an IAA invading the rectum, and few case reports on this topic have been published. This invasion can lead to gastrointestinal symptoms such as rectal bleeding, often leading to misdiagnosis or delayed diagnosis due to its nonspecific presentation.In the complex case of a 75-year-old male with hematochezia, a series of diagnostic and therapeutic interventions were performed. The initial enhanced abdominal CT scan revealed an aneurysmal rupture near the right IIA. A patient's progressively decreasing Hb levels indicated active bleeding. Emergency interventions included arterial angiography and iliac artery stent placement under local anesthesia, which are

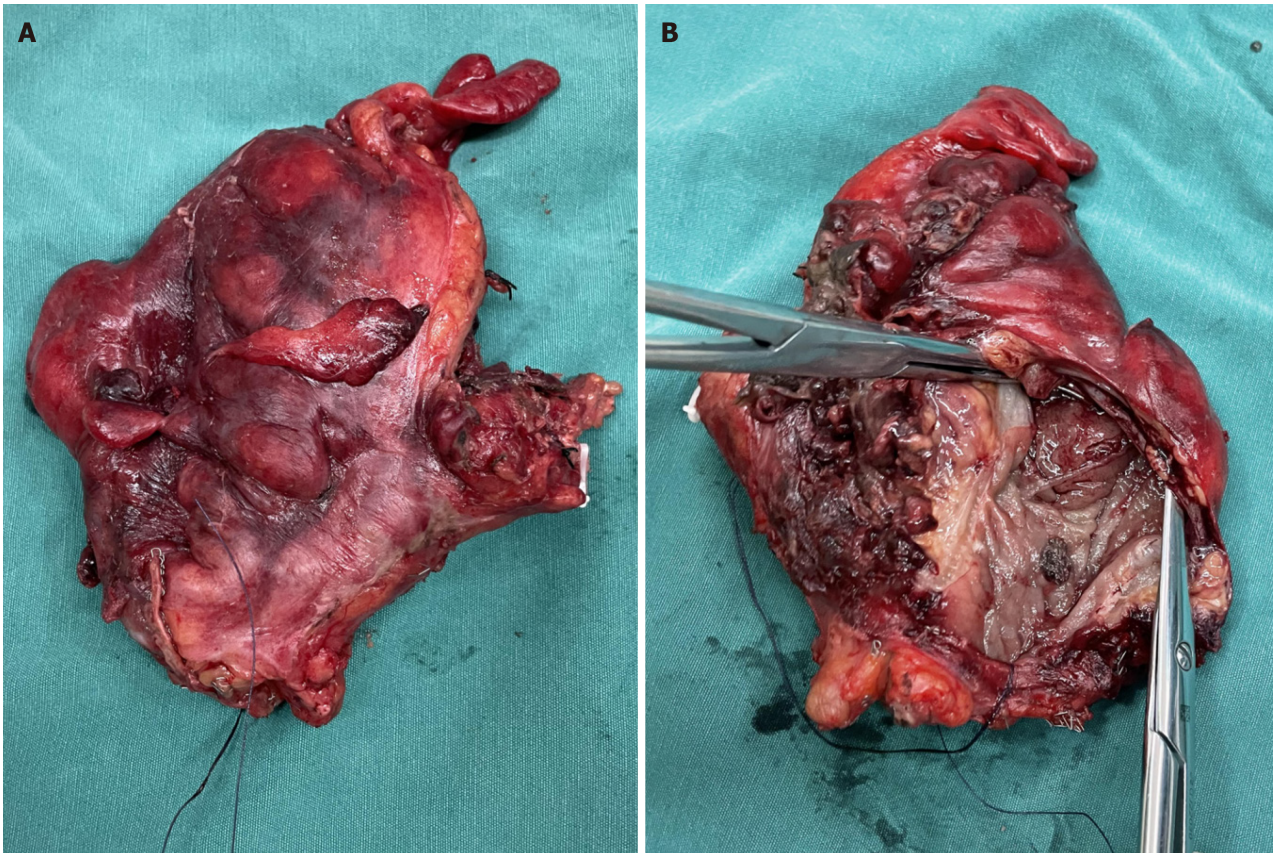

Figure 6 Photograph of the resected rectum. A: Macroscopic appearance of the rectal surgery specimen; B: The appearance of the luminal cross-section of the incised rectal wall shows that on one side of the intestinal wall, there was visible congestion, erosion, and edematous tissue, with purulent necrotic secretions attached, and a perforation approximately 0.8 cm in size in the intestinal wall.

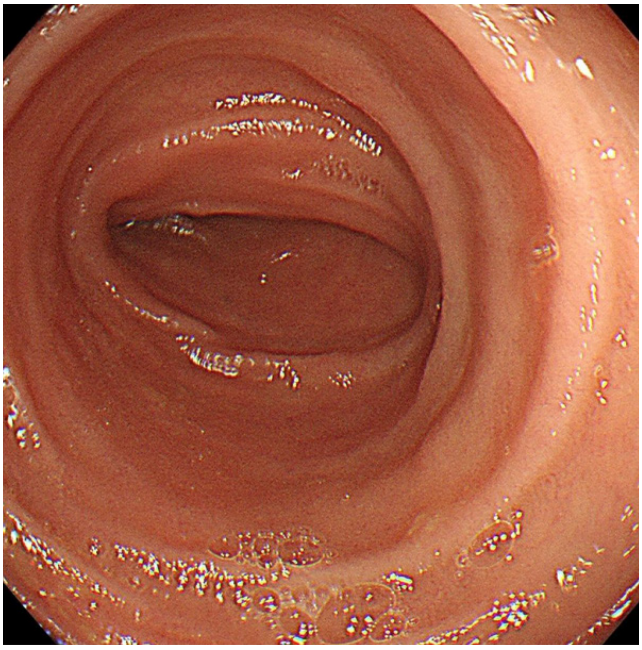

Figure 7 Postoperative colonoscopic images. Six months after discharge, colonoscopy revealed a normal anastomotic site, with no intestinal stenosis, ulceration, or mass formation.

crucial for stabilizing the patient's condition. Despite these measures, the patient continued to experience minor rectal bleeding, which led to further investigations. A colonoscopic examination revealed a neoplasm in the proximal rectum and potential perforation. Surgical intervention, consisting of exploratory laparotomy, hematoma removal, partial rectal resection, and ileostomy, was performed. The pathologic findings were consistent with complications arising from aneurysmal rupture. With respect to initial management, a prompt response to the patient's hemodynamic instability and the use of arterial angiography and stenting were appropriate and effective approaches. These steps are in line with current best practices for managing aneurysmal ruptures, where immediate stabilization is critical. In terms of surgical intervention, the decision to proceed with exploratory surgery following persistent symptoms was necessary. This approach allowed direct visualization and management of the complications associated with aneurysmal rupture and rectal neoplasm.

This report describing a rare case of an IAA invading the rectum and causing hematochezia has significant implications for clinical practice, particularly for vascular surgery and gastroenterology. The findings underscore the need to consider vascular etiologies in patients who present with gastrointestinal bleeding, especially in those of advanced age or with other risk factors. These presentations, though unusual, demand a high degree of clinical vigilance and a broad differential diagnosis.

The successful resolution of this complex case underscores the importance of an interdisciplinary approach involving specialists from emergency medicine, radiology, gastroenterology, and surgery. This collaborative effort is pivotal in managing such multifaceted cases, where the interplay of different organ systems and pathologies presents unique diagnostic and therapeutic challenges. Moreover, this case holds substantial value in informing clinical practice guidelines. This study provides insights into the management of rare and complex cases, highlighting the necessity for these guidelines to be adaptable and inclusive of atypical presentations and complications. The dynamic nature of such cases calls for comprehensive guidelines that are also sufficiently flexible to accommodate the nuances of individual patient presentations.

We are aware that there are several challenges and limitations in the management of this case. These challenges not only highlight areas for improvement but also underscore the complexity inherent in managing such atypical and severe vascular pathologies. First, early detection is challenging. One of the primary difficulties encountered in this case, and generally in similar cases, was the early detection of IAAs. The asymptomatic nature of these tumors, coupled with their deep pelvic location, often results in a delayed diagnosis. As observed in this case, the aneurysm was identified only after significant symptoms had developed, indicating a late stage of the disease. This delay in detection underscores the need for more proactive screening measures, especially in high-risk populations such as elderly individuals or those with a history of vascular diseases. Second, the unpredictable growth rate of these aneurysms presents another significant challenge. In this case, the rapid expansion of the aneurysm leading to rectal invasion highlights the dynamic nature of these aneurysms. This unpredictability necessitates a highly flexible and individualized approach to treatment, which can be difficult to standardize across different clinical settings. The development of predictive models or markers for aneurysm growth could potentially aid in more effective monitoring and timely intervention. Finally, uncertainties in the treatment of IIA aneurysms, as observed in this case, underscore the need for more extensive research and clinical trials. The management of IIA aneurysms also presents unique challenges. In this case, the rarity of IIA aneurysm invasion into the rectum added to the complexity of choosing the appropriate treatment strategy. The less defined treatment protocol for IIA aneurysms, due to their rarity, poses a challenge in developing a standardized approach. This uncertainty calls for more extensive research and clinical trials to establish clear guidelines for the management of such rare yet severe aneurysm presentations. Addressing these challenges requires concerted effort in research, clinical practice, and guideline development, focusing on early identification, understanding the natural history of aneurysms, and refining treatment protocols for rare and complex vascular conditions.

This case report not only provides a roadmap for managing a rare and complex medical scenario but also contributes to the broader understanding of interdisciplinary management of IAAs with gastrointestinal complications. This highlights the importance of integrating advanced imaging, prompt surgical intervention, and collaborative care in the treatment of such patients. Furthermore, the uniqueness of this case contributes valuable information for future research and educational endeavors in vascular surgery and gastroenterology. In particular, this study elucidates the management of IAAs with gastrointestinal complications, a relatively unexplored area. This case study could lead to advancements in both diagnostic approaches and therapeutic strategies for similar complex clinical scenarios. In summary, this case not only enhances the current clinical understanding but also serves as a guide for future explorations and improvements in patient care.

CONCLUSION

This case report of a rare IAA invading the rectum and resulting in hematochezia illustrates several critical aspects of vascular and gastrointestinal disease management. This highlights the need to consider vascular causes in elderly patients presenting with gastrointestinal symptoms, particularly when these symptoms are atypical. This case report not only elucidates the complex nature of managing IAAs but also highlights key areas for improving early detection, understanding the natural history of aneurysms, and refining treatment protocols for rare and complex vascular conditions. Addressing these challenges requires concerted efforts in research, clinical practice, and guideline development.

In conclusion, this case report is a significant contribution to the current literature on IAAs and their rare complications, offering important insights into their diagnosis and management and the need for ongoing research. Clinical

guidelines should be developed to better address such complex medical situations, thus improving patient care and outcomes in similar cases.

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FOOTNOTES

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CASE REPORT

Colonoscopy-assisted removal of an impaction foreign body at the rectosigmoid junction: A case report

Peng-Fei Zhou, Jin-Gen Lu, Jia-Dong Zhang, Jia-Wen Wang

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Abstract

BACKGROUND

When an anorectal foreign body is found, its composition and shape should be evaluated, and a timely and effective treatment plan should be developed based on the patient's symptoms to avoid serious complications such as intestinal perforation caused by displacement of the foreign body.

CASE SUMMARY

A 54-year-old male was admitted to our outpatient clinic on June 3, 2023, due to a rectal foreign body that had been embedded for more than 24 h. The patient reported using a glass electrode tube to assist in the recovery of prolapsed hemorrhoids, however, the electrode tube was inadvertently inserted into the anus and could not be removed by the patient. During hospitalization, the patient underwent surgery, and the foreign body was dragged into the rectum with the aid of colonoscopy. The anus was dilated with a comb-type pulling hook and an anal fistula pulling hook to widen the anus and remove the foreign body, and the local anal symptoms were then relieved with topical drugs. The patient was allowed to eat and drink, and an entire abdominal Computed tomography (CT) and colonoscopy were reviewed 3 d after surgery. CT revealed no foreign body residue and colonoscopy showed no metal or other residues in the colon and rectum, and no apparent intestinal tract damage.

CONCLUSION

The timeliness and rationality of the surgical and therapeutic options for this patient were based on a literature review of the clinical signs and conceivable conditions in such cases. The type, material and the potential risks of rectal foreign bodies should be considered.

Key Words: Foreign body impaction; Surgical therapy; Rectum-sigmoid colon; Colonoscopy; Case report

Core Tip: There are various reasons for the embedding of rectal foreign bodies. Depending on the type and shape of the embedded foreign body, timely and appropriate therapeutic measures to avoid intestinal damage caused by the foreign body are the key to effective treatment. We report the case of a patient with an impacted rectal foreign body for more than 24 h. As the embedded foreign body in this patient was a glass tube with metal needles at the end, removal of the foreign body was carried out in conjunction with gastrointestinal endoscopy.

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INTRODUCTION

Depending on the entry route, foreign bodies can be classified as oral, anal, or endogenous in the gastrointestinal tract[1]. Localized injuries to the gastrointestinal tract caused by foreign bodies most frequently occur in the physiological corners or narrow portions of the gastrointestinal tract and are closely linked to the material, size and sharp edges of the foreign body. The two most prevalent areas are the ileocecal and sigmoid colon[2]. There are numerous sources of intestinal foreign bodies, including, but not limited to, masturbators, fruits, vegetables and glass. Various treatment approaches are required, depending on the composition of the foreign body. A foreign body consisting of soft material, smooth edges, and a small volume can be considered for removal through the anus; fruits and vegetables that are fragile may be extracted *via* the anus or following decomposition of a larger foreign body[3]. Due to the large size or fragility of glass products, such as wine bottles, these can easily cause damage to the intestinal wall, resulting in more serious complications. Therefore, multiple factors should be considered, including imaging examinations, to ensure patient safety[4].

CASE PRESENTATION

Chief complaints

A 54-year-old male was admitted to our hospital with the chief complaint of "rectal foreign body impaction for more than 24 h".

History of present illness

Rectal foreign body impaction for more than 24 h, was accompanied by difficulty in defecation, low stool volume, bloody stools, and a small amount of red blood discharged from the anus.

History of past illness

The patient reported that 24 h previously, due to prolapsed hemorrhoids (Figure 1A), he used an electrode tube for assisted reduction and inadvertently inserted the electrode tube into the anus, which could not be removed. He then used vascular forceps to clamp it, which could not be removed either. Moreover, according to the results of computed tomography (CT) in another hospital (not reported), the foreign body had reached the sigmoid colon, and the patient was unable to remove it following oral lactulose and enemas.

Personal and family history

The patient denied any family history of disease.

Physical examination

On physical examination, his vital signs were as follows: Temperature: 36.8 °C, pulse: 75 bpm, respiration: 15 breaths/min, blood pressure: 120/80 mmHg. The patient was conscious and cooperative. Pain associated with lower abdominal pressure, rebound pain, muscle tension, and mobile turbid sounds were negative.

Laboratory examinations

Laboratory tests on admission showed the following: White blood cells: 8.23 10^9/L, hemoglobin: 136 g/L, platelets: 207 10^9/L, and C-reactive protein: 26.71 ng/L.

Imaging examinations

A CT of the entire abdomen (Figure 1B) revealed an elliptical, cylindrical, metal-dense foreign body in the rectum

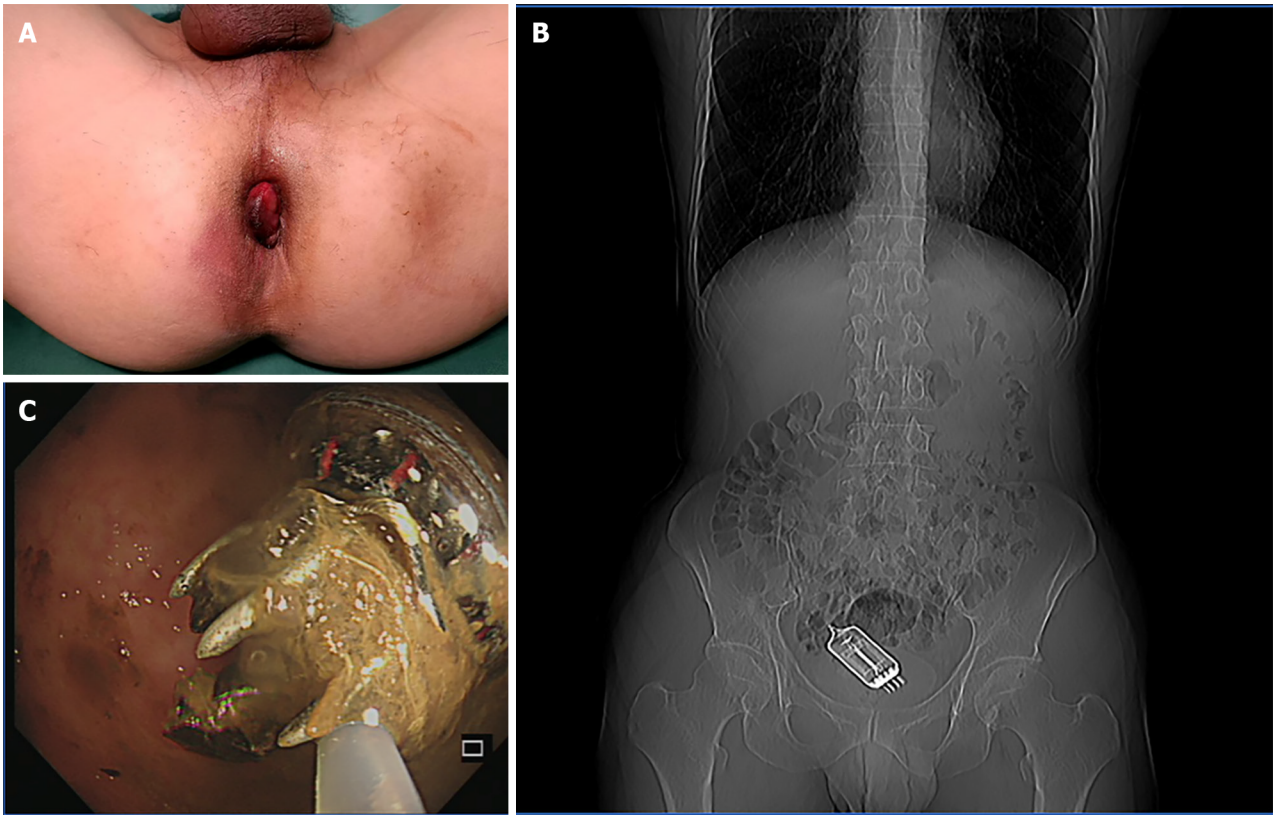

Figure 1 Computed tomography localization of the intestinal foreign body before surgery. A: The patient had anal opening edema, acute prolapsed internal anal hemorrhoids, and surface congestion and erosion prior to surgery; B: Preoperatively, the foreign body was located at the junction of the rectum and sigmoid colon by computed tomography scanning; C: During preoperative colonoscopy, a foreign body was found at the junction of the rectum and sigmoid colon, with the tail end wrapped in intestinal secretions.

measuring approximately 3 cm in diameter and 5.8 cm in length.

FINAL DIAGNOSIS

The final diagnosis in the patient was foreign body impaction at the rectosigmoid junction.

TREATMENT

Rectal foreign body removal was performed under subarachnoid block anesthesia in the operating room. After anesthesia induction, colonoscopy-assisted removal of the foreign body was attempted as finger examination and surgical instruments were unable to reach the foreign body, and gastrointestinal endoscopy revealed that the foreign body had shifted position and was located at the recto sigmoid junction (Figure 1C). The foreign body was characterized by a glass cylinder with metal spikes at the bottom (Figure 2A), and attempts to remove it using a foreign body net pocket during colonoscopy were unsuccessful. After using a ring lasso device and other aids, the foreign body was dragged to the anal canal. After expansion of the anus using comb-type hooks and anal fistula hooks, finger expansion was performed. Subsequently, curved vascular pliers were used to clamp the bottom of the foreign body, which contained metal needles, to facilitate removal of the object from the anus (Figure 2B).

OUTCOME AND FOLLOW-UP

The patient was allowed to eat and drink, and an entire abdominal CT (Figure 3A) and colonoscopy (Figure 3B) were reviewed 3 d after surgery. The CT revealed no foreign body residue, and colonoscopy showed no metal or other residues in the colon and rectum, and no apparent intestinal tract damage. 3 d after surgery, the symptoms of internal prolapsed hemorrhoids disappeared (Figure 3C). And this work has been reported in line with the Surgical case report criteria[5].

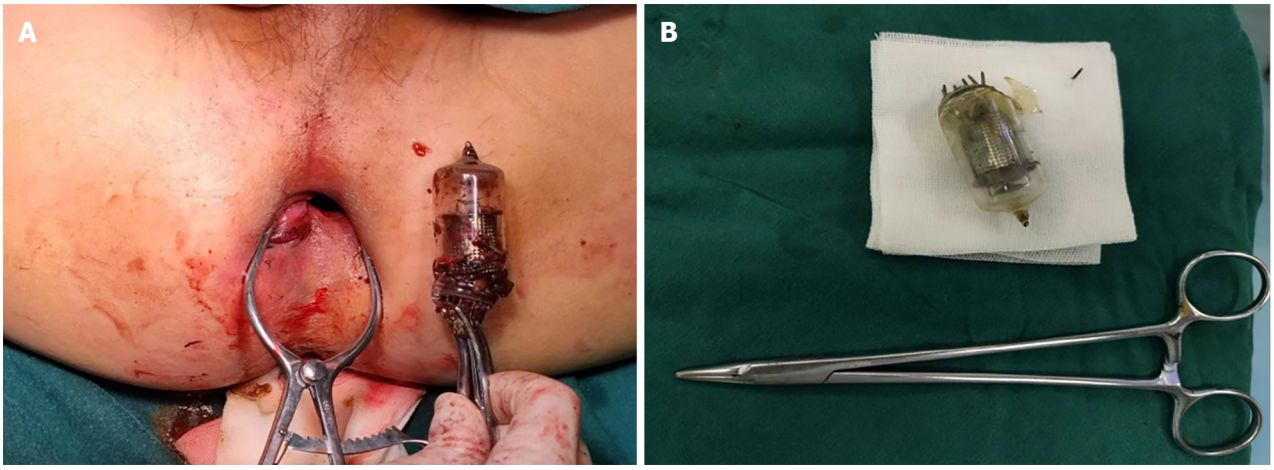

Figure 2 Postoperative foreign body morphology. A: The foreign body was tractioned to the anal opening with the aid of digestive endoscopy, and was then removed by manipulation with the aid of a comb-type pulling tool; B: Comparison of foreign object to a needle receptacle.

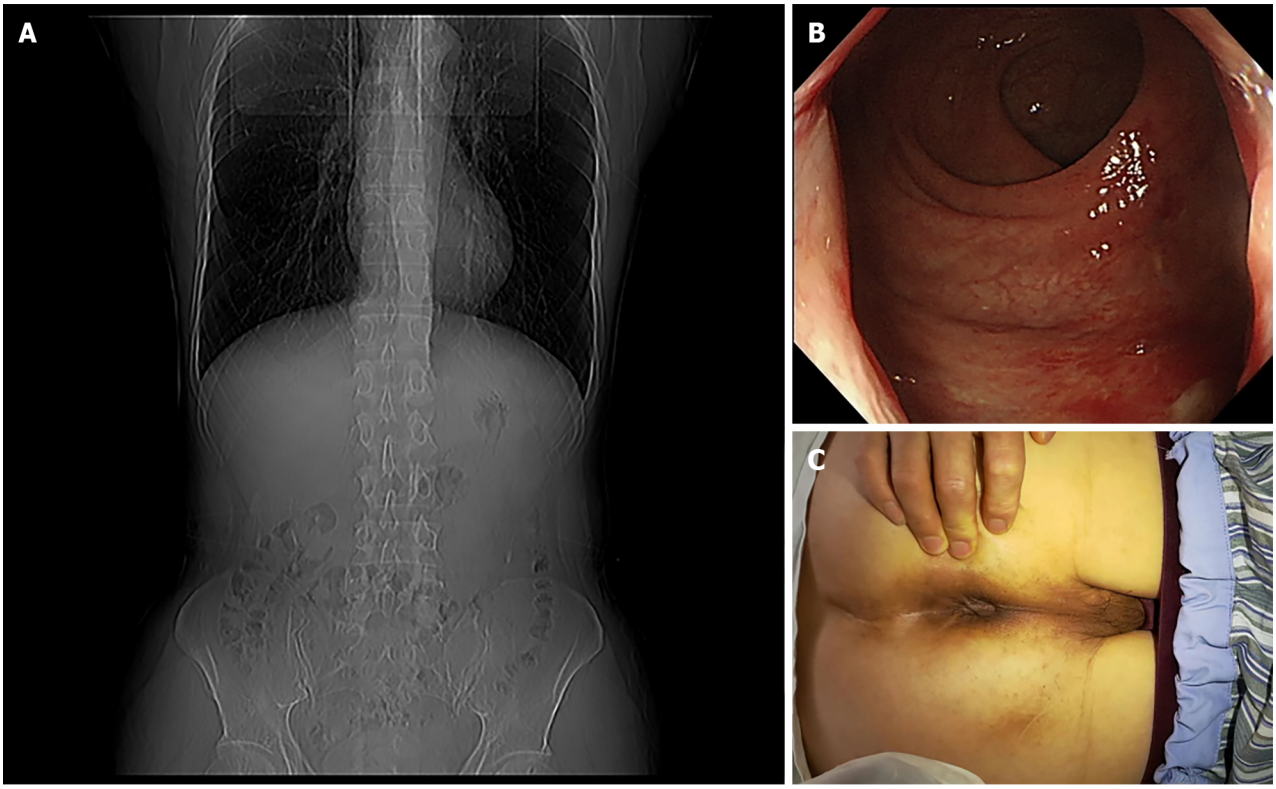

Figure 3 Postoperative evaluation of gastrointestinal foreign body and intestinal lumen status. A: After 3 d of postoperative follow-up, no foreign objects or residues were found on computed tomography scanning; B: 3 d later, a follow-up colonoscopy was performed, and there was no damage to the intestinal cavity and no foreign body residue; C: 3 d after surgery, the symptoms of internal prolapsed hemorrhoids disappeared.

DISCUSSION

The incidence of rectal foreign bodies is approximately 15 per 10000000 individuals[6]. Approximately 20% of rectal foreign bodies are initially masked by different complaints, such as pain, hemorrhage, or constipation, and are undetected until additional inquiries are made regarding the cause of the condition[7]. For example, in the case reported by Husain *et al*[8], the patient mainly presented with abdominal pain, and it was only discovered by chest CT that a perforation of the large intestine had been caused by a fishbone. Unlike Raja Husain's case where foreign bodies entered through the mouth, in this case, the foreign body entered through the anus, providing us with a basis for diagnosis and treatment. Rectal foreign bodies are an urgent and challenging issue for emergency physicians and anorectal surgeons. Patients may be admitted to the hospital and report abdominal discomfort to their attending physicians. Moreover, there is a tendency to conceal the cause of abdominal pain, and the presence of abdominal pain due to a rectal foreign body is given less consideration by physicians. Often, bowel function is preserved despite the patient's abdominal discomfort and inability

to defecate, which is one of the reasons why some physicians consider it an intestinal obstruction[8]. Rectal foreign bodies may be caused by sexual gratification, mental illness, physical assault, or surgical procedures[9]. The foreign body location is not limited to the rectum; however, in severe cases, it can result in tissue or organ injury, with complications including mucosal lacerations, foreign body migration to areas adjacent to the bowel, intestinal obstruction, perforation, peritonitis, and septicemia[10]. Yildiz *et al*[10] analyzed 30 patients with foreign bodies and found that 90% of patients complained of perianal pain, while 70% complained of abdominal pain. Consequently, the patient, in this instance, was hospitalized and fully informed of the patient's right to information prior to surgery, including the risks of the surgical process. The case reported by Simbila *et al*[11] was a male patient who inserted a lubricated plastic detergent bottle into the anus for sexual satisfaction, causing a 10 cm tear and perforation from the rectum to the sigmoid colon. Therefore, the patient underwent colostomy. In our case, during the treatment process, we adopted timely and effective treatment measures, which combined imaging, digestive endoscopy, and anorectal surgery, to select the most appropriate treatment and resolve the foreign body implantation issue.

Rectal foreign bodies and their effects on localized colorectal tissue necessitate systematic evaluation to develop treatment plans. In order to provid a more rational approach, the specific patient's condition in conjunction with a comprehensive physical and digital examination along with abdominal imaging, such as X-rays, and CT scans should be considered, to aid in the assessment and localization of the foreign body, as well as ancillary investigations to determine whether it is possible to attempt manual grasping of the object or endoscopic removal[12]. According to the literature [13], the success rate of removing foreign bodies at the bedside and in the emergency room is 16%-75%. Repeated attempts to remove foreign objects can lead to pain and severe involuntary intestinal spasms, which is one of the reasons for removal failure[14]. In this case, the patient used oral lactose and enemas, but failed to remove the foreign body, which resulted in its movement upward through the anus, and it eventually stopped at the junction of the rectum and sigmoid colon. If physical examination or imaging reveals peritonitis or perforation, surgical intervention should be considered immediately[15]. According to reports, 67% of rectal foreign body injuries do not penetrate the entire length of the rectal wall and thus do not necessitate surgical intervention. When the entire rectal wall is damaged, surgical intervention becomes more difficult, and peritoneal involvement may exacerbate the condition[16]. To minimize the complexity of removing a rectal foreign body, it is important to consider the shape, size, and composition of the object. Depending on the characteristics of the foreign body, methods such as sigmoidoscopy, endoscopy, or Foley catheters can be considered[17].

CONCLUSION

In this case, the embedded foreign body was composed of glass with spiny protrusions, and the location was too high for bedside removal. Therefore, the patient agreed to undergo colonoscopy. Simultaneously, due to the specificity of the embedded foreign body, for industrial diodes, glass products, first and foremost, have the risk of breaking, and once broken, will cause damage to the patient's intestinal lumen, not only increasing the difficulty of the operation but also placing the patient's life in jeopardy. In addition, due to the uncertainty of whether the diode's interior and exterior contain heavy metals and other uncertain materials, and whether it will cause toxicity, there is also a degree of surgical uncertainty; therefore, timely and effective removal of the foreign body is essential. The drawback in this case is that we did not have a more suitable tool to remove the foreign body, which caused damage to the glass when paired with a colonoscope hook. This poses a hidden danger in this type of surgery. However, subsequent observations revealed that this did not lead to other concurrent symptoms. Due to the timely management of this patient, the foreign body was successfully removed. Therefore, in the future, it is necessary to have a suitable surgical plan and surgical tool when dealing with similar clinical cases. The foreign body embedded in the rectum, in this case, was composed of glass, which is easily damaged. Consequently, violent removal should not be conducted during the surgical process to avoid glass breakage, which may injure the intestine.

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LETTER TO THE EDITOR

Intestinal flora: New perspective of type 2 diabetes

Yan Liu, Jun Chang, Li-Ding Bai

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Abstract

Diabetes comprises a group of metabolic diseases characterized by hyperglycemia stemming from various factors. Current diabetes management primarily focuses on blood glucose control, yet it is inherently progressive, necessitating increased reliance on exogenous blood glucose control methods over time. Therefore, there is an urgent need to explore novel intervention strategies addressing both diabetes and its complications. The human intestinal microbiota, often referred to as the "second genome", exhibits significant diversity and plays a pivotal role in insulin resistance, glucose and lipid metabolism, and inflammatory response. Notably, Li and Guo have elucidated the involvement of intestinal flora in the pathogenesis of type 2 diabetes mellitus (T2DM) and proposed a novel therapeutic approach targeting intestinal microbes. This advancement enhances our comprehension of the multifaceted and multi-target regulation of T2DM by intestinal microflora, thereby offering fresh avenues for understanding its pathogenesis and clinical management. This letter briefly summarizes the role of intestinal flora in T2DM based on findings from animal experiments and clinical studies. Additionally, it discusses the potential clinical applications and challenges associated with targeting intestinal flora as therapeutic interventions.

Key Words: Microbial metabolites; Intestinal flora; Probiotics; Insulin resistance; Type 2 diabetes

Core Tip: With the global prevalence of diabetes continuing to rise, China faces a particularly high burden, with diabetes and its complications affecting up to 10% of the population. Type 2 diabetes mellitus (T2DM) constitutes over 90% of these cases. While insulin remains the primary treatment for T2DM, its efficacy is limited in addressing the chronic, progressive, low-grade inflammatory, and the simple reduction of exogenous blood glucose can no longer meet the control of diabetes and its complications, nature of the disease. Consequently, there is an urgent need to identify safe and effective new therapeutic avenues. This letter corroborates the significance of intestinal flora in T2DM, as asserted by Li and Guo. It briefly outlines the role of intestinal flora in T2DM through insights from both animal experiments and clinical studies. Additionally, it discusses the potential clinical applications and challenges associated with targeting intestinal flora as therapeutic targets.

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TO THE EDITOR

We have carefully read the review article "Gut microbiome: New perspectives for type 2 diabetes prevention and treatment" by Li and Guo[1]. We acknowledge the authors' assertion regarding the involvement of gut microbiota in the etiology and progression of type 2 diabetes mellitus (T2DM), emphasizing the potential of gut microbiota modulation as a novel therapeutic avenue for T2DM. We are grateful to the authors for their dedicated exploration of intestinal flora in T2DM, which offers new insights into the mechanisms influencing blood glucose regulation and presents innovative treatment approaches for T2DM and its associated complications.

The intestinal flora, constituting the largest microecosystem within the human body, exerts a significant impact on metabolic processes and energy homeostasis. Recent studies suggest that in addition to obesity, genetics, and islet dysfunction, intestinal flora disturbance could be an important contributor to T2DM[2]. However, long-term consumption of a high-sugar, high-fat, and high-protein diet may be attributed to changes in bacterial membrane permeability, the SOS response, and bacterial composition and diversity caused by diet-induced inflammation[3]. We concur with Li and Guo[1] on the pathogenesis of intestinal flora in T2DM, including bile acid theory, the theory of short-chain fatty acids, and the endotoxin theory. Notably, the relationship between intestinal flora and bile acid metabolism is bidirectional. Guo *et al*[4] speculated that intestinal flora regulates the metabolism, synthesis, and reabsorption of bile acids, wherein bile acids regulate the growth and diversity of intestinal flora. This important bidirectional imbalance may serve as a pivotal factor leading to various diseases, including T2DM. Moreover, short-chain fatty acids (SCFAs), a derivative of the gut microbiota, play an important role in T2DM. In addition to their roles elucidated by Li and Guo[1], SCFAs contribute to regulating liver glycogen metabolism and improving skeletal muscle insulin resistance. Moreover, hepatic insulin resistance is an early symptom of T2DM. Similarly, Zhao *et al*[5] reported that the G protein-coupled receptor 43 (GPR43)-β-arrestin2-AMPK-PGC1-α signaling pathway plays an important role in the regulation of liver glycogen metabolism by butyric acid. Importantly, skeletal muscle insulin resistance is an indicator of T2DM severity. Yang *et al*[6] observed that exercise affected the distribution of intestinal microbiota in T2DM model rats, mainly because acetic acid improved insulin resistance by increasing the autophagy of skeletal muscle, which is involved in the SCFAs/GPR43 signaling axis. Additionally, metabolic endotoxemia with altered microbiota induces systemic inflammatory responses by stimulating the immune system through bacterial translocation. Lipopolysaccharide, an endotoxin, is also an important factor in inducing T2DM and its complications. Moreover, diabetes is a risk factor for Alzheimer's disease (AD). Liu *et al*[7] reported that the CCAAT/enhancer-binding protein/asparagine endopeptidase signaling pathway of neurons activated by inflammation is associated with diabetes and AD, inducing AD pathology and cognitive impairment. Given the substantial impact of intestinal flora on T2DM onset, interventions targeting intestinal flora have merged as promising therapeutic strategies, dietary modifications, probiotics, prebiotics, and fecal bacteria transplantation.

While Li and Guo[1] focused on the basic experimental aspects of the relationship between intestinal flora and T2DM, clinical studies have garnered considerable attention in recent years. Larsen *et al*[8] reported significant differences in the intestinal flora composition between patients with T2DM and a normal population. Compared with normal people, the number of *Bifidobacteria, Clostridium,* and *Firmicutes* in the intestinal flora of diabetic patients was significantly reduced, while that of *Bacteroides* and β-proteus was significantly increased[9]. SCFAs can improve blood glucose, body mass, insulin resistance, and glucose tolerance in patients with T2DM[10,11]. Furthermore, clinical studies found that SCFAs affected the viability of human islet cells in a concentration-dependent manner, prevented streptozotocin-induced β cell apoptosis, and prevented streptozotocin-induced β cell oxygen consumption by supporting mitochondrial respiratory function[12]. However, the specific mechanisms underlying SCFAs and glucose-stimulated insulin secretion (GSIS) necessitate further elucidation. While animal experiments suggest that acetic acid promotes GSIS through parasympathetic nerve activation[13], clinical studies have yielded different results, likely attributable to the pharmacological properties of free fatty acid receptor 2, an important receptor of SCFAs, and the species differences of experimental subjects[14]. In addition, free fatty acid receptor 1 mediates a multitude of functions in the body including release of incretins, secretion of insulin as well as sensation of pain[15]. It is worth noting that free fatty acid receptor is a promising new therapeutic target for T2DM. Therefore, large-scale clinical trials to promote the clinical transformation of basic research results and

better serve patients are required.

In summary, T2DM represents a burgeoning global health concern, characterized by its chronic, progressive, low-grade inflammatory nature, exerting significant impacts on multiple functions of human circulation, nervous system, urinary system, digestion, and other systems. Consequently, it diminishes the patient's quality of life while imposing significant healthcare burdens. Therefore, it is imperative to study the pathological mechanism and effective prevention and treatment of T2DM. As the "second genome" of humans, intestinal flora holds promise as a new therapeutic target for T2DM, offering avenues for reducing insulin resistance, improving glucose and lipid metabolism, and mitigating inflammatory response, thereby laying the groundwork for standardized treatment approaches.

FOOTNOTES

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