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ABOUT COVER

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EDITORIAL

Pitfalls in internal jugular vein cannulation

Deb Sanjay Nag, Amlan Swain, Seelora Sahu, Bhanu Pratap Swain, Merina Sam

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Abstract

Central venous catheter insertion in the internal jugular vein (IJV) is frequently performed in acute care settings, facilitated by its easy availability and increased use of ultrasound in healthcare settings. Despite the increased safety profile and insertion convenience, it has complications. Herein, we aim to inform readers about the existing literature on the plethora of complications with potentially disastrous consequences for patients undergoing IJV cannulation.

Key Words: Catheterization; Central venous; Complications; Thoracic duct; Arteriovenous fistula; Vocal cord paralysis; Pneumothorax; Cardiac tamponade

Core Tip: Central venous catheter placement is widely performed in healthcare settings, including critical care units, operating rooms, emergency departments, and patient-care wards. Although its safety profile has significantly increased with the routine use of ultrasound guidance, it is often associated with potential risks. The internal jugular vein remains the most preferred route for central venous cannulation. Potential complications can be due to anatomical variations or vascular, neural, pulmonary, cardiac, or lymphatic injuries, even with normal anatomy.

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INTRODUCTION

Central venous catheter (CVC) placement is an essential procedure performed

regularly in critical care setups, operating rooms, emergency department scenarios, and all wards throughout any healthcare setup. Although multiple major veins can be cannulated, the internal jugular vein (IJV) is one of the most preferred sites of cannulation. The indications of CVC cannulation include nutritional support, administration of vasoactive drugs, monitoring of hemodynamic status, and therapeutic interventions such as hemodialysis. The enhanced safety profile of IJV cannulation has dramatically increased following the wide usage of ultrasonography (USG) in identifying and cannulating IJV. IJV cannulation is frequently performed in acute care settings throughout the hospital and is associated with a plethora of complications[1].

Several vascular complications have been reported after IJV cannulation, ranging from inadvertent misplacements to multiple attempts (Table 1)[2]. While cannulating the IJV, aberrant neck vascular anatomy has led to arterial and venous injuries and subsequent endovascular salvage procedures[3,4]. Lucas *et al*[3] reported that CVC completely penetrated the right IJV into the right subclavian artery that terminates in the aortic arch. The carotid artery is a major structure with reported inadvertent puncture. It has a 3%-10% incidence, independent of the chosen technique or operator experience[5, 6].

Table 1 Complications associated with internal jugular vein cannulation

	Complications
Abnormal anatomy	Right sided arch of aorta
	Congenital persistence of a left-sided vena cava, with or without a bridging innominate vein
Vascular	Arterial injury
	Venous injury (lacerations of the vena cava, the mediastinal vessels, and the right atrium)
	Bleeding
	Hematoma
Neural	Recurrent laryngeal nerve injury
	Vocal cord palsy
	Sympathetic chain injury
	Brachial plexus injury
	Phrenic nerve injury
	Horner's syndrome
Pulmonary	Pneumothorax
	Pneumomediastinum
	Chylothorax
	Tracheal injury
	Injury to the recurrent laryngeal nerve
	Air embolus
Cardiac	Premature atrial and ventricular contractions
	Arrythmias
	Injury to tricuspid valves,
	Perforation of right ventricle
	Cardiac tamponade
	Cardiac arrest
Lymphatic	Iatrogenic lymphatic
	Thoracic duct injuries
Device related	Fibrin sheath formation
	Fracture
	Thrombosis
	Central venous stenosis
	Infection

Moreover, arteriovenous (AV) fistula formation has been reported with IJV cannulation, especially after removing accidental arterial catheters; these have manifested as profound hemiparesis symptoms and an innocuous humming in the ear[7,8]. Although AV fistula is more common on the right side, the left-sided AV fistula has been reported after left IJV cannulation attempt[9].

Prolonged arterial catheterization can lead to thrombus formation with chances of stroke and risk of neurological deficits. Katyal *et al*[10] (2018) reported a case of acute ischemic stroke from an inadvertently placed CVC into the right common carotid artery. Another rare complication of CVC placement using the landmark technique was its misplacement into the vertebral vein with subsequent subdural effusion in a 4-month-old infant[11]. The next complication of IJV cannulation is the unintentional and potentially life-threatening injury to the right thyrocervical trunk, even when the procedure was performed under the USG guidance[12].

Neural complications such as vocal cord palsy and Horner's syndrome have also been reported[13,14]. Regarding the vocal cord palsy, the right IJV cannulation was performed with the landmark technique, which was associated with transient hoarseness of voice, potentially due to deep infiltration of local anesthetic. Repeated puncture attempts, use of landmark technique, and hematoma formation caused Horner's syndrome in the aforementioned case reports[13,14].

Pneumothorax, pneumomediastinum, chylothorax, tracheal injury, hydrothorax, and air embolism are among the multiple pulmonary complications seen during a CVC insertion[6,15]. Cardiac complications include premature atrial and ventricular contractions, injury to the tricuspid valves, perforation of the right ventricle, and cardiac tamponade. Additionally, proximity to the AV node can lead to cardiac arrest scenarios[16].

Due to the anatomic proximity of the thoracic duct in the superior mediastinum, left IJV cannulation is also associated with lymphatic injury[6,17]. The US-guided IJV cannulation is practiced frequently and considered a safe approach with few complications; its use is recommended by several regulatory bodies. A Cochrane review on ultrasound guidance *vs* landmark technique showed a high success rate with the use of USG vis-a-vis landmark technique with a discernible decrease in overall complication rates[18].

CONCLUSION

Globally, IJV cannulation is a frequently practiced procedure in healthcare settings. The advent of USG has made it convenient and safe to cannulate IJV. However, it is pertinent to note and be wary of the various pitfalls of IJV cannulation to avoid potentially catastrophic therapeutic misadventures.

FOOTNOTES

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MINIREVIEWS

Discontinuation of therapy in inflammatory bowel disease: Current views

Antonio Meštrović, Marko Kumric, Josko Bozic

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Abstract

The timely introduction and adjustment of the appropriate drug in accordance with previously well-defined treatment goals is the foundation of the approach in the treatment of inflammatory bowel disease (IBD). The therapeutic approach is still evolving in terms of the mechanism of action but also in terms of the possibility of maintaining remission. In patients with achieved long-term remission, the question of de-escalation or discontinuation of therapy arises, considering the possible side effects and economic burden of long-term therapy. For each of the drugs used in IBD (5-aminosalycaltes, immunomodulators, biological drugs, small molecules) there is a risk of relapse. Furthermore, studies show that more than 50% of patients who discontinue therapy will relapse. Based on the findings of large studies and meta-analysis, relapse of disease can be expected in about half of the patients after therapy withdrawal, in case of monotherapy with aminosalicylates, immunomodulators or biological therapy. However, longer relapse-free periods are recorded with withdrawal of medication in patients who had previously been on combination therapies immunomodulators and anti-tumor necrosis factor. It needs to be stressed that randomised clinical trials regarding withdrawal from medications are still lacking. Before making a decision on discontinuation of therapy, it is important to distinguish potential candidates and predictive factors for the possibility of disease relapse. Fecal calprotectin level has currently been identified as the strongest predictive factor for relapse. Several other predictive factors have also been identified, such as: High Crohn's disease activity index or Harvey Bradshaw index, younger age (< 40 years), longer disease duration (> 40 years), smoking, young age of disease onset, steroid use 6-12 months before cessation. An important factor in the decision to withdraw medication is the success of re-treatment with the same or other drugs. The decision to discontinue therapy must be based on individual approach, taking into account the severity, extension, and duration of the disease, the possibility of

side adverse effects, the risk of relapse, and patient's preferences.

Key Words: Inflammatory bowel disease; Therapy discontinuation; Therapy de-escalation; Ulcerative colitis; Crohn's disease

Core Tip: Tailoring treatment for inflammatory bowel disease (IBD) hinges on timely drug initiation aligned with treatment objectives. While therapy approaches evolve, achieving and sustaining remission prompts discussions on de-escalating or halting treatment, weighed against long-term therapy risks. With each IBD drug category, relapse risks persist post-discontinuation, impacting over 50% of patients. Withdrawal following combination therapies shows prolonged relapse-free periods, yet randomized trials on medication cessation are limited. Identifying relapse predictors and suitable candidates is pivotal. Re-treatment success underpins therapy withdrawal decisions. Individualized assessments, considering disease severity, duration, side effects, relapse risk, and patient preferences all guide prudent discontinuation choices.

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INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by chronic, lifelong intestinal inflammation, often displaying alternate periods of remission and relapse[1,2]. Clinically, we distinguish two subtypes of IBD: Ulcerative colitis (UC) and Crohn's disease (CD). The etiology of IBD is ambiguous and is considered a combination of genetic, environmental, dietary, microbial, and immunological factors. While the exact origin of the disease remains uncertain, both UC and CD are characterized by the presence of common pathogenesis resulting from an unregulated immune response to antigenic components of the normal commensal microbiota found within the intestine[3].

IBD globally impacts various age groups with a rising incidence in developing countries, posing a significant strain on healthcare systems[4]. It commonly manifests during adolescence or childhood, with around a quarter of patients experiencing onset before the age of 20[5,6]. Although IBD predominantly affects young adults, it can occur at any age. Approximately 20% of children will present with IBD before reaching 10 years of age, and approximately 5% will present even before reaching 5 years of age, showing a varied age range for its occurrence[5,6]. As IBD is a chronic disease which usually appears at a young age, it implies the need for long-term treatment, often accompanied with high financial costs.

The treatment of IBD has evolved in recent decades. The increased introduction of therapy still represents the basis of a rational approach to the treatment of each IBD patient individually, contributing to the severity and extension of the disease[7,8]. Treatment includes anti-inflammatory drugs, immunomodulators and, most recently, biological therapy, with the introduction of small molecule therapy several years ago[7,8]. The field of IBD is very attractive to drug researchers, which is evident in numerous ongoing clinical studies exploring new medications primarily targeting immune response mechanisms. This underscores the persistent presence of patients who are facing challenges in achieving and sustaining adequate remission, partly due to the loss of response to the treatment. Traditionally, treatment goals centred on clinical remission, inflammation reduction, and mucosal healing. However, recent focus has shifted towards the overarching objective of enhancing quality of life, recognizing the substantial impact of IBD on both physical and mental well-being[9,10].

For certain IBD patients, the treatment efficiently keeps them in long-term remission, posing a dilemma for clinicians on the necessity and duration of continued treatment. However, current guidelines do not anticipate when therapy should be discontinued[7,8]. Furthermore, the continuation of biological treatment for an indefinite time is encouraged, with the aim of maintaining remission for as long as possible[7,8].

Weighing the possibility of relapse and lack of response to reintroduction of therapy against the risk of side effects such as infections and the risk of inducing malignant diseases due to prolonged use of immunomodulators and immunosuppressive therapy is crucial when considering the possible cessation of treatment. Apart from health risks, the financial aspect of treatment is also relevant. The continuous introduction of advanced medications incurs expenses for the healthcare system, which now surpass the costs associated with surgical procedures and hospital stays[11-14].

The outlined complexities underscore the necessity for a tailored approach to treating IBD patients-one that aligns with medical and financial rationale while also meeting the patient's needs and preferences.

Therapy goals in the treatment of IBD

The International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) in 2021 updated the previous goals for the treatment of IBD from 2015, known as the Initiative to Select Therapeutic Targets in Inflammatory Bowel Diseases (STRIDE)[9,10]. STRIDE represents a treat-to-target strategy based on evidence and consensus, which foresees an individual approach to patients according to local possibilities, all with the aim of improving treatment outcomes[9,10]. A

systematic review included 435 relevant papers from a pool of 11278 manuscripts[10]. The original STRIDE recommendations (STRIDE I) defined the following important treatment goals: Clinical response and remission, endoscopic healing, and normalization of C-reactive protein (CRP, or rate of erythrocyte sedimentation rate) and calprotectin[9].

STRIDE II reaffirmed these goals while adding long-term objectives like absence of disability, improvement in quality of life, and maintaining normal growth in children[10]. Improvement in symptoms and normalization of inflammatory parameters in serum (CRP/erythrocyte sedimentation rate) and stool (fecal calprotectin) are proclaimed short-term treatment goals[10]. However, transmural healing in CD and histological healing of the mucosa in UC are not considered final treatment goals, but represent a measure of the magnitude of remission[10].

The absence of disability and normalization of health-related quality of life is the long-term goal of treatment, according to the IOIBD recommendations[10]. However, it should be emphasized that the quality of life should be the aim in each phase of treatment. The treatment goals are summarized in Table 1, with a strong recommendation to reassess therapeutic approaches if these goals are not achieved.

Exit strategies in specific therapeutic approaches

In 2017, a consensus expert panel convened by the European Crohn's and Colitis Organization gave practical instructions for exit strategies in the treatment of IBD[11]. The likelihood of relapse with stopping a specific class of IBD therapy was also reviewed[11].

It is important to emphasize that each major class of IBD medications, whether used alone or combined (such as 5-aminosalicyclates, immunomodulators, biologic agents), confers a risk of relapse following reduction or discontinuation of treatment[11]. An individualized approach, involving shared decision-making with patients, is crucial. Decisions on discontinuation should consider relapse risks and treatment effectiveness upon re-initiation.

In particular, the actual disadvantage of withdrawal should not be recognized by the rate of relapse after discontinuation itself, but by the increase in the rate of relapse over the rate of relapse with continued therapy, because a considerable number of patients may still relapse even if therapy is continued[15].

5-Aminosalicylates

5-Aminosalicylates (5-ASA) are the cornerstone therapy for patients with mild to moderate UC[8]. Furthermore, it is estimated that 88%-97% of patients receive 5-ASA therapy within one year of the initial diagnosis, and 60%-87% continue to use it in the following 10 years[16,17]. 5-ASA is a widely prescribed drug and accounts for 25% of the total cost of treatment in patients with UC[18,19].

Contrary to the European Crohn's and Colitis Organisation (ECCO) guidelines, 5-ASA are also frequently prescribed drugs in the treatment of CD[7]. Moreover, one-third of patients with CD receive long-term therapy with 5-ASA, despite the lack of proven benefit[7,20-22]. On the other hand, in UC, 5-ASA have been proven successful as well-tolerated drugs with a high safety profile[8]. The role of 5-ASA in the prevention of colorectal cancer, possibly due to its potential direct chemoprotective effect, should be especially highlighted[23].

A meta-analysis of 31 observational studies encompassing 2137 cases of colorectal neoplasia, 76% of which were cancer, revealed that therapeutic doses of 5-ASA were significantly associated with reduced neoplasia in UC [risk ratio (RR) 0.54, 95% confidence interval (95%CI): 0.38-0.64], but this effect was not observed in patients with CD (RR 0.76, 95%CI: 0.43-1.33). Notably, there was no observed benefit with sulfasalazine[24]. Additionally, a separate systematic review and meta-analysis involving 26 observational studies, incorporating 15460 subjects, highlighted the chemopreventive effect of 5-ASA on colorectal cancer (excluding dysplasia)[25]. This effect exhibited significance exclusively in clinical studies (OR = 0.51; 95%CI: 0.39-0.65) and among patients diagnosed with UC (OR = 0.46, 95%CI: 0.34-0.61). Moreover, the protective effect against colorectal cancer was notably more pronounced with a mesalazine dosage of 1.2 g/d compared to dosages below 1.2 g/d[25].

Ardizzone *et al*[26] conducted a comparison of 12-month relapse rates concerning the duration of remission before therapy withdrawal. Patients who had sustained remission for more than 2 years before discontinuing 5-ASA did not exhibit a significantly higher relapse rate compared to those who continued treatment. Conversely, patients in remission for 1-2 years prior to 5-ASA withdrawal demonstrated a notably higher relapse rate than the continuation group (49% *vs* 23%). The authors concluded that maintaining 5-ASA treatment is essential for patients who have been in remission for less than 2 years.

Regarding topical (rectal) 5-ASA therapy, existing studies provide compelling evidence. Six randomized clinical trials collectively revealed higher relapse rates in the placebo group vs the 5-ASA treatment group using topical monotherapy [27-32]. Reported relapse rates in the placebo group ranged from 52% to 85% at 12 months and up to 91% at 24 months. Conversely, relapse rates among patients continuing 5-ASA ranged from 20% to 48% at 12 months and reached 55% at 24 months. Authors across all studies uniformly concluded that discontinuing topical therapy in distal UC significantly increased the likelihood of disease relapse. Although studies analyzing dose de-escalation are lacking, reducing the frequency of administration is commonly practiced upon achieving remission[8].

Recent American Gastroenterological Association guidelines for managing moderate to severe UC propose the possibility of discontinuing 5-ASA therapy in patients achieving remission with biologic agents, immunomodulators, or tofacitinib[33]. A retrospective analysis utilizing two national databases in Denmark and the United States, comprising 3178 patients, compared adverse events among individuals who ceased oral 5-ASA within 90 d of commencing anti-tumor necrosis factor (TNF) therapy with those who maintained 5-ASA. Results indicated that discontinuing 5-ASA did not elevate the risk of adverse clinical events, corticosteroid usage, hospitalization, or surgery in either the United States or Danish cohort[34].

Table 1 Treatment goals in patients with inflammatory bowel disease

	Short/intermediate-term goals	Long-term goals
Clinical	Clinical response	Clinical remission; In children, the return of normal development is a long-term goal
Endoscopic		Endoscopic healing; Histological healing is not a defined goal of treatment in CD or UC
Laboratory	Normalization of CRP, ESR and fecal calprotectin	
Quality of life	Absence of disability and normalization of health-related quality of life	

CD: Crohn's disease; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; UC: Ulcerative colitis.

Moreover, Singh *et al*[35] conducted a pooled analysis of individual participant data from five infliximab and golimumab trials in UC, encompassing 2183 patients treated with infliximab or golimumab (78.6% receiving 5-ASA), aiming to evaluate whether concurrent 5-ASA use influences clinical outcomes in these patients. Their findings indicated that the concurrent use of 5-ASA did not correlate with increased odds of achieving clinical remission or mucosal healing. These outcomes remained consistent across trials for both induction and maintenance therapies and across infliximab and golimumab treatments[35]. Similarly, a retrospective observational cohort study focusing on vedolizumab, a monoclonal antibody targeting α4β7 Leukocyte integrin in UC patients, arrived at the same conclusion. Ma *et al*[36] reported that concomitant 5-aminosalicylate use among individuals treated with vedolizumab did not demonstrate significant differences in achieving clinical or endoscopic remission, sustained vedolizumab use, or secondary loss of response.

In general, discontinuing oral 5-ASA as a standalone therapy tends to result in a higher relapse rate. When considering the withdrawal of 5-ASA in UC patients, it's crucial to approach it on a case-by-case basis, involving the patient in decision-making. This decision should hinge on the presence or absence of specific risk factors. However, for UC patients displaying high adherence to the drug, experiencing a mild disease course, showcasing low levels of fecal calprotectin, and/or demonstrating complete mucosal healing, a reduction in the maintenance dose of 5-ASA could be contemplated [8]. Conversely, patients diagnosed with left-sided and extensive colitis typically anticipate higher relapse rates, and these individuals might benefit from a higher maintenance dose of therapy.

Immunomodulators

As widely acknowledged, ECCO guidelines recommend thiopurine monotherapy to sustain remission in individuals with steroid-dependent UC or those unable to tolerate 5-ASA[8]. Additionally, thiopurines are endorsed for sustaining remission in steroid-dependent CD patients[7]. Nonetheless, concerns regarding the potential complications, including non-melanoma skin cancer, myeloproliferative, and lymphoproliferative disorders associated with long-term thiopurine use, raise substantial safety considerations[37-39].

The potential adverse effects of long-term immunomodulator therapy prompt consideration about its discontinuation and the optimal timing for such a decision. A comprehensive systematic review conducted by Torres *et al*[40] synthesized data from 69 studies comprising 4672 IBD patients, revealing that more than 50% of individuals discontinuing immunomodulators or biological-based therapies experienced disease relapse. Notably, randomized clinical trials investigating withdrawal possibilities and their impact on disease progression and relapse remain scarce. One of the early studies on immunomodulatory withdrawal in CD, led by Bouhnik *et al*[41], shed light on this aspect. Their retrospective analysis revealed that among patients continuing therapy, the cumulative probabilities of relapse at 1 and 5 years stood at 11% and 32%, respectively. Notably, female gender, younger age, and a longer time to achieve remission (over 6 months) were associated with a heightened risk of relapse in this cohort. In contrast, for patients who ceased therapy, the probabilities of relapse at 1 and 5 years were notably higher, at 38% and 75%, respectively. Factors such as male sex, younger age, and shorter duration of remission (less than 4 years) correlated with an increased risk of relapse in this group. The authors concluded that after 4 years of remission under these medications, the risk of relapse appeared comparable regardless of therapy continuation or cessation. This finding led to questioning the utility of prolonged immunomodulator use in such patients[41].

Further analyses dissuade the discontinuation of immunomodulators in the absence of long-term remission. French *et al*[42] conducted a meta-analysis involving five studies encompassing 256 CD patients and 168 controls. Their findings highlighted the benefits of continuing azathioprine or 6-mercaptopurine for a minimum of 18 months to uphold previously attained remission. The study revealed that maintaining thiopurine therapy reduced the relapse risk at 6, 12, and 18 months, displaying pooled odds ratios of 0.22, 0.25, and 0.35, respectively[42]. Similarly, in UC patients, although data are limited, comparable results have emerged. A sole published double-blind randomized clinical trial involving withdrawal of azathioprine in UC patients depicted one-year relapse rates of 59% after azathioprine withdrawal *vs* 36% with sustained therapy, particularly notable in patients experiencing short-term remission (less than 6 months)[43].

A multicentre observational Italian retrospective study concluded that discontinuation of azathioprine while UC is in remission is associated with a high rate of relapse. In a study with 127 patients who were followed for a median of 55 months or until relapse after drug withdrawal, one-third of the patients relapsed within 12 months, half within 2 years, and two-thirds within 5 years[44]. The BERENICE study yielded interesting results, providing insight into the risks after stopping medications[45]. In the above-noted study, the authors developed a model-based risk-benefit analysis of withdrawing thiopurines in CD patients in prolonged remission. For patients without extensive colitis, continuing thiopurines marginally increased life expectancy for 35-year-old men and women, but decreased life expectancy for 65-

year-old men and women. According to the study findings, the withdrawal strategy became the preferred approach at approximately 40 years for men and approximately 45 years for women without extensive colitis. In patients with extensive colitis, the continuation strategy was favored regardless of age[45].

In a previously mentioned systematic review, Torres *et al*[40] clearly highlighted high rates of relapse in patients with CD or UC after stopping immunomodulator monotherapy. Roughly 75% of patients experienced relapse within 5 years after discontinuing therapy. However, in the case of combination therapy (immunomodulator + anti-TNF therapy) in patients with CD, discontinuing the immunomodulator do not affect the relapse rate compared to those who continued the drug. Analysis of multiple studies showed that 55%-60% experienced disease relapse 24 months after stopping the immunomodulator. The only study in patients with UC supported the ongoing use of immunomodulators[40]. In the same systematic review, the authors identified factors associated with a higher risk of CD relapse: Elevated CRP, increased leukocyte or neutrophil count, low hemoglobin levels, high-risk disease (perianal involvement), younger age, male gender, short duration of remission, a shorter time since the last steroids, higher dose of azathioprine, thiopurine reduction before de-escalation, and smoking cessation[40].

The factors linked to an increased risk of relapse in UC were outlined as follows: Increased leukocyte count, extensive disease (pancolonic/extensive), younger age, male sex, number of relapses with azathioprine, shorter duration of azathioprine, and longer time from diagnosis to azathioprine. From this, we can deduce that higher disease activity, poor prognostic factors, and a complex or recurring disease course are correlated with future relapse[40]. These findings underscore the necessity for an individualized approach in deciding whether to discontinue therapy, contingent upon each patient's disease course and severity.

Concerning exit strategies, the ECCO review board concluded that there is a cumulative risk of relapse over time after immunomodulatory monotherapy withdrawal in both CD and UC. It is estimated that approximately 30% of patients experience a relapse within 2 years, and between 50% to 75% relapse within 5 years[11]. The discontinuation of immunomodulator monotherapy is evidently associated with an increased risk of relapse. In a systematic review and meta-analysis encompassing ten randomized controlled trials with 587 included patients, Dohos *et al*[46] concluded that continued immunomodulator monotherapy should remain the preferred approach among patients with CD, despite concerns about long-term toxicity. However, the withdrawal of immunomodulator monotherapy did not exhibit a significantly higher risk of relapse within 24 months of follow-up in UC (RR = 1.39, 95%CI: 0.85-2.26, respectively). Moreover, discontinuing an immunomodulator in combination with biologics did not demonstrate a higher risk of relapse compared to continuing both drugs (RR = 1.30, 95%CI: 0.81-2.08)[46].

As previously mentioned, the removal of the immunomodulator from a combination with anti-TNF treatment do not yield a significantly higher relapse rate. In the study conducted by van Assche *et al*[47], continuing combination therapy showed no evident clinical benefit. Nonetheless, concurrent therapy involving any immunomodulators affects the pharmacokinetics of antibodies against infliximab and adalimumab[48,49]. Moreover, a comprehensive meta-analysis indicated that combination therapy correlates with reduced immunogenicity[50]. The potential withdrawal of immunomodulators from the combination regimen might lead to a heightened risk of antidrug antibody formation, although its impact on clinical outcomes might take more than a year to manifest[46].

In short, the decision to withdraw immunomodulators in IBD treatment is complex, as studies show varying relapse rates upon discontinuation. While discontinuing immunomodulator monotherapy in both CD and UC correlates with an increased risk of relapse, the withdrawal from combination therapy with anti-TNF treatment doesn't significantly heighten relapse rates. However, the removal of immunomodulators from these combined regimens could potentially impact antibody formation, affecting the long-term clinical outcomes of IBD treatment.

Biological therapy

Biological therapy has emerged as a primary treatment for moderate to severe CD and UC, aligning with established guidelines[7,8]. An extensive examination of healthcare expenditures in IBD was conducted among 1289 patients across 21 countries over a 5-year span, revealing a substantial rise in the costs attributed to biological treatments, comprising 73% in CD and 48% in UC cases[13]. While a test-based de-escalation approach demonstrated potential cost savings for CD patients in remission on optimized infliximab, it underscores the necessity for rethinking subsequent therapy management[51]. Presently, there is insufficient data supporting a clear recommendation for maintaining or stopping anti-TNF therapy upon achieving prolonged remission in IBD patients, and the absence of randomized trials complicates the decision-making process. Observational studies hint that discontinuing anti-TNF therapy might lead to a higher relapse risk compared to immunomodulators, with approximately 50% of patients experiencing relapse within two years, emphasizing the crucial role of clinical judgment in withdrawal decisions[11,51].

The STORI trial, the initial prospective study observing infliximab withdrawal after a year of remission in 115 CD patients on concurrent immunomodulatory therapy, noted relapse in 44% of patients within the first year[52]. Identified risk factors for relapse in the multivariate analysis included male gender, lack of surgical resection, elevated white blood cell count (> 6.0 × 10^9/L), lower hemoglobin (≤ 145 g/L), normal CRP levels (< 5.0 mg/L), and higher fecal calprotectin (≥ 300 μg/g)[52]. In the extended follow-up of the STORI trial, among patients maintaining remission on combined infliximab and immunomodulators, around 70% did not experience treatment failure even seven years after withdrawing infliximab. Yet, a fifth of these patients encountered significant complications over the same period[53].

In a comprehensive meta-analysis spanning 27 studies focusing on infliximab and adalimumab, Gisbert *et al*[54] found that after discontinuing anti-TNF therapy, the overall relapse risk stood at 44% for CD and 38% for UC patients. Within a year, 40% of CD and 28% of UC patients relapsed. For CD patients achieving endoscopic remission alongside clinical remission before stopping anti-TNF therapy, the relapse rate dropped notably to 26% after one year. Importantly, the study highlighted a positive response to retreatment using the same anti-TNF medication. Factors associated with a higher risk of relapse encompassed younger age, smoking habits, longer disease duration, perianal CD fistulization, and

specific laboratory markers such as low hemoglobin, elevated CRP levels, and high fecal calprotectin. Conversely, lower serum anti-TNF levels and mucosal healing appeared linked to a decreased risk of relapse following anti-TNF discontinuation[54].

When deciding to discontinue therapy, the question arises regarding the success of reintroducing therapy in case of disease relapse. The multicentre retrospective EVODIS study, which enrolled 1055 patients with CD and UC, with a median follow-up of 34 months, assessed the risk of long-term relapse after the discontinuation of anti-TNF[55]. The results showed that the cumulative incidence of relapse was 50%: 19% in year one and 48% in 5 years of follow-up[55]. However, of the 60% of patients who had been retreated with the same anti-TNF after relapse, 73% regained remission [55]. The introduction of vedolizumab further improved the effectiveness of the treatment of IBD. However, there is a lack of data in the literature on relapse after drug withdrawal. In one retrospective observational study, from 21 tertiary centers, Martin *et al*[56] assessed the risk of relapse after the vedolizumab therapy was discontinued. The results showed that two-thirds of the patients had relapse within the first year after discontinuation of vedolizumab[56]. Retreatment with vedolizumab was effective in two-thirds of patients. However, many of them were treated with anti-TNF before the first treatment with vedolizumab was introduced[56].

Information regarding the withdrawal of anti-IL12/23 antibody, specifically ustekinumab, is scarce primarily because it was predominantly utilized as secondary or tertiary treatment post previous therapy failures[57].

The OCTAVE Open investigation assessed tofacitinib retreatment effectiveness and safety in UC patients who previously experienced treatment failure after 8 wk[58]. Results showed that after discontinuation, the median treatment failure time was 169 d for induction remitters and 123 d for responders who did not achieve remission. Reintroducing 10 mg bid tofacitinib proved effective and safe, with clinical response rates in year 3 reaching 60.6% for induction remitters and 42.4% for induction responders who did not achieve remission[58].

According to the ECCO conclusion on exit strategy, individuals achieving clinical, biological, and endoscopic remission likely face reduced relapse risks upon stopping anti-TNF therapy, making them potential candidates for withdrawal[11]. However, patients with a previous need for anti-TNF dose increase seem to be at high risk of relapse after discontinuation [11]. On the other hand, continuing immunomodulator treatment post anti-TNF discontinuation seems to lower the relapse risk[11].

Monitoring after withdrawal from therapy and predictive factors of relapse

The ECCO topical review on exit strategies suggests close monitoring during the initial year post-withdrawal, as the majority of relapses, particularly with anti-TNF agents, tend to happen within 6 to 12 months after cessation[11]. In clinical practice, a fundamental concern revolves around post-withdrawal patient monitoring and, notably, identifying relapse risks. Consequently, monitoring approaches utilizing non-invasive markers have been suggested.

In a recent prospective study monitoring patients after withdrawing from immunomodulator monotherapy, fecal calprotectin emerged as the most sensitive biomarker for relapse compared to CRP and white blood cell count[59]. Other research also supports the pivotal role of fecal calprotectin, indicating its rise preceding clinical or endoscopic relapse[60]. This suggests the possibility of its use as a predictive marker for identifying patients requiring close follow-up[60]. This suggests its potential as a predictive marker for identifying patients needing closer monitoring[60]. Another prospective study by Molander *et al*[60] tracking patients after anti-TNF withdrawal found significant correlations between fecal calprotectin and later relapse in UC (RR: 3.3; 95%CI: 1.2-10) and CD patients (hazard ratio: 4.5; 95%CI: 1.4-12.5)[60]. However, maintaining normal levels during follow-up proved highly predictive of clinical and endoscopic remission[60].

In a study by Buisson *et al*[61], the predictive value of fecal calprotectin in assessing relapse risk after therapeutic de-escalation was confirmed. Using a receiver operating characteristic curve, the authors determined that a fecal calprotectin level > 100 μg/g was the optimal threshold for predicting clinical relapse after de-escalation (area under the curve = 0.84) [61]. Some authors proposed predictive models for relapse as clinical practice recommendations. In a meta-analysis involving 14 studies and 1317 patients, Pauwels *et al*[62] proposed a predictive model for CD relapse post-cessation of anti-TNF therapy. Several factors were identified as predictive of relapse strength: Clinical symptoms (*e.g.*, CD activity index of 150 or higher, Harvey Bradshaw index of 5 or higher, Physicians' Global Assessment above 0), younger age (< 40 years), longer disease duration (> 40 years), smoking, age at diagnosis of 16 years, steroid use 6-12 months before cessation, absence of immunosuppressant use, age between 40-60 years, and disease duration of 30-40 years[61]. Figure 1 illustrates the most commonly recognized factors associated with risk of relapse.

After discontinuation of therapy, relapse can be expected in a large portion of patients within 6 to 12 months[11]. For this reason, strict monitoring of clinical and non-invasive parameters is recommended, especially within the first year [57]. The non-invasive parameters primarily include fecal calprotectin and CRP[11]. In case of withdrawal of the anti-TNF therapy, elevated CRP and fecal calprotectin level was observed even several months before the clinical relapse[57]. If elevated values are confirmed by retesting, for further research, in the form of endoscopic revaluation is requested.

Current knowledge from clinical practice dictates the need for endoscopic and/or radiological assessment in case of CRP and fecal calprotectin elevation during follow-up after drug withdrawal. Further studies are needed in order to establish the optimal monitoring interval of non-invasive markers and treatment algorithms during follow up, as well as the time of endoscopic re-evaluation. Timing of endoscopic re-evaluation in the situation of sustained clinical remission after withdrawal should also be clarified.

Future directions

It remains important to distinguish and select patients with the lowest risk of relapse after discontinuation or de-escalation of therapy. For this purpose, it would be valuable to design scoring systems to predict the possibility of relapse using various clinical, endoscopic, and laboratory parameters. As previously mentioned, the role of fecal calprotectin has been indisputably proven in this matter[59-61]. Future research is expected to focus on identifying the best non-invasive

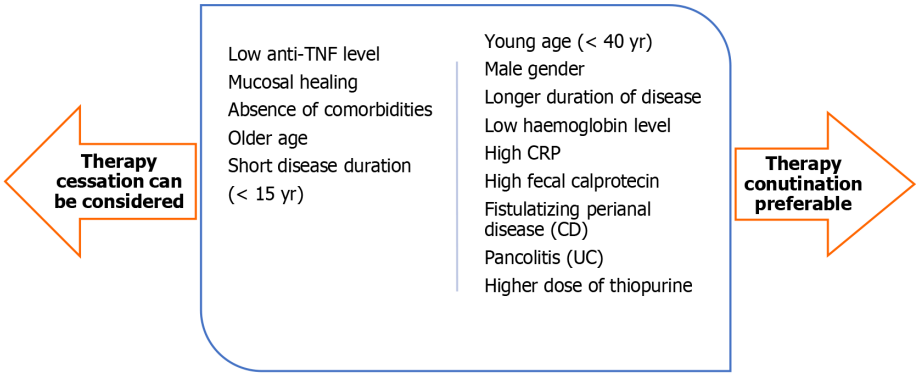

Figure 1 Possible predictive factors of disease relapse after withdrawal of therapy in inflammatory bowel disease patients. CD: Crohn's disease; CRP: C-reactive protein; TNF: Tumor necrosis factor; UC: Ulcerative colitis.

markers for assessing disease severity and predicting relapse after drug withdrawal[63]. There is considerable anticipation regarding the role of intestinal ultrasound as a convenient imaging method. Until now, intestinal ultrasound has been established as a cross-sectional imaging tool, accurate in assessing IBD activity in real time[64]. It not only positively impacts patient compliance but also aids in quick clinical decision-making[64]. It is worth highlighting the possibility of machine learning models that could be used for designing suitable algorithms for assessing the severity of the disease and the possibility of relapse. This is consistent with the increasingly present idea of using artificial intelligence in the field of IBD[65,66]. Additionally, the optimal and timely monitoring of patients after stopping IBD therapy is an important consideration. Current knowledge favors periodic fecal calprotectin checks every three months [59]. Larger randomized clinical studies are necessary to evaluate the possibility of relapse and the safety of drug withdrawal in both monotherapy and combination therapy models. Likewise, there is a lack of comprehensive studies on therapies involving anti-integrins, anti-IL12/23 drugs, and small molecules, particularly in primarily resistant cases, warranting further investigation.

CONCLUSION

According to the currently available data, patient in clinical, laboratory, and endoscopic remission, has a better chance of experiencing an extended period of remission. Since long-term immunosuppressive therapy might result in adverse events, it is reasonable to consider reducing or discontinuing treatment in some patients. In patients with a low risk of relapse, discontinuation of treatment can be recommended. While 5-ASA are recommended, mainly due to their chemoprotective effect, discontinuation of immunomodulators or biological therapy could be suggested, particularly in cases of combination treatment. Although reintroducing therapy within the same drug group can be successful, retreatment will not be effective in at least one third of patients. However, the key challenge in the clinical practice lies in identifying patients at risk of relapse. Therefore, there is a strong need to develop exit strategies tailored to individual patients.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Two-stage extraction by partial grinding of impacted mandibular third molar in close proximity to the inferior alveolar nerve

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Abstract

BACKGROUND

Extraction of impacted third molars often leads to severe complications caused by damage to the inferior alveolar nerve (IAN).

AIM

To proposes a method for the partial grinding of an impacted mandibular third molar (IMM3) near the IAN to prevent IAN injury during IMM3 extraction.

METHODS

Between January 1996 and March 2022, 25 patients with IMM3 roots near the IAN were enrolled. The first stage of the operation consisted of grinding a major part of the IMM3 crown with a high-speed turbine dental drill to achieve sufficient space between the mandibular second molar and IMM3. After 6 months, when the root tips were observed to be away from the IAN on X-ray examination, the remaining part of the IMM3 was completely removed.

RESULTS

All IMM3s were extracted easily without symptoms of IAN injury after extraction.

CONCLUSION

Partial IMM3 grinding may be a good alternative treatment option to avoid IAN injury in high-risk cases.

Key Words: Partial grinding; Impacted mandibular third molar; Inferior alveolar nerve; Cone-beam computed tomography

Core Tip: The use of cone-beam computed tomography (CBCT) may prevent damage to the inferior alveolar nerve (IAN), but not reduce the risk of injuries to IAN during impacted mandibular third molar extraction. In our clinic, although the incidence of IAN injury is very low because of adoption of CBCT, we have adopted two-stage extraction in order to avoid injury to IAN to the greatest extent. Compared with other existing methods, our method is safer and better, which is worth promoting.

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INTRODUCTION

Impacted mandibular third molar (IMM3) is frequently the most commonly impacted tooth. An impacted third molar often requires extraction. Prolonged retention of IMM3 in the oral cavity can lead to various complications, including gingivitis, infection, caries in adjacent teeth, and bone cysts. IMM3s can be retained only if they are in a favorable position and exhibit good occlusal contact with the opposing teeth[1-4].

The clinical use of cone-beam computed tomography (CBCT) allows three-dimensional examination. CBCT can be helpful in determining the positional relationship of the inferior alveolar nerve (IAN) with an IMM3 by providing coronal and axial views. However, the use of CBCT does not reduce the risk of damage to the IAN during IMM3 extraction[5-8].

Although the incidence of IAN injury is very low, sensory deficits and temporary or permanent lower lip numbness can occur if the IAN is injured[9-11]. These are severe complications of IMM3 extraction that may interfere with daily life activities, such as talking and chewing. In our clinic, we have adopted a two-stage extraction method for cases of IMM3 near the IAN to avoid IAN damage to the greatest extent.

MATERIALS AND METHODS

In all, 25 patients (15 males, 10 females) determined by panoramic X-ray examination to have an IMM3 near the IAN that needed to be removed were included. Each patient was informed about the surgical purpose, surgical protocol, recovery period, possible complications, and potential risks and signed a consent form.

Both stages of all extraction procedures were performed under local anaesthesia with 2% lidocaine (Shanghai Hefeng Pharmaceutical Co., Ltd., Shanghai, China) to anaesthetize the tongue, buccal nerve, and IAN. After flap elevation and bone removal, a major part of the IMM3 crown was ground with a high-speed turbine dental drill. The wound was rinsed with 0.9% saline solution after grinding and then sutured with 4-0 silk; the sutures were removed after 5-7 d. After 6-12 months, when the root tips were observed to be away from the IAN on X-ray examination, the remaining part of the IMM3 was removed. A total of 25 IMM3s that were in close proximity to the IAN were successfully extracted without damage to the IAN.

RESULTS

In our retrospective study of 25 cases, there were no cases of lower lip numbness after the extraction of IMM3s in close proximity to the IAN, based on postoperative chief complaints.

DISCUSSION

Direct IAN-IMM3 contact is considered a risk factor for complications and postoperative sensory impairment following surgical removal of the IMM3 and causes great concern among dentists. However, there have also been studies showing that there is no association between IAN injury and direct IAN-IMM3 contact, whereas there is an association with cortication status. To avoid injuring the IAN, dentists have attempted many methods, such as IMM3 extraction after orthodontic treatment to separate the IAN and IMM3[10,12-17].

For temporary lower lip numbness after IAN exposure, the neurotrophic drug mecobalamin can be administered; moreover, according to our clinical experience, the neurosensory deficits and symptoms of IAN injury can gradually resolve after a certain period. Some surgical interventions can also be used to relieve symptoms of IAN injury[18-20]. However, at present, there is no effective treatment for permanent damage to the IAN.

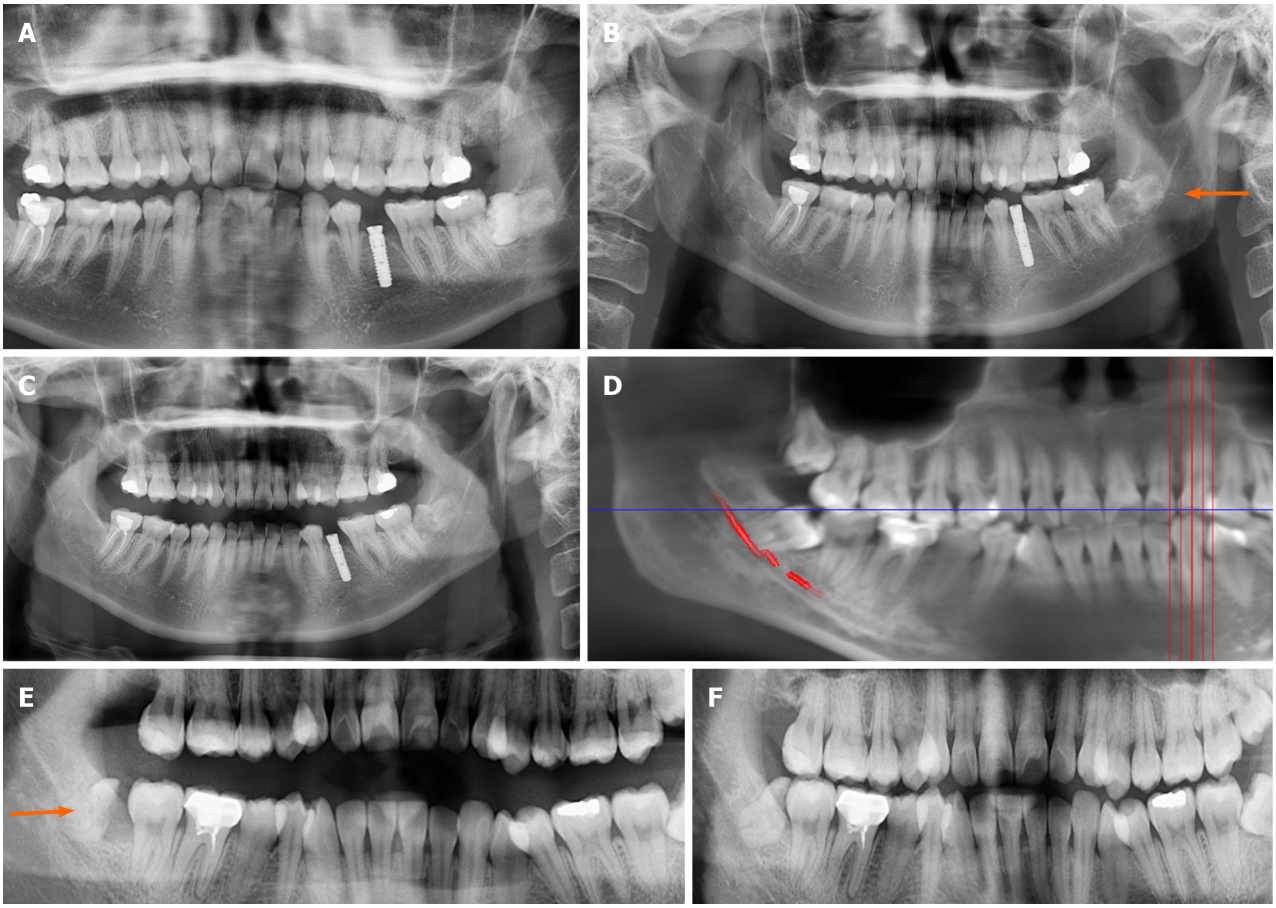

Figure 1 Panoramic views showing changes in relationship between the inferior alveolar nerve and impacted mandibular third molar root position by partial grinding in two cases (arrow indicates the mandibular canal). A: Preoperative panoramic radiograph of Case 1 depicting direct contact between the inferior alveolar nerve (IAN) and the impacted mandibular third molar (IMM3); B: Post-partial grinding panoramic radiograph of Case 1, demonstrating sufficient eruption space between the impacted tooth and adjacent teeth; C: Six-month post-partial grinding view illustrating space between the root of the IMM3 and the superior wall of the IAN canal in Case 1; D: Preoperative panoramic radiograph of Case 2 revealing the IMM3 passing through the IAN; E: Post-partial removal of IMM3 (Phase 1) panoramic radiograph of Case 2, displaying adequate eruption space between the impacted tooth and adjacent teeth; F: Panoramic view after 6 mo of partial grinding indicating that in Case 2, the root of the IMM3 had moved away from the IAN canal following 6 months of partial grinding.

We adopted a two-stage method for IMM3 extraction. The first stage of the operation consists of grinding a major part of the IMM3 crown to obtain sufficient space for mesial movement of the IMM3. After 6-12 months, when there is distance between the root tips of the remaining part of the IMM3 and the IAN, IMM3 can be completely extracted (Figure 1).

CBCT is expensive and only used in larger dental institutions, and can only clarify the three-dimensional relationship between IMM3 and the IAN. However, if IMM3-IAN is close or IMM3 passes through IAN, routine removal of IMM3 cannot avoid postoperative complications. This approach avoids damage to the IAN. We believe that this method is worth popularizing, especially in grassroots hospitals, which may only have the capability for dental radiography and not CBCT.

CONCLUSION

Partial IMM3 grinding may be a good alternative treatment option to avoid IAN injury in high-risk cases.

ARTICLE HIGHLIGHTS

Research background

The conventional method of extracting impacted mandibular third molars (IMM3) that are closely related to the inferior alveolar nerve (IAN) can easily damage the nerve.

Research motivation
To avoid damaging the IAN during tooth extraction.

Research objectives
To proposes a method for the partial grinding of an IMM3 near the IAN to prevent IAN injury during IMM3 extraction.

Research methods
The first stage was to use a high-speed turbo drill to grind and cut most of the IMM3 dental crowns, leaving the roots in place. After 6-12 months, when the IMM3 root left the nerve canal, complete extraction of the IMM3 root was performed.

Research results
Although it seemed to take longer after two stages, all IMM3s were completely removed, and there were no cases of complications of damaging the IAN.

Research conclusions
Two-stage extraction of IMM3 located closer to the IAN canal can minimize nerve damage to the greatest extent possible.

Research perspectives
Partial IMM3 grinding may be a good alternative treatment option to avoid IAN injury in high-risk cases.

FOOTNOTES

Author contributions: Luo GM performed the experiment, contributed significantly to manuscript preparation, performed the data analyses, and wrote the manuscript; Yao ZS, Huang WX, Zou LY, and Yang Y contributed to the conception of the study and helped perform the analysis with constructive discussions.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Kunming Medical University School and Hospital of Stomatology.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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Clinical efficacy of femtosecond laser-assisted phacoemulsification in diabetic cataract patients

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Abstract

BACKGROUND

Diabetic patients with cataracts encounter specific difficulties during cataract surgery due to alterations in microcirculation, blood supply, metabolism, and the microenvironment. Traditional phacoemulsification may not fully tackle these issues, especially in instances with substantial preoperative astigmatism. The utilization of femtosecond laser-assisted phacoemulsification, in conjunction with Toric intraocular lens (IOL) implantation, offers a potentially more efficient strategy. This research seeks to evaluate the efficacy and possible complications of this approach in diabetic cataract patients.

AIM

To investigate the clinical efficacy and complications of femtosecond laser-assisted phacoemulsification combined with Toric IOL implantation in diabetic cataract patients, comparing it with traditional phacoemulsification methods.

METHODS

This retrospective study enrolled 120 patients with diabetes cataract from May 2019 to May 2021. The patients were divided into two groups: the control group underwent traditional phacoemulsification and Toric IOL implantation, while the treatment group received Len Sx femtosecond laser-assisted treatment. Outcome measures included naked eye vision, astigmatism, high-level ocular phase difference detection, clinical efficacy, and complication.

RESULTS

There were no significant preoperative differences in astigmatism or naked eyesight between the two groups. However, postoperative improvements were observed in both groups, with the treatment group showing greater enhancements in naked eye vision and astigmatism six months after the procedure. High-level corneal phase difference tests also indicated significant differences in favor of the treatment group.

CONCLUSION
This study suggests that femtosecond laser-assisted phacoemulsification combined with Toric IOL implantation appears to be more effective in enhancing postoperative vision in diabetic cataract patients compared to traditional methods offering valuable insights for clinical practice.

Key Words: Diabetic cataract; Femtosecond laser-assisted phacoemulsification; Toric intraocular lens implantation; Naked vision

Core Tip: Retrospective studies have shown that femtosecond laser-assisted phacoemulsification produces favorable clinical results in the management of cataracts related to diabetes. This method significantly improves vision after surgery and provides important information for the clinical treatment of cataracts.

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INTRODUCTION

The microcirculation, blood supply, metabolism and microenvironment in diabetic patients differ from those in normal individuals, resulting in abnormal blood supply and terminal circulation. This leads to lens epithelial cell disorder, lens fiber cell opacity, and cataract development[1,2]. Cataract, affecting the eye lens, can be influenced by factors such as trauma, aging, immune dysfunction, poisoning, metabolic abnormalities, nutritional disorders, radiation, and genetics[3]. It is characterized by the opacity due to lens protein degeneration and metabolic dysfunction. Age-related cataract specifically refers to cataracts that develop as individuals age, with progressive vision impairment as the main clinical manifestation[4].

Cataract surgery has now advanced into the realm of refractive surgery. In many countries, approximately 23.0% to 47.0% of cataract patients have preoperative astigmatism greater than 1.0 diopter (D)[5]. In China, this percentage is 25.4% for cataract patients with preoperative astigmatism greater than 1.5D. When astigmatism exceeds 0.75D, it can lead to symptoms such as blurred vision, double images, halos, glare, and others[6]. Currently, the Toric intraocular lens (IOL) is being used to correct cataract and corneal astigmatism. However, he design of this lens, which accounts for astigmatism, significantly affects the visual quality of postoperative patients, including factors like centering, rotational stability and final axis position in the eye after implantation[7]. Cataract patients with an axial length greater than 24 mm often have an excessively large lens capsule due to the elongated axial length, which makes ordinary IOL implantation prone to lens deflection and rotation[8]. There are limited clinical reports on the impact of Toric IOL implantation in patients with long axial lengths and high corneal astigmatism. The use of femtosecond laser technology in cataract surgery has gained attention among clinical ophthalmologists with this in mind, our hospital conducted a study to explore the clinical effectiveness and complications of femtosecond laser-assisted phacoemulsification combined with Toric IOL implantation in patients with diabetic cataract. The current research findings are reported as follows.

MATERIALS AND METHODS

General information

In this study, we selected 120 patients with diabetic cataract who underwent surgery at our hospital from May 2019 to May 2021 as the retrospective research subjects. All of the patients had monocular cataracts. They were divided into a control group and a treatment group of 60 patients each using the random residue grouping method. Prior to the start of the study, the patients and their families were informed about the study and signed an informed consent form, adhering to principles of voluntariness, confidentiality, benefit, and harmlessness. The study also received approval from the medical ethics committee of our hospital. The general data, such as gender and age, of the two patient groups did not have any impact on the test results, as shown in Table 1.

Inclusion and exclusion criteria

The inclusion criteria for this study were as follows: (1) All patients met the "diabetic macular edema management in Asian population: Expert panel consensus guidelines" for the diagnosis of diabetic cataract, and had a clear history of type 2 diabetes, combined with cataracts, and required surgical treatment[9]; (2) The study included patients with progressive decline in vision, blurred vision, or even light perception, but no symptoms such as eye pain, photophobia,

Table 1 Comparison of general information between the two groups (*n*, mean ± SD)

Group	Control group (*n* = 60)	Therapy group (*n* = 60)	χ^2/*t*/*z*	*P* value
Gender (men and women)	28/32	27/33	0.034	0.855
Average age (yr)	79.78 ± 4.32	80.62 ± 2.66	-1.171	0.245
Eye axis (mm)	23.2 (20.1-26.7)	22.9 (21.2-25.6)	0.019	0.992
Intraocular pressure (mmHg)	14.78 ± 3.32	13.62 ± 3.66	1.660	0.100

and tearing. The axial length of the eye ranged from 24 mm to 30 mm; and (3) The affected eye had a dilated pupil with a diameter of at least 6mm, and regular corneal astigmatism of 0.75D and above. The exclusion criteria were as follows: (1) Patients with corneal disease, nuclear hardness above grade 4, glaucoma, eyelid adhesion, small eyelid fissure, nystagmus, lens dislocation, those who had undergone corneal or internal eye surgery, and those who could not cooperate; (2) Patients with severe systemic diseases, those who could not tolerate surgery, patients with mental illness, and other patients who could not cooperate with surgery; and (3) Patients who could not undergo surgery, those with neurological or infectious diseases, and those with disorders of consciousness.

Method

The treatment group utilized the Len-Sx femtosecond laser for adjuvant treatment. During the procedure, the patient is seated and the corneal parameters are positioned at 0 and 180° under the slit lamp. The axial direction for Toric IOL implantation is determined by the corneal locator mark and the axial direction obtained from the toric calculator (www.acrysoft-calculator.com). The femtosecond group of patients undergoes several steps with the femtosecond laser system (United States Alcon's LenSx femtosecond laser system), including capsulorhexis, nucleus splitting and incision making. The size of the anterior capsular opening is set to 5.2 mm. The main incision position is consistent with the position set in the preoperative Toric calculation program, with a width of 2.4 mm. Phacoemulsification is performed using the American Alcon Centurion cataract intelligent phacoemulsification instrument. Toric IOL is then implanted, and the viscoelastic agent is removed after the lens is completely extracted. The IOL axis is adjusted to the predetermined angle of the mark, and the center of the IOL is gently pressed to ensure attachment to the capsular bag and water tightness (Figure 1).

The control group underwent phacoemulsification combined with Toric IOL implantation. Conventional disinfection drapes were used, and a 5% povidone-iodine stock solution was used to rinse the second conjunctival sac after the upper eyelid opener. The main side of the cornea incision, capsulorhexis, and water separation along the mark were performed. The Centurion phacoemulsification instrument was used, and the phacoemulsification nucleus chopping method was employed for nuclear processing and lens nucleus, aspiration. Cortex aspiration was done using IA. Toric IOL was implanted, and the back of the IOL was first aspirated with Viscoelastic agent. The axis of the IOL was adjusted to align with the marking line, and imbibition cortex was applied to the IOL. The viscoelastic agent in front of the IOL was then sucked out, and the mouth was closed with appropriate water. The third conjunctival sac was flushed with a 5% povidone-iodine stock solution, and tobramycin and dexamethasone ophthalmic ointment was applied to the conjunctival sac. The eye was bandaged, and the operation was completed.

Follow-up and observation indicators

Logarithm of the minimum angle of resolution visual acuity was assessed using various tools including uncorrected visual acuity, intraocular pressure, IOL-Master, and Od-sCAIII visual quality analyzer. Among these, OPD-SCAN III was used to detect 5 indicators related to the corneal area: the sum of all the advanced phase differences of 0-8 orders (TOTAL), IOL tilt prism (tilt), the sum of all the advanced phase differences of 3-8 orders (high), high-order coma (S3 + S5 + S7), and high-order spherical aberration (S4 + S6 + S8). The online calculation program (www.acrysoftoriccalculator. com) can be used to calculate the prism power and positioning axis of Toric IOLs. The surgical induced astigmatism entered into the computer program is calculated based on the postoperative data collected from the surgeon before the operation, with an input of 0.3D. Follow-up with the patients will be conducted for 6 months after the surgery.

Statistical methods

All statistical data in this study were entered into the excel software by the first author and the corresponding author, respectively. The included data was tested using the Shapiro Wilk method to determine if it conformed to a normal distribution. Measurement data that conformed to the normal distribution were described using the mean ± SD. Between-groups comparisons were performed using independent sample or paired sample *t*-tests. Count data were described using integers or percentages (%), and χ^2 tests were used for comparisons between or within groups. Data that did not conform to the normal distribution were described using M (QR) and analyzed using the Mann-Whitney test with a significance level of $\alpha = 0.05$.

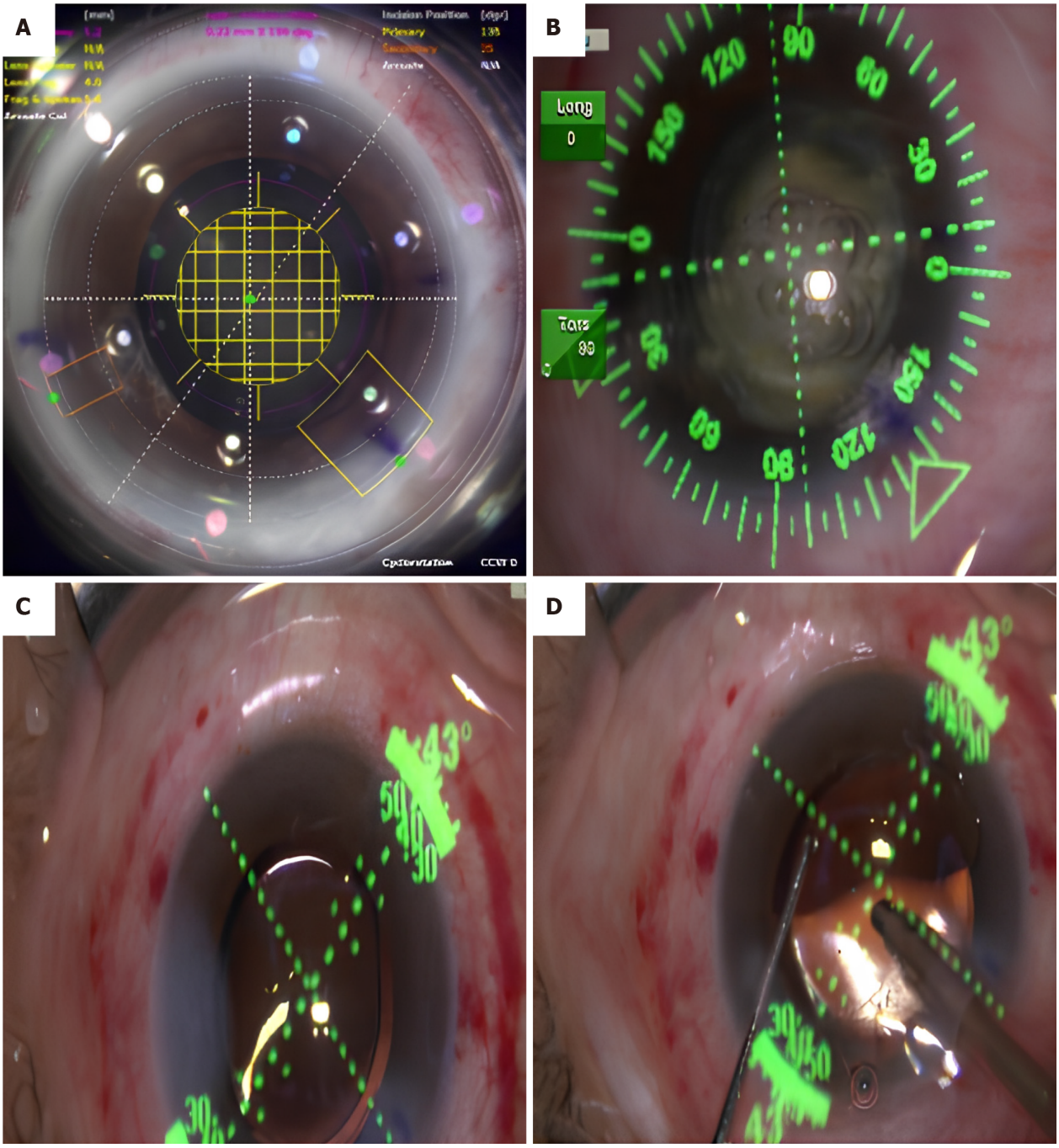

Figure 1 Determination of the navigation implant location of Toric intraocular lens. A: Axial and main incision position; B: The intraoperative navigation system verion system was used to calibrate the position and axis of the main incision before superlactation, and to observe whether the position of manual slit lamp marking was consistent with that before operation; C: Watertight incision and final determination of crystal position and axial accuracy; D: Complete removal of viscous elastic agent before and after crystal removal and accurate alignment of axial direction.

RESULTS

Comparison of general information

In the 60 therapy group, the mean age was 80.62 ± 2.66 years with 81.82% of the participants being male. The eye axis (mm) was measured at 22.9 (21.2 to 25.6) and the intraocular pressure (mmHg) was 13.62 ± 3.66. In the control group of 60 participants, the mean age was 79.78 ± 4.32 years with 87.5% of the participants being male. The eye axis (mm) was measured at 23.2 (20.1-26.7) and the intraocular pressure (mmHg) was 14.78 ± 3.32. There were no significant differences in gender, age, eye axis, and intraocular pressure between the two groups ($P > 0.05$) (Table 1).

Comparison of naked eye vision

Before surgery, the control group had a measured naked eye visual acuity of 1.15 ± 0.10, while the treatment group had a visual acuity of 1.16 ± 0.12. There was no statistical significance between the two groups ($P > 0.05$). However, one day

after surgery, the naked eye visual acuity of the control group decreased to 0.28 ± 0.02, whereas the treatment group had a visual acuity of 0.46 ± 0.04. The difference between the two groups was significant ($P < 0.05$). After one month of treatment, the naked eye visual acuity of the control group improved to 0.35 ± 0.02, and the treatment group had a visual acuity of 0.61 ± 0.11. Once again, the difference between the two groups was significant ($P < 0.05$). At the six-month mark after surgery, the naked eye visual acuity of the control group was 0.48 ± 0.12, while the treatment group had a visual acuity of 0.65 ± 0.10. Once more, the difference between the two groups was significant ($P < 0.05$). These results indicate a gradual improvement in naked eye visual acuity for both groups after surgery (Table 2).

Comparison of astigmatism

Before surgery, the naked eye astigmatism of the two groups was measured. In the control group, it was 2.62 ± 0.36, while in the treatment group, it was 2.56 ± 0.54. There was no statistically significant difference between the two groups ($P > 0.05$). One day after surgery, the naked eye astigmatism was 0.28 ± 0.02 in the control group and 2.40 ± 0.32 in the treatment group. The difference between the groups was not statistically significant ($P > 0.05$). After one month of treatment, the naked eye astigmatism measured 2.43 ± 0.63 in the control group and 2.33 ± 0.64 in the treatment group, with no statistically difference ($P > 0.05$). Half a year after surgery, the naked eye astigmatism was measured. It was 2.14 ± 0.23 in the control group and 1.18 ± 0.24 in the treatment group. The difference between the groups was found to be significant ($P < 0.05$). These results indicate an improvement in naked eye astigmatism in both groups six months after the operation (Table 3).

High-level phase difference detection of the cornea

The initial total value of naked eyes in the control group and was 2.52 ± 0.63 and in the treatment group was 2.08 ± 0.32. There was a significant difference observed between the two groups ($P < 0.05$). The tilt values of naked eyes were 0.62 ± 0.16 in the control group and 0.94 ± 0.10 in the treatment group, showing a significant difference ($P < 0.05$). Similarly, the naked eye high values were 0.46 ± 0.10 in the control group and 0.60 ± 0.12 in the treatment group, with a significant difference ($P < 0.05$). The combined values of S3 + S5 + S7 in the naked eye were 0.31 ± 0.06 in the control group and 0.53 ± 0.08 in the treatment group, with a significant difference ($P < 0.05$). Similarly, the combined values of S4 + S6 + S8 in the naked eye were 0.24 ± 0.03 in the control group and 0.35 ± 0.11 in the treatment group, with a significant difference ($P < 0.05$) (Table 4).

DISCUSSION

The corneal epithelium and endothelium of diabetic patients are easily damaged and have a slow recovery rate. Additionally, due to abnormal metabolism of microvascular and peripheral nerves, diabetic cataract surgery is more prone to complications such as miosis, iris hemorrhage, and corneal incision edema[10,11]. Diabetic cataract patients are also more sensitive to surgical stimulation. IOL implantation, which is a common method for treating cataracts with corneal astigmatism, has been widely used in refractive cataract surgery. Diabetes, being a metabolic disease that affects the entire body, impairs microvascular function and damages body tissues[12]. Traditional phacoemulsification , with its excessive release of ultrasound energy, can be particularly irritating to the eyes of diabetic patients[13]. However, with the continuous development of society and technology, femtosecond laser technology has gained popularity in eye surgery, especially in cataract surgery[14]. The femtosecond laser, operating in a pulsed form using near-infrared light, offers precise targeting and positioning accuracy, making it more accurate than conventional surgery. This technology is now being used in clinical practice[6]. During femtosecond laser surgery, a single pulse of light creates micro-plasma bubbles, which contain CO_2 and H_2O, These bubbles gradually approach and fuse with each other, resulting in a gradual decrease in tissue adhesion between the bubbles[15].

To achieve the purpose of precise tissue separation, femtosecond laser-assisted surgery can be employed. This technique reduces intraoperative ultrasound energy, lowers the risk of postoperative corneal edema, and promotes early recovery of corneal transparency and refractive stability[16]. However, miosis, which is the constriction of the pupil, is a common complication of femtosecond laser anterior lens capsulotomy. To prevent this, preoperative administration non-steroidal anti-inflammatory drugs can be used to reduce the energy and the number of negative pressure suctions during laser operations[17].

Our study demonstrated a significant improvement in both astigmatism of the ametropia and naked eye vision after six months of surgery. The mean astigmatism was 1.18 ± 0.24. Similar results were reported by Rückl *et al*[18], who observed a significant reduction in dioptometric astigmatism after femtosecond laser-assisted arcuate keratotomy (FSAK) procedure involves a pair of curved incisions with an arc diameter of 7.5 mm within the corneal stroma. Another study by Day *et al*[19] investigated intra-corneal FSAK in 196 eyes and found a 39% decrease in corneal astigmatism from 1.21D before surgery to 0.74D after surgery. Furthermore, our study revealed a gradual and statistically significant improvement in astigmatism and naked eye vision six months after operation. The comparison of various corneal phase difference tests between the two groups of patients, including TOTAL, tilt, high, S3 + S5 + S7, and S4 + S6 + S8, also showed significant differences and statistical significance. The comparative study of diabetic cataract shows that femtosecond laser-assisted phacoemulsification has a better clinical effect, effectively improving postoperative vision in patients. Toric IOL can also be used in patients with traumatic cataract and binocular cataract. There is no statistical difference between photopic, photopic glare, scotopic vision, and scotopic glare when compared to ordinary IOLes. The use of toric IOL does not increase discomfort in cataract patients and does not affect proper vision. The results of this study demonstrate that the toric IOL is relatively stable, with only a slight position shift. The shift angle of more than 90%

Table 2 Comparison of naked eye vision between the two groups (mean ± SD)

Group	Control group (60)	Therapy group (60)	*t*	*P* value
Before surgery	1.15 ± 0.10	1.16 ± 0.12	-0.453	0.652
1 d after surgery	0.28 ± 0.02	0.46 ± 0.04	-28.460	0.000
1 month after surgery	0.35 ± 0.02	0.61 ± 0.11	-16.444	0.000
6 months after surge	0.48 ± 0.12	0.65 ± 0.10	-7.696	0.000

Table 3 Comparison of astigmatism between the two groups (mean ± SD)

Group	Before surgery	Therapy group (60)	*t*	*P* value
Before surgery	2.62 ± 0.36	2.64 ± 0.30	0.302	0.763
1 d after surgery	2.56 ± 0.54	2.40 ± 0.32	1.802	0.075
1 month after surgery	2.43 ± 0.63	2.33 ± 0.64	0.787	0.433
6 months after surgery	2.14 ± 0.23	1.18 ± 0.24	20.421	0.000

Table 4 Comparison of high-order phase difference detection of cornea between two groups of patients (mean ± SD)

Group	Control group (60)	Therapy group (60)	*t*	*P* value
TOTAL (μm)	2.52 ± 0.63	2.08 ± 0.32	4.403	0.000
Tilt (μm)	0.62 ± 0.16	0.94 ± 0.10	-11.993	0.000
High (μm)	0.46 ± 0.10	0.60 ± 0.12	-6.338	0.000
S3 + S5 + S7 (μm)	0.31 ± 0.06	0.53 ± 0.08	-15.556	0.000
S4 + S6 + S8 (μm)	0.24 ± 0.03	0.35 ± 0.11	-6.822	0.000

of patients is less than 10°, which has minimal impact on postoperative vision. The corneal phase difference test reveals significant differences in TOTAL, tilt, high, S3 + S5 + S7, S4 + S6 + S8, and other high-order corneal phase difference tests between the two patient groups. This may be attributed to the negative pressure generated during femtosecond laser operation, such as the making of suction ring or incision, which increases corneal high-order coma. However, further confirmation of this finding requires larger clinical datasets[20]. After cataract surgery, the intraocular high-order phase difference of the IOL in the affected eye is mostly produced by the IOL in addition to the influence of the retina of the affected eye. The displacement and deflection of the lens will cause the phase difference to change[15].

Macular cystoid edema (CME) is a frequently observed condition following femtosecond laser-assisted surgery, particularly in patients with diabetes[21]. This condition is known to have a negative impact on vision, especially during the 7-60 d follow-up period[22,23]. Even minimal and non-central preoperative CME in patients with diabetes can worsen after cataract surgery[24]. Therefore, based on the current findings, it can be concluded that femtosecond laser-assisted cataract surgery may lead to a significant decline in short-term vision when compared to conventional phacoemulsification surgery.

CONCLUSION

Although this study is somewhat innovative, it also has its limitations. The clinical impact of Len Sx femtosecond laser as an adjuvant treatment for diabetic cataract is notably significant, but its specific mechanism has not been thoroughly investigated. The cases collected for this study were solely from one hospital, which may not adequately represent the general population. The criteria for participant selection were subjective, potentially leading to biased outcomes. In conclusion, the comparative study on diabetic cataracts using femtosecond laser-assisted phacoemulsification demonstrates improved clinical outcomes and postoperative vision for patients, providing valuable insights for the clinical treatment of diabetic cataracts.

ARTICLE HIGHLIGHTS

Research background

Diabetic cataract is a common complication among diabetic patients, characterized by altered ocular physiology. Traditional cataract surgery methods have limitations in addressing the unique challenges posed by the diabetic eye. The integration of femtosecond laser-assisted phacoemulsification with Toric intraocular lens (IOL) implantation presents a novel approach in the treatment of diabetic cataracts.

Research motivation

This study was motivated by the need to improve surgical outcomes in diabetic cataract patients. The specific focus was on evaluating whether the advanced technique of femtosecond laser-assisted phacoemulsification combined with Toric IOL implantation could offer better results compared to traditional methods, particularly in terms of postoperative vision and complication rates.

Research objectives

The primary objective was to assess the clinical efficacy and potential complications of femtosecond laser-assisted phacoemulsification combined with Toric IOL implantation in diabetic cataract patients. The study aimed to compare this method with traditional phacoemulsification techniques.

Research methods

A retrospective study design was employed, involving 120 diabetic cataract patients from May 2019 to May 2021. They were randomly divided into a control group (traditional phacoemulsification with Toric IOL) and a treatment group (Len Sx femtosecond laser-assisted surgery). Key metrics for evaluation included naked eye vision, astigmatism levels, high-level ocular phase difference detection, clinical efficacy, and analysis of complications.

Research results

The study found no significant preoperative differences between the two groups in terms of astigmatism and naked eye vision. However, postoperatively, the treatment group showed more significant improvements in both naked eye vision and astigmatism at the six-month follow-up. High-level corneal phase difference tests also indicated better outcomes for the treatment group.

Research conclusions

Femtosecond laser-assisted phacoemulsification combined with Toric IOL implantation is more effective in improving postoperative visual outcomes in diabetic cataract patients than traditional phacoemulsification. This method could represent a significant advancement in the surgical treatment of diabetic cataracts.

Research perspectives

This study opens up new perspectives for the treatment of diabetic cataracts. Future research should focus on further refining femtosecond laser-assisted techniques, exploring long-term outcomes, and broadening the scope to include diverse patient populations. Additionally, further studies could delve into the underlying mechanisms of improved outcomes with this method.

FOOTNOTES

Author contributions: Tang YF and Duan ZH executed this study; Tang YF wrote the manuscript and data analysis; Duan ZH reviewed the manuscript; all authors read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of the Han Yang Eyegood Ophthalmic Hospital, No. AG-BNZ-201903.

Informed consent statement: The data used in the study were not involved in the patients' privacy information, and all patient data obtained, recorded, and managed only used for this study, without any harm to the patient. So the informed consent was waived by the Ethics Committee of Han Yang Eyegood Ophthalmic Hospital.

Conflict-of-interest statement: All authors had no conflict of interest in this study.

Data sharing statement: Data should be addressed to the corresponding author, Zhi-Hui Duan, dzh8409@163.com.

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ORIGINAL ARTICLE

Retrospective Study

Impact of transcranial electrical stimulation on serum neurotrophic factors and language function in patients with speech disorders

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Abstract

BACKGROUND

Speech disorders have a substantial impact on communication abilities and quality of life. Traditional treatments such as speech and psychological therapies frequently demonstrate limited effectiveness and patient compliance. Transcranial electrical stimulation (TES) has emerged as a promising non-invasive treatment to improve neurological functions. However, its effectiveness in enhancing language functions and serum neurofactor levels in individuals with speech disorders requires further investigation.

AIM

To investigate the impact of TES in conjunction with standard therapies on serum neurotrophic factor levels and language function in patients with speech disorders.

METHODS

In a controlled study spanning from March 2019 to November 2021, 81 patients with speech disorders were divided into a control group (n = 40) receiving standard speech stimulation and psychological intervention, and an observation group (n = 41) receiving additional TES. The study assessed serum levels of ciliary neurotrophic factor (CNTF), glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF), as well as evaluations of motor function, language function, and development quotient scores.

RESULTS

After 3 wk of intervention, the observation group exhibited significantly higher serum levels of CNTF, GDNF, BDNF, and NGF compared to the control group. Moreover, improvements were noted in motor function, cognitive function, language skills, physical abilities, and overall development quotient scores. It is worth mentioning that the observation group also displayed superior perfor-

mance in language-specific tasks such as writing, reading comprehension, retelling, and fluency.

CONCLUSION
This retrospective study concluded that TES combined with traditional speech and psychotherapy can effectively increase the levels of neurokines in the blood and enhance language function in patients with speech disorders. These results provide a promising avenue for integrating TES into standard treatment methods for speech disorders.

Key Words: Transcranial electrical stimulation; Serum neurofactor levels; Developmental level; Language features

Core Tip: This study highlights the potential of transcranial electrical stimulation (TES) as a valuable additional therapy for individuals with speech disorders. Through the combination of TES with conventional speech and psychological interventions, our research shows significant enhancements in serum neurofactor levels and language functions. These results support the integration of TES into treatment plans, potentially transforming the management of speech disorders. This progress not only presents a novel approach to therapy but also emphasizes the significance of innovative, non-invasive methods in improving patient outcomes within the field of speech and language therapy.

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INTRODUCTION

The language development disorder refers to a condition where a patient's language skills lag behind those of their peers in terms of both expression and compre hension[1]. Common symptoms include difficulties in understanding language, limited vocabulary, and slow cognitive learning, all of which can have negative impacts on social communication, daily functioning, and overall development[2]. Current clinical approaches, for language rehabilitation and psychological intervention tend to be conventional and may lack patient compliance, leading to variable outcomes[3]. Transcranial electrical stimulation therapy is a non-invasive and painless method commonly used to treat nervous system disorders, with high patient compliance and acceptance among families[4-6]. The aim of our study was to investigate the effects of transcranial electrical stimulation on language function, serum neurofactor levels, and developmental progress in patients with speech disorders. The following section presents the results of our research.

MATERIALS AND METHODS

General information

Between March 2019 and November 2021, our department conducted a retrospective study involving 81 patients with language disorders. These patients were randomly assigned into two groups using a random number table method. The observation group consisted of 40 patients, comprising 22 males and 18 females, with an average age of (45.33 ± 15.55) years (range, 2-5 years). The control group included 41 cases with 25 males and 16 females, and an average age of (44.51 ± 14.73) years (range, 2-6 years). Baseline data analysis showed no significant differences between the two groups ($P > 0.05$), ensuring their comparability. The selection criteria required patients to meet specific diagnostic criteria for language disorders and for informed consent to be obtained from the patient's family[7]. Exclusion criteria encompassed severe hearing impairment, severe mental retardation, epilepsy, or other mental illnesses.

Methods

The control group underwent a comprehensive speech rehabilitation training program along with psychological intervention. The speech rehabilitation training included activities such as listening to radio, music, and watching TV to enhance the patient's text comprehension ability, providing auditory language stimulation, and giving feedback to improve reading and understanding skills. Mouth movements were guided to control various muscles, correct articulation movements, and strengthen mouth muscles through exercises like extending the tongue and whistling. Auxiliary gestures were used in daily communication to deepen understanding of phrases, enhance memory, and expand vocabulary. Patience and support were maintained throughout the training process, with active participation encouraged from the patients. Family and social networks were involved to foster understanding, care, and communication. Targeted intervention measures addressed the psychological characteristics of the patients, providing guidance for their psycho-

logical changes during 3-wk intervention.

Evaluation criteria

Serum neurofactor levels: Venous blood samples of 5 mL were collected from both groups before and after the intervention. After routine centrifugation for 10 min, the upper layer of serum was collected for the detection of ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and glial cell-derived neurotrophic factor (GDNF) along with their respective levels using enzyme-linked immunosorbent assay.

The development of patients in the two groups was evaluated using the Gesell Infant Development Scale before and after intervention. The scale assessed four functional areas: language ability, responder ability, motor ability and responder ability. Patients were classified into different developmental quotients based on their scores: < 70 as low developmental quotient, 70-85 as low developmental quotient, 86-114 as normal developmental quotient, and 115-129 as high developmental quotient. A score of 130 or above was considered as excellent development.

The language function of patients in both groups was evaluated using the Boston Diagnostic Aphasia Scale (BDAE) before and after the intervention. The evaluation included reading comprehension (38 points), fluency (35 points), retelling (26 points), and writing (68 points). A higher score indicates better language function.

Statistical tools

SPSS 26.0 software was utilized to analyze the data of 81 patients with speech disorders. The incidence of gastrointestinal tract and other counting data were represented using percentages (%), and χ^2 was used for verification. The measurement data of pulmonary function and blood routine were represented as (mean ± SD), and T was used for verification. A significance level of $P < 0.05$ was considered statistically significant.

RESULTS

Serum neurofactors

After a duration of 3 wk of intervention, the levels of NGF, BDNF, GDNF and CNTF in the observation group were found to be significantly higher compared in the control group ($P < 0.05$), as indicated in Table 1.

Before the intervention, there were no significant differences in the levels of GDNF, BDNF, CNTF, and NGF among all groups ($P = 0.6198$, $P = 0.2848$, $P = 0.9156$, $P = 0.8506$, respectively). Following the intervention, the GDNF levels in the control group and observation group were 378.65 ± 40.57 and 433.28 ± 48.71, respectively, showing a significant increase compared to pre-GDNF intervention ($^aP < 0.05$). Similarly, the BDNF levels in the control group and observation group were 23.05 ± 3.54 and 30.96 ± 4.15, respectively, demonstrating a significant increase post-intervention. The CNTF levels in the control group and observation group after intervention were 19.92 ± 3.21 and 23.17 ± 3.14, respectively, also showing a significant increase compared to pre-CNTF intervention. Furthermore, the NGF levels in the control group and observation group after intervention were 22.54 ± 3.25 and 33.48 ± 4.02, respectively, significantly higher than before the intervention ($^aP < 0.05$).

Developmental level

After a duration of 3 wk of intervention, the observation group exhibited higher scores in human ability, functional ability, motor ability, language ability and developmental quotient compared to the control group. These differences were found to be statistically significant ($P < 0.05$), as presented in Table 2.

In the study reports significant post-intervention improvements in both groups. Language ability in the control group rose from 66.78 ± 5.81 to 71.83 ± 6.22 and in the observation group from 67.01 ± 5.77 to 79.54 ± 5.69 ($P < 0.05$), with the latter showing a higher increase. Functional ability improved from 78.23 ± 5.75 to 81.34 ± 6.22 in the control group and from 78.17 ± 5.82 to 85.34 ± 6.11 in the observation group ($P < 0.05$), with the observation group surpassing the control. Human ability levels increased from 77.13 ± 6.09 to 80.54 ± 7.11 in the control group and from 76.94 ± 6.13 to 84.02 ± 6.51 in the observation group ($P < 0.05$). Motor ability also saw significant gains, from 77.25 ± 5.83 to 80.57 ± 6.94 in the control group and from 77.02 ± 5.93 to 82.96 ± 5.31 in the observation group. Finally, developmental quotient levels climbed from 58.69 ± 6.34 to 75.77 ± 7.49 in the control group and from 58.81 ± 6.27 to 85.64 ± 2.11 in the observation group ($P < 0.05$), with the observation group demonstrating a more pronounced increase.

Language functions

After a period of 3 wk of intervention, the observation group demonstrated an increasing trend in scores for writing, retelling, fluency, and reading comprehension compared to the control group. These differences were found to be statistically significant ($P < 0.05$), as presented in Table 3. The study demonstrates significant improvements in various cognitive skills post-intervention. The control group exhibited a notable increase in reading comprehension, from 17.18 ± 2.09 to 23.61 ± 2.54, and the observation group from 17.02 ± 5.93 to 29.54 ± 1.93 (both $P < 0.05$). However, no significant differences were observed between the groups in reading comprehension either pre- or post-intervention ($P > 0.05$). Retelling skills also improved significantly. In the control group, the retelling level rose from 11.48 ± 2.62 to 15.81 ± 2.04, and in the observation group from 11.61 ± 2.59 to 19.74 ± 2.05 (both $P < 0.05$). No significant difference was found between the groups pre-intervention, but post-intervention differences were significant ($P = 0$). Fluency levels too increased post-intervention, from 14.38 ± 2.42 to 20.68 ± 3.52 in the control group and from 14.27 ± 2.45 to 24.97 ± 3.77 in the observation group (both $P < 0.05$). Similar to retelling, no significant difference was observed pre-intervention, but

Table 1 Comparison of serum neurofactors between the two groups before and after intervention (mean ± SD, pg/mL)

Group		Control group (*n* = 40)	Observation group (*n* = 41)	*t*	*P* value
GDNF	Before the intervention	365.22 ± 39.84	369.71 ± 41.25	0.4981	0.6198
	After the intervention	378.65 ± 40.57[a]	433.28 ± 48.71[a]	5.4776	
BDNF	Before the intervention	21.88 ± 3.87	20.98 ± 3.65	1.077	0.2848
	After the intervention	23.05 ± 3.54[a]	30.96 ± 4.15[a]	9.2186	
CNTF	Before the intervention	18.83 ± 3.35	18.91 ± 3.42	0.1063	0.9156
	After the intervention	19.92 ± 3.21[a]	23.17 ± 3.14[a]	4.6063	
NGF	Before the intervention	19.79 ± 3.11	19.92 ± 3.08	0.189	0.8506
	After the intervention	22.54 ± 3.25[a]	33.48 ± 4.02[a]	13.4492	

[a]$P < 0.05$, comparison before and after intervention in the group.
CNTF: Ciliary neurotrophic factor; GDNF: Glial cell-derived neurotrophic factor; BDNF: Brain-derived neurotrophic factor; NGF: Nerve growth factor.

Table 2 Comparison of development levels between the two groups before and after intervention (mean ± SD, point)

	Control group (*n* = 40)		Observation group (*n* = 41)	
	Before the intervention	After the intervention	Before the intervention	After the intervention
Language ability	66.78 ± 5.81	71.83 ± 6.22[a]	67.01 ± 5.77	79.54 ± 5.69[a,b]
Functional ability	78.23 ± 5.75	81.34 ± 6.22[a]	78.17 ± 5.82	85.34 ± 6.11[a,b]
Human ability	77.13 ± 6.09	80.54 ± 7.11[a]	76.94 ± 6.13	84.02 ± 6.51[a,b]
Motor ability	77.25 ± 5.83	80.57 ± 6.94[a]	77.02 ± 5.93	82.96 ± 5.31[a,b]
Developmental quotient	58.69 ± 6.34	75.77 ± 7.49[a]	58.81 ± 6.27	85.64 ± 2.11[a,b]

[a]$P < 0.05$, comparison before and after intervention in the group.
[b]$P > 0.05$, compared between groups after intervention.

Table 3 Comparison of language function between the two groups before and after intervention (mean ± SD, point)

		Control group (*n* = 40)	Observation group (*n* = 41)	*t*	*P* value
Reading comprehension	Before the intervention	17.18 ± 2.09	16.85 ± 2.12	0.0146	0.9884
	After the intervention	23.61 ± 2.54[a]	29.54 ± 1.93[a]	0.4838	0.6297
Retelling	Before the intervention	11.48 ± 2.62	11.61 ± 2.59	0.4345	0.6649
	After the intervention	15.81 ± 2.04[a]	19.74 ± 2.05[a]	4.3645	0
Fluency	Before the intervention	14.38 ± 2.42	14.27 ± 2.45	1.0718	0.2881
	After the intervention	20.68 ± 3.52[a]	24.97 ± 3.77[a]	5.7166	0
Writing	Before the intervention	27.49 ± 2.11	28.12 ± 2.08	0.5213	0.6034
	After the intervention	46.12 ± 3.15[a]	50.54 ± 3.52[a]	0.1837	0.8546

[a]$P < 0.05$, comparison before and after intervention in the group.

post-intervention differences were significant ($P = 0$). However, writing levels decreased post-intervention in both groups, from 27.49 ± 2.11 to 46.12 ± 3.15 in the control group and from 28.12 ± 2.08 to 50.54 ± 3.52 in the observation group (both $P < 0.05$). No significant difference was noted between the groups in writing levels, either pre- or post-intervention ($P > 0.05$).

DISCUSSION

The etiology of language disorders in patients is complex, often involving environmental factors and cognitive impairments, resulting in difficulties in peer communication. Studies indicate that around 5%-8% of individuals experience language disorders or delays, impacting various aspects such as language function, learning, and psychological well-being[8,9]. The Broca area, situated in the left hemisphere of the brain, plays a critical role in speech production. Stimulation of this area can have dual effects, either inhibiting or exciting the cerebral cortex, thereby enhancing induced currents in the tissue. This stimulation aids in improveing the brain's neural connections and contributes positively to the recovery of language and cognitive functions in patients[10,11]. While speech rehabilitation and psychological interventions can offer some relief, the lack of targeted treatments hinders long-term outcomes. Transcranial electrical stimulation, a non-invasive method that stimulates cerebral nerves through magnetic signals, has been widely used in neurological diseases and rehabilitation. It has bidirectional effects on brain activity, regulating excitation and inhibition on within the brain[12,13].

Relevant studies have shown that NGF plays a crucial role in the repair and growth of nerve cells, and its levels can indicate the patient's condition and treatment effectiveness[14,15]. The findings of this study revealed that after 3 wk of intervention, the observation group exhibited an increasing trend in the levels of GDNF, BDNF, CNTF, and NGF compared to the control group. This suggests that transcranial electrical stimulation is more effective than simple speech rehabilitation and psychological intervention in enhancing the levels of nerve factors in the serum of patients. Transcranial electrical stimulation stimulates brain nerves through magnetic signals, which promotes the activation of dormant brain cells, reduces cell death, facilitates nerve function regeneration, and enhances the expression of BDNF[16]. Furthermore, transcranial electrical stimulation also improves cell charge and accelerates blood circulation, leading to enhanced local blood flow, increased oxygen carrying capacity, and improved metabolic enzyme activity. These effects are beneficial for cell repair, nerve plasticity, and brain development[17].

The BDAE scale has high clinical value in detecting both language and non-language function. It allows for qualitative and quantitative analysis of patients' language communication level and helps assess the severity of language dysfunction with high credibility[18,19]. In this study, after a 3-wk intervention, the language, action, and observation group patients showed an increasing trend in their development quotient scores compared to the control group. Similarly, their reading comprehension, fluency, retelling, and writing scores also showed an increasing trend compared to the control group. Transcranial electrical stimulation significantly promoted the development level and enhanced the function of language. Language training can enhance patients' cognitive and communication abilities, as well as other functional training. It also promotes their active oral movement ability, language learning, and social adaptation. This contributes to the improvement of patients' language function[20]. Psychological intervention helps medical staff understand the psychological state of patients, allowing them to provide relief, encouragement, and support. This plays a positive role in promoting the improvement of language function and development level in patients[21,22]. Transcranial electrical stimulation, as a neural electrophysiological technique, has a two-way effect of inhibition or excitation on the brain. When the induced current intensity threshold excites nerve tissue, it can cause local depolarization of nerve cells, thus improving the brain's neural network, increasing synaptic plasticity, and improving the patient's language and cognitive function[23]. Transcranial electrical stimulation can facilitate the penetration of pulsed magnetic field from the skull into the cortex, resulting in physiological and biochemical reactions that stimulate motor potential. This repeated stimulation can have cumulative and long-term effects. From a physiological perspective, transcranial electrical stimulation can enhance cerebral blood circulation through induced current, promoting the repair of damaged brain cells. As a result, it can improve language function and developmental level in patients[24]. Previous studies have also demonstrated that the combination of transcranial electrical stimulation and conventional rehabilitation training can effectively enhance language and motor function rehabilitation in patients with cerebral palsy, which aligns with the findings of this study[25]. However, it is important to acknowledge the limitations of this research. The young age of the patients may have led to poor adherence to the intervention treatment, potentially influencing the study results. Additionally, the development level and language function can be influenced by subjective factors, which may result in varying outcomes. Future studies should incorporate more objective indicators to provide more comprehensive clinical references.

CONCLUSION

The combination of transcranial electrical stimulation intervention, speech rehabilitation training, and psychological intervention has demonstrated promising results in enhancing serum nerve factors levels and patients' developmental progress. This intervention has also been shown to improve the language function of individuals with needle speech disorder. These findings are clinically significant and warrant further investigation. However, the study was limited by small sample sizes and short-term treatment, failing to comprehensively assess long-term effects and potential adverse reactions. Therefore, future research should focus on expanding sample sizes, extending observation periods, and delving deeper into treatment mechanisms to enhance the generalizability and accuracy of the conclusions.

ARTICLE HIGHLIGHTS

Research background

Speech disorders significantly affect individuals' communication abilities and quality of life. Traditional treatments often show variable outcomes and patient compliance issues. The exploration of innovative, non-invasive therapies like transcranial electrical stimulation (TES) is crucial for advancing treatment effectiveness in this field.

Research motivation

This study is motivated by the need to find more effective, patient-friendly treatment options for speech disorders. The potential of TES as a novel intervention, capable of enhancing neurotrophic factors and improving language functions, drives this research.

Research objectives

The primary objective is to assess the impact of TES, alongside conventional speech and psychological therapies, on serum neurofactor levels and language functions in individuals with speech disorders.

Research methods

A controlled study was conducted with 81 patients, divided into a control group receiving standard therapies and an observation group receiving additional TES. The study evaluated serum levels of various neurofactors and conducted comprehensive assessments of language and motor functions over a 3-wk period.

Research results

The observation group demonstrated significantly higher levels of serum neurofactors (ciliary neurotrophic factor, glial cell-derived neurotrophic factor, brain-derived neurotrophic factor, nerve growth factor) and improved scores in language functions (writing, reading comprehension, retelling, fluency) and development quotient, compared to the control group.

Research conclusions

TES, in combination with standard therapies, significantly improves neurofactor levels and language functions in patients with speech disorders. This suggests TES as an effective adjunct therapy in the treatment of speech impairments.

Research perspectives

The promising results from this study advocate for further research into TES as a treatment modality for speech disorders. Future studies could explore long-term effects, optimize stimulation protocols, and investigate the underlying mechanisms of TES in neurological rehabilitation. This line of research has the potential to significantly impact clinical practices and patient outcomes in speech therapy.

FOOTNOTES

Co-first authors: Li Sun and Kai Xiao.

Author contributions: Sun L and Wang S conceptualized and designed the article; Sun L conducted the feasibility analysis; Implementation of the research by Sun L, Xiao K, and Shen XY, as well as the statistical analysis; Data collection was carried out by Sun L and Xiao K; Sun L was responsible for paper writing and revision; Wang S oversaw quality control, proofreading, and overall responsibility, supervision, and management of the article.

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ORIGINAL ARTICLE

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Identification of marker genes associated with N6-methyladenosine and autophagy in ulcerative colitis

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Abstract

BACKGROUND

Both N6-methyladenosine (m6A) methylation and autophagy are considered relevant to the pathogenesis of ulcerative colitis (UC). However, a systematic exploration of the role of the com-bination of m6A methylation and autophagy in UC remains to be performed.

AIM

To elucidate the autophagy-related genes of m6A with a diagnostic value for UC.

METHODS

The correlation between m6A-related genes and autophagy-related genes (ARGs) was analyzed. Finally, gene set enrichment analysis (GSEA) was performed on the characteristic genes. Additionally, the expression levels of four characteristic genes were verified in dextran sulfate sodium (DSS)-induced colitis in mice.

RESULTS

GSEA indicated that BAG3, P4HB and TP53INP2 were involved in the inflammatory response and TNF-α signalling *via* nuclear factor kappa-B. Furthermore, polymerase chain reaction results showed significantly higher mRNA levels of BAG3 and P4HB and lower mRNA levels of FMR1 and TP53INP2 in the DSS group compared to the control group.

CONCLUSION
This study identified four m6A-ARGs that predict the occurrence of UC, thus providing a scientific reference for further studies on the pathogenesis of UC.

Key Words: Ulcerative colitis; m6A; Autophagy; Characteristic genes; Immune infiltration

Core Tip: Both N6-methyladenosine (m6A) methylation and autophagy are considered relevant to the pathogenesis of ulcerative colitis (UC). This study identified four m6A-related genes and autophagy-related genes that predict the occurrence of UC, thus providing a scientific reference for further studies on the pathogenesis of UC.

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INTRODUCTION

Ulcerative colitis (UC) is a complex, chronic, immune-mediated, colitis disease. The UC lesions are mostly located in the sigmoid colon and rectum even the whole colon[1]. The clinical manifestations of UC can take many forms, with bloody diarrhoea as the most obvious early symptom. Other symptoms include abdominal pain, bloody stool, weight loss, tenesmus and vomiting. UC is characterised by the alternation of the active phase and remission phase; however, its clinical process is unclear[2]. The incidence rate of UC is on the rise worldwide, with treatment proving to be difficult. Approximately 15% of patients with UC experience an aggressive course, and some will even develop colorectal cancer. Current non-surgical treatment options include 5-aminosalicylic acid (5-ASA), glucocorticoids, immunosuppressants, biological agents and probiotics, which are limited by high recurrence rates and varying side effects. Current research on the pathogenesis of UC mainly focuses on microbiota, genetics, immunity and intestinal mucosal barrier. However, the exact pathogenesis of UC remains unclear. Therefore, exploring the aetiology of UC is of great significance for the diagnosis and treatment of UC[3].

N6-methyladenosine (m6A) methylation is one of the most common RNA modifications and plays a key role in the development and progression of various diseases. It has been reported that changes related to m6A are associated with intestinal microbiota changes and gastrointestinal cancer development[4]. Currently, studies have investigated m6A methylation in UC, which revealed the role of m6A methylation in the pathogenesis of UC[5,6].

Autophagy is a conservative degradation process, which is critical for regulating major cellular functions and biological metabolic processes. Thus, impaired autophagy could lead to many diseases, including cancer, cardiomyopathy, neurodegenerative diseases and ageing. Moreover, autophagy disorder can also lead to inflammation, intestinal barrier destruction and intestinal homeostasis imbalance, thus increasing the risk of colon disease[7]. Recently, autophagy-related gene polymorphisms have been reported to be strongly associated with an increased risk of UC. Additionally, the therapeutic effect of certain UC drugs is indicated to be mediated by regulating the autophagy pathway [8]. Recent studies have shown that the methylation of m6A RNA can regulate autophagy gene expression and affect autophagy function. Both m6A modification and autophagy play a key role in the occurrence and development of human diseases; however, the combined role of m6A and autophagy in UC remains unexplored[9].

In this study, we used publicly available data related to UC and comprehensive bioinformatics methods to elucidate the autophagy-related genes of m6A with a diagnostic value for UC. Additionally, animal models were also used to validate and explore the potential regulatory mechanism of m6A-autophagy in UC, thereby contributing to the development of treatment options for patients with UC.

MATERIALS AND METHODS

Data extraction

UC-related datasets (GSE8747 and GSE75214) were downloaded from the Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/). The training set was the GSE87473 dataset, which comprised 21 normal and 106 UC samples. The GSE75214 dataset, comprising 11 normal and 97 UC samples, was used as the external validation set. In total, 222 ARGs were acquired from the Human Autophagy database (http://www.autophagy.lu/index.html) (Supplementary Table 1). Furthermore, 23 m6A-related genes were obtained from the published literature (Supplementary Table 1)[10].

Identification and functional analysis of differentially expressed genes between the UC and normal groups

The mRNA expression levels between the UC and normal groups in the GSE87473 dataset were compared using the 'limma' package (version 3.52.4) with adj $P < 0.05$ and $|\log_2 FC| \geq 0.5$[11]. Subsequently, the 'clusterProfiler' R package (version 4.4.4) was used to perform the biological functional enrichment analysis of differentially expressed genes (DEGs) between the UC and normal groups with Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG)($P < 0.05$)[12].

Identification and Establishment of a protein-protein interaction network of m6A-Autophagy-Related DEGs

Correlations between the m6A-related genes and ARGs were calculated using the 'rcorr' function of the 'Hmisc' R package (version 4.7-1) ($P < 0.05$). The intersection of the m6A-autophagy-related genes (m6A-ARGs) and DEGs was performed using the Venn tool to acquire m^{6}A-AR DEGs. STRING was adopted to explore the protein-protein interaction (PPI) of m^{6}A-AR DEGs. Furthermore, Cytoscape (version 3.8.0) was utilised to visualise the co-expression network of m6A-ARGs and the PPI network of m6A-AR DEGs.

Screening of characteristic genes

Univariate logistic regression was used to initially screen variables in the identified m6A-AR DEGs. Additionally, the least absolute shrinkage and selection operator (LASSO) and support vector machines (SVM) were further applied for screening characteristic genes. Moreover, the diagnostic value for UC of the characteristic gene was assessed using receiver operating characteristic (ROC) curves and the area under the curve (AUC).

Immune infiltration analysis

The CIBERSORT algorithm (version 1.03) was utilised to assess the infiltrating abundance of 22 immune cells between the UC and normal groups in the training set[13]. Differences between UC and normal groups were analysed using a Wilcox test, and a boxplot was plotted using the 'ggplot2' R package (version 3.3.6). Additionally, the correlation between characteristic genes and differential immune cells was analysed using the cor function of R language.

Gene set enrichment analysis of characteristic genes

Based on the median value of the expression of the characteristic genes, the samples in GSE87473 were grouped into high and low-expression groups, and differential analysis was performed. Hallmark gene sets were downloaded using the 'msigdbr' R package (version 7.5.1) as a reference. Sorted DEGs were subjected to enrichment analysis (adj. $P < 0.05$).

Expression of characteristic genes in external validation datasets

To further demonstrate the validity of our results, the expression levels of the characteristic genes were compared between the UC and normal groups in the GSE87473 and GSE75214 datasets for external validation.

Animal

C57BL/6 mice (6-8 wk old, Quality Certification of Laboratory Animals: SCXK (Shanghai) 2017-0012) were housed in the Animal Experiment Centre of Shanghai University of Traditional Chinese Medicine, at a temperature of 22°C ± 2°C, alternating between light and dark (SPF class), 50% ± 10% relative humidity. All animals had unlimited access to standard diet and water and general health status was checked daily by veterinarians. All animals ($n = 20$) were divided randomly into two groups (five animals per cage): control group ($n = 10$) and dextran sulfate sodium (DSS) group ($n = 10$). The mice in the DSS group were given DSS solution (3.5%) for seven days. Mice in the control group drank water normally. All animal experiments conformed to the internationally accepted principles for the care and use of laboratory animals (No. PZSHUTCM210611001, the Animal Ethics Committee of the Shanghai University of Traditional Chinese Medicine).

Evaluation of disease activity index

Colitis was evaluated by disease activity index (DAI) score, including body weight, stool consistency, and fecal occult blood or gross bleeding[14]. DAI was calculated by grading on a scale of 0 to 4 using the following parameters: loss of body weight (0: normal; 1: 0%-5%; 2: 5%-10%; 3: 10%-15%; 4: > 15%); stool consistency (0: normal; 2: loose stools; 4: watery diarrhea); and occult blood (0: negative; 2: positive; 4: gross bleeding). The final result was expressed as the average of the three.

Sample collection

At the end of the experiments, all animals were euthanized by intraperitoneal injection of 80 mg/kg 1% sodium pentobarbital. After euthanasia, the whole colon was collected and the feces and surrounding connective tissue were removed. Freshly isolated organs were kept frozen at –80 °C for RNA isolation and analyses of gene expression.

Quantitative real-time polymerase chain reaction

After the experiment, colonic tissues were collected for quantitative real-time polymerase chain reaction (Table 1). Total RNA was extracted with TRIzol by homogenizing the tissue. Total RNA quality was assessed by measuring the absorbance at 260 and 280 nm using a NanoDrop-2000c spectrophotometer (Thermo Fisher Scientific, Waltham, MA, United States) and the 260/280 ratio ranged between 1.8 and 2.0. Then samples were used to reverse transcription and synthesize cDNA by the Evo M-MLV RT Premix. The samples were diluted using the SYBR® Green Premix Pro Taq HS quantitative real-time polymerase chain reaction (qPCR) Kit (High Rox Plus) (Accurate Biology, China). qPCR and

Table 1 Primer sequences

Gene		Sequence (5'-3')	PCR products (bp)
Mus BAG3	Forward	CACCTTTTCCATGCCTACTCCC	108
	Reverse	TTCTGTCATGCCGCCACGTA	
Mus P4HB	Forward	TCACTGAACAGACAGCTCCGAA	144
	Reverse	ATAGGATCTTGCCCTTGAAGCC	
Mus FMR1	Forward	ATGTCATACAGGTTCCACGAAAC	77
	Reverse	GTCCACGATCTCTTGAATCAGC	
Mus TP53INP2	Forward	CATTGAGCATCCCAGCATGTCC	117
	Reverse	TCTCCATCGCTGAGGTCCTG	

PCR: Polymerase chain reaction.

melting-curve analyses were performed using StepOnePlus Real-Time PCR System (Applied Biosystems, Foster City, CA, United States). The PCR reactions were set for 40 cycles. Each cycle was fixed at 95 °C for 30 s, 95 °C for 3 s, and 60 °C for 30 s. These primers have been validated for specificity and efficiency using conventional RT-PCR. Relative gene expression was calculated based on $2^{-\Delta\Delta Ct}$ method.

RESULTS

Acquisition and enrichment analysis of DEGs between the UC and normal groups

In total, 3512 DEGs were identified between the UC and normal groups in GSE87473 (Figure 1A and B). Enrichment analysis revealed a total of 1247 GO BP, 143 GO MF and 97 GO CC that were related to DEGs, such as small molecule catabolic process, oxidoreductase activity, catabolism of organic acids process, acting on CH-OH group of donors, mitochondrial matrix, peroxisomal matrix and microbody lumen (Figure 1C). Moreover, there were 67 KEGG pathways such as retinol metabolism, co-factors biosynthesis and cytokine-cytokine receptor interaction, that were related to DEGs (Figure 1D).

Construction of the PPI Network of m6A-AR DEGs

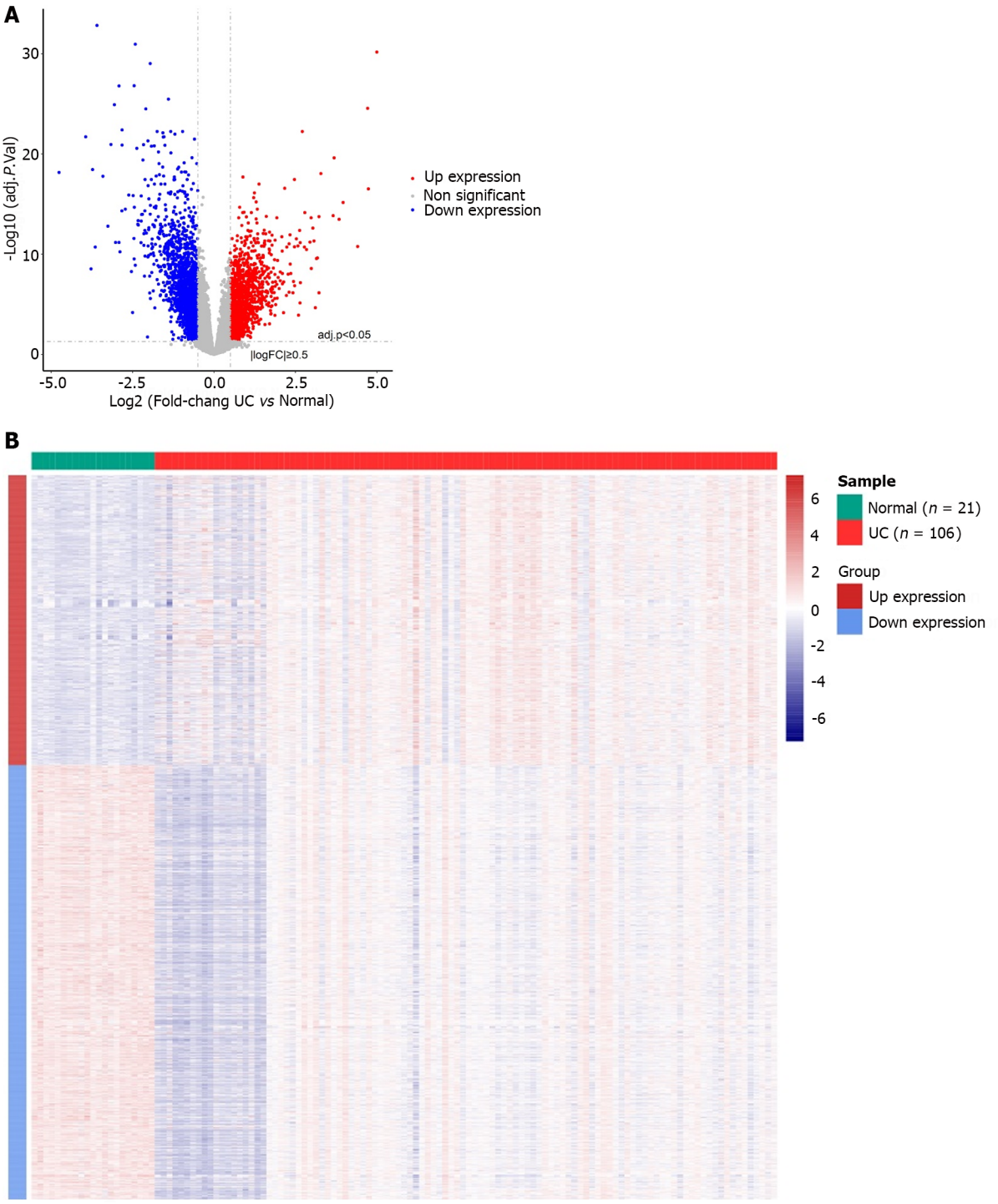
All 23 m6A-related genes and 222 ARGs were observed to be related to each other. Figure 2A presents the co-expression network of m6A-autophagy-related genes that contains 14 m6A-related genes and 64 ARGs ($|r| > 0.8$ and $P < 0.05$) (Supplementary Table 2). A total of 43 m6A-AR DEGs were obtained by the intersection of m6A-autophagy-related genes and DEGs between the UC and normal groups (Figure 2B). Moreover, using the PPI network of m6A-AR DEGs, a strong reciprocal relationship was observed between heat shock protein family A (Hsp70) member 5 (HSPA5) and dnaJ heat shock protein family member B9 (DNAJB9), HSPA5 and tumour protein P53 inducible nuclear protein 2 (TP53INP2), death-associated protein kinase 2 (DAPK2) and mitogen-activated protein kinase 3 (MAPK3) (Figure 2C). However, four proteins did not interact with other proteins, namely Cathepsin L, eukaryotic elongation factor 2 kinase, a regulator of G protein signalling 19 and tumour suppressor candidate 1 (TUSC1) (Figure 2C).

Acquisition of characteristic genes

Univariate logistic regression revealed that all 43 m6A-AR DEGs were associated with the occurrence of UC (Figure 3A). Nine characteristic genes were further identified using LASSO, namely BLC2-associated athanogene 3 (BAG3), CC Chemokine Ligand 2, prolyl 4-hydroxylase subunit beta (P4HB), proliferation and apoptosis adaptor protein 15, serpin family a member 1, fragile X mental retardation 1 (FMR1), MAPK3, TP53INP2 and TUSC1 (Figure 3B). From the SVM algorithm, we obtained nine eigengenes, namely DNAJB9, BAG3, TP53IMP2, recombinant human caspase-1, P4HB, breast tumour kinase/protein-tyrosine kinase 6, DAPK2, FMR1, leucine-rich pentatricopeptide repeat containing (Figure 3C). Finally, four characteristic genes (FMR1, BAG3, P4HB and TP53IMP2) were selected through the cross-talk between LASSO and SVM (Figure 3D). The diagnostic accuracy of the four characteristic genes was evaluated using ROC curve analysis in GSE87466 and GSE75214. The AUC values of the four genes were greater than 0.7 in both datasets, indicating their high predictive accuracy for the occurrence of UC (Figure 3E and F).

Immuno-infiltration analysis in the UC and normal groups

The infiltrating abundance of the 22 immune cells between the UC and normal groups was demonstrated using a bar chart, which showed that the content of B cells and T cells was higher in the UC group (Figure 4A). The correlation of infiltration levels of the 22 immune cells with each other was demonstrated using a heat map (Figure 4B). Moreover, 14 immune cells significantly differed between the UC and normal groups (Figure 4C), such as M0 macrophages, neutrophils and activated NK cells. Finally, correlation analysis between characteristic genes and differential immune


A
30
20
10
0
-Log10 (adj.P.Val)
-5.0
-2.5
0.0
2.5
5.0
Log2 (Fold-chang UC vs Normal)
adj.p<0.05
|logFC|≥0.5
Up expression
Non significant
Down expression
B
Sample
Normal (n = 21)
UC (n = 106)
Group
Up expression
Down expression
6
4
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-2
-4
-6

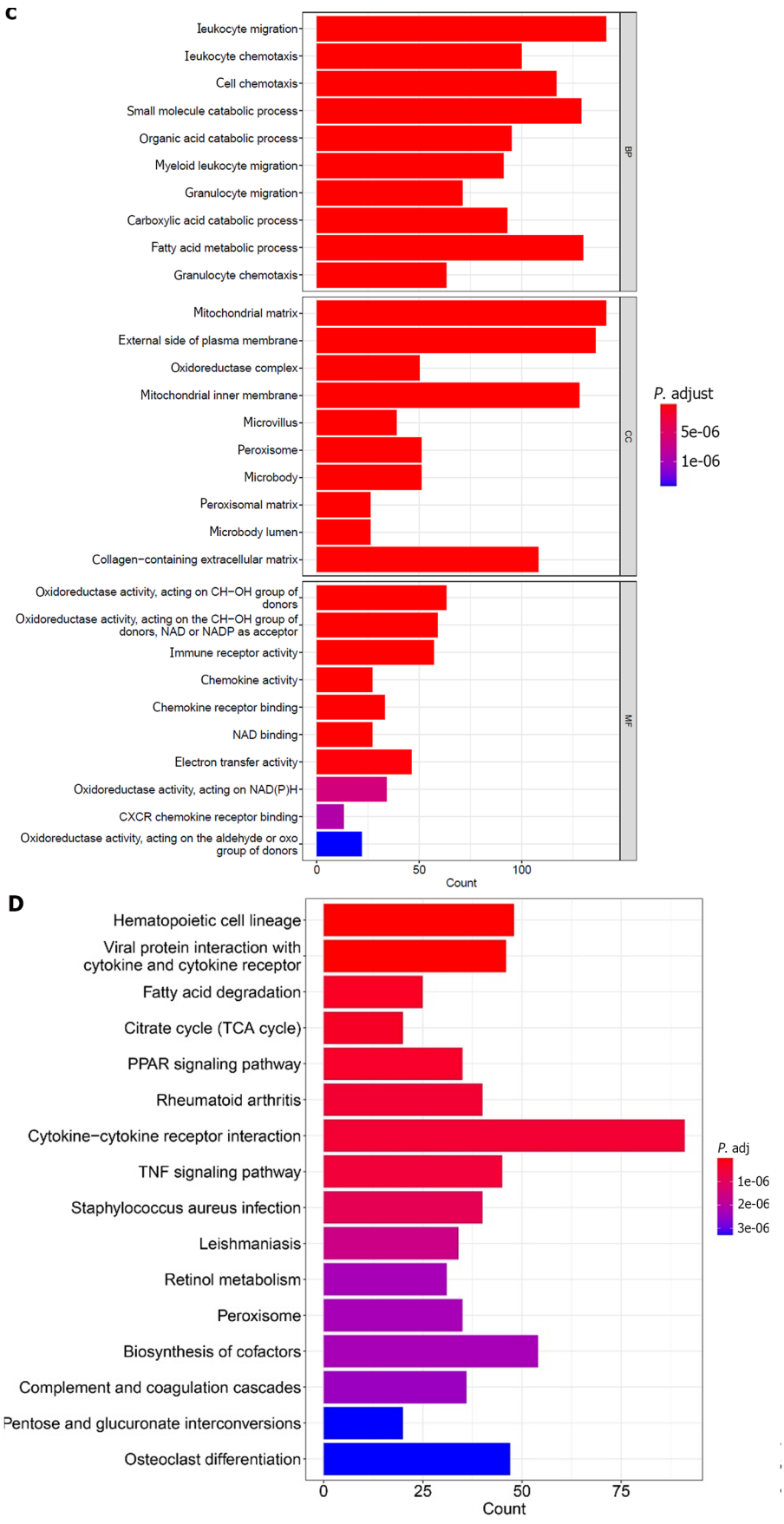


Figure 1 Analysis differentially expressed genes between the ulcerative colitis and normal groups. A: Volcanic map of differentially expressed genes (DEGs); B: Heat map of DEGs; C: Enrichment results of Gene Ontology functional classification; D: Enrichment results of Kyoto Encyclopaedia of Genes and Genomes pathway.

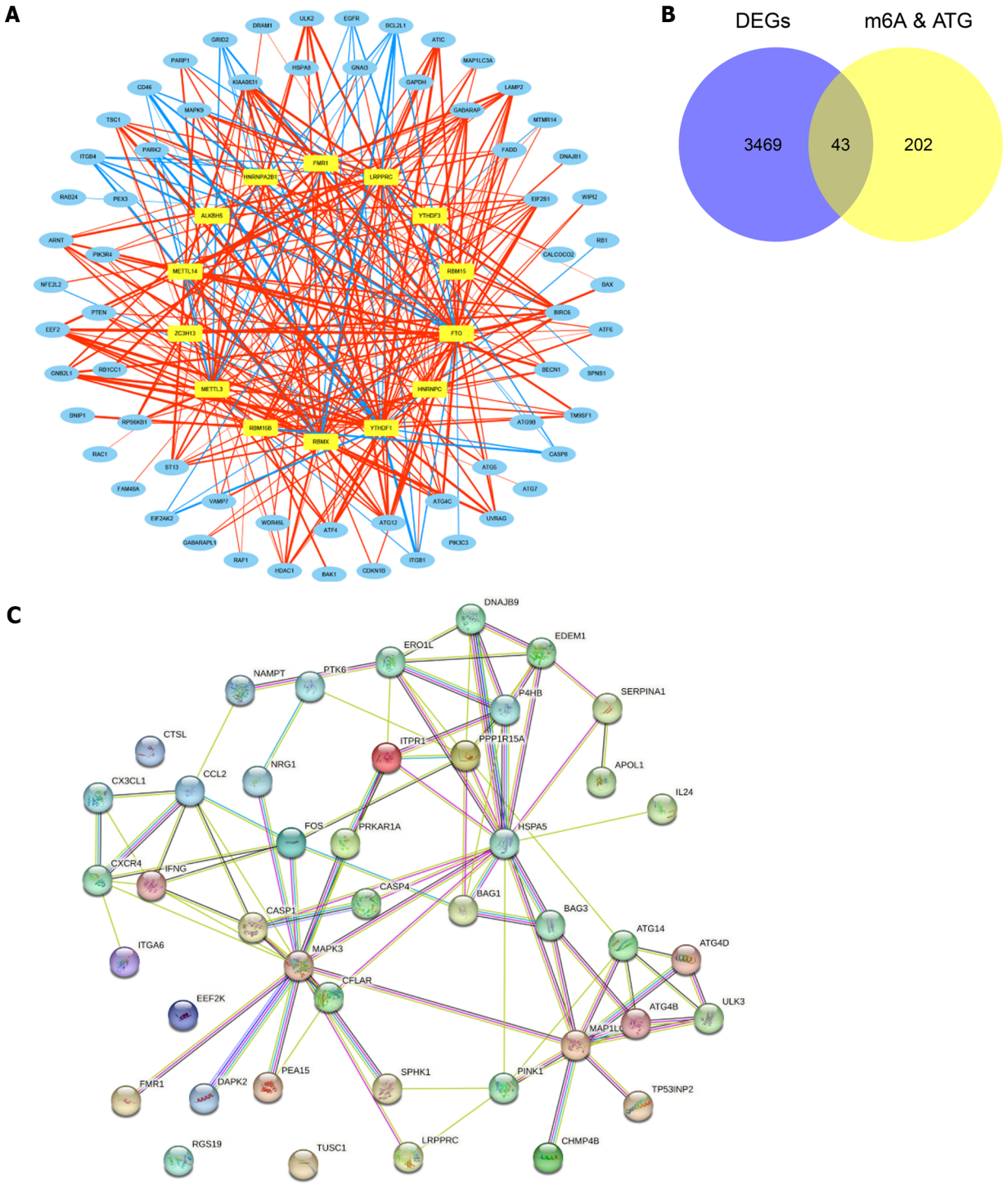


Figure 2 The protein-protein interaction network of m6A-autophagy-related differentially expressed genes. A: N6-methyladenosine (m6A)-autophagy genes (ATG) related network; B: Venn diagrams of m6A-ATG and Differentially Expressed Genes. C: Protein-Protein Interaction network of differential m6A-Autophagy-Related Differentially Expressed Genes. DEGs: Differentially expressed genes; m6A: N6-methyladenosine; ATG: Autophagy genes.

cells showed that TP53INP2 had the strongest positive correlation with M2 macrophages, while FMR1 had the strongest negative correlation with naive B cells (Figure 4D).

Gene set enrichment analysis of characteristic genes

To further understand the impact of the characteristic genes on the development of UC, we performed gene set enrichment analysis (GSEA) of the characteristic genes. BAG3, P4HB and TP53INP2 were found to be involved in the inflammatory response and tumour necrosis factor-α (TNF-α) signalling through nuclear factor kappa-B (NF-κB) (Figure 5A-C). Notably, BAG3 and P4HB were positively associated with the two signalling pathways, whereas TP53INP2 was negatively correlated. FMR1 was mainly enriched in adipogenesis, MYC targets V1, E2F targets, oxidative phosphorylation and fatty acid metabolism (Figure 5D).

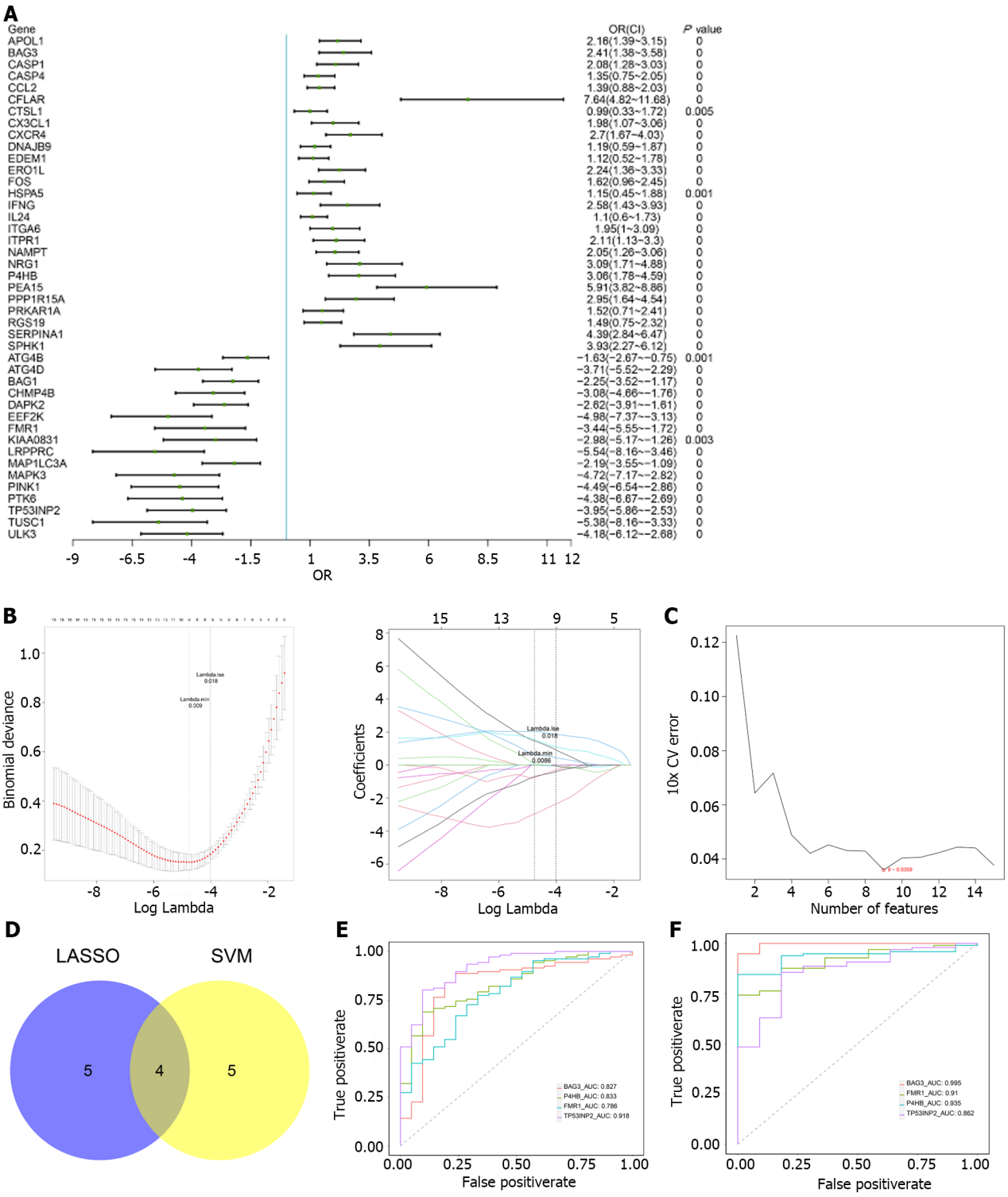
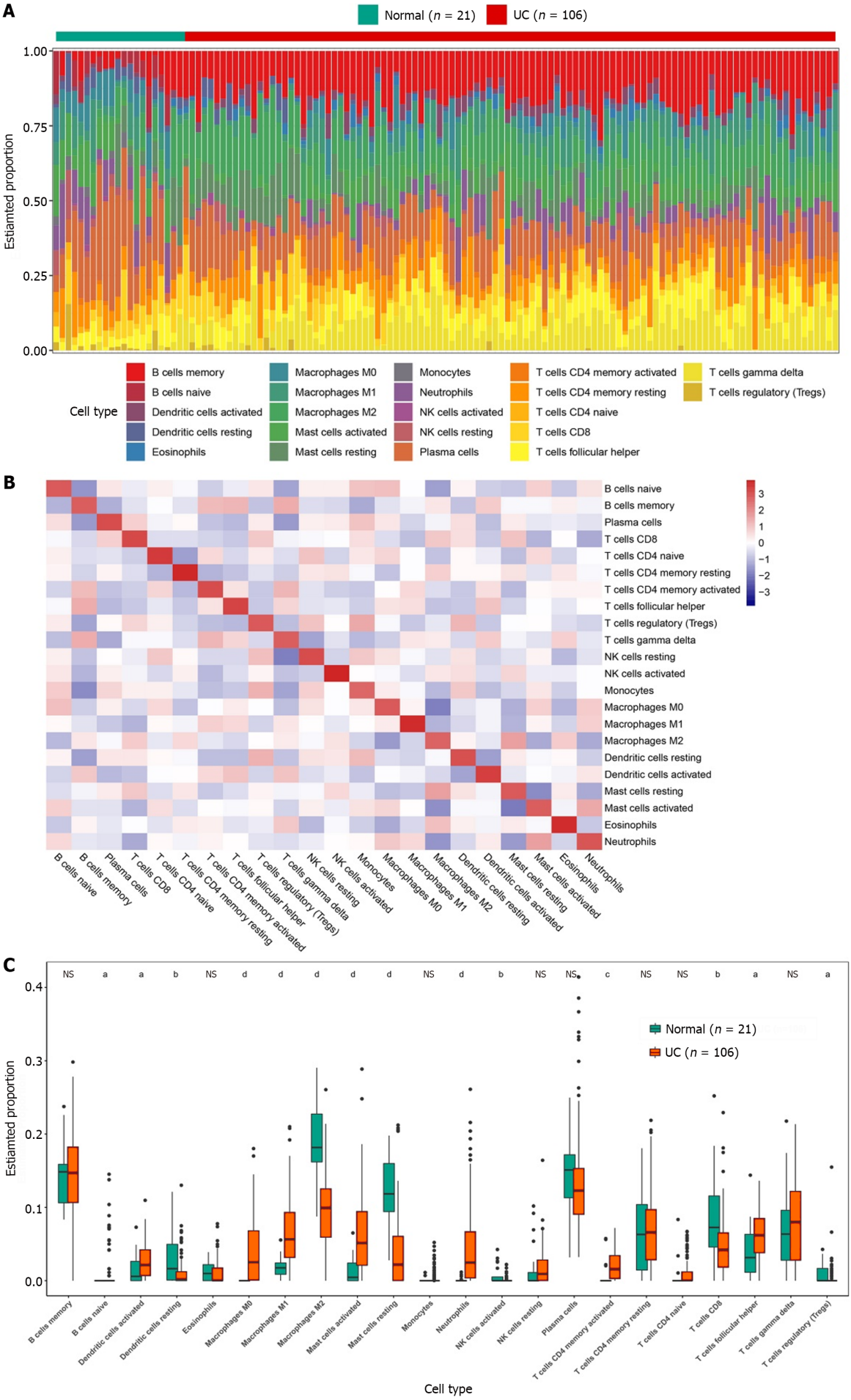


Figure 3 Analysis of characteristic genes. A: Forest map of univariate logistic regression; B-I/II: Least absolute shrinkage and selection operator (LASSO) regression; C: Relationship between generalisation error and the characteristic number of support vector machines (SVM) algorithm; D: Venn diagram of LASSO and SVM; E: Training set: Receiver operating characteristic (ROC) curve; F: Validation set: ROC curve. LASSO: Least absolute shrinkage and selection operator; SVM: Support vector machines.

The mRNA levels of characteristic genes

The visualised data exhibited the expressions of BAG3, FMR1, P4HB and TP53IMP2. The expression of four characteristic genes were shown in the GSE87473 and GSE75214 datasets (Figure 6A and B). The expression of the four characteristic genes between the normal and UC groups was significantly different. Moreover, the expression trends of the four genes were consistent in both datasets, with BAG3 and P4HB expressions elevated in the UC group whereas TP53INP2 and FMR1 expressions were lowered. The results suggested that these four genes had great diagnostic value in predicting the occurrence of UC.


A
Normal (n = 21)
UC (n = 106)
Estiamted proportion
1.00
0.75
0.50
0.25
0.00
Cell type
B cells memory
B cells naive
Dendritic cells activated
Dendritic cells resting
Eosinophils
Macrophages M0
Macrophages M1
Macrophages M2
Mast cells activated
Mast cells resting
Monocytes
Neutrophils
NK cells activated
NK cells resting
Plasma cells
T cells CD4 memory activated
T cells CD4 memory resting
T cells CD4 naive
T cells CD8
T cells follicular helper
T cells gamma delta
T cells regulatory (Tregs)
B
3
2
1
0
−1
−2
−3
C
Estiamted proportion
Normal (n = 21)
UC (n = 106)
Cell type

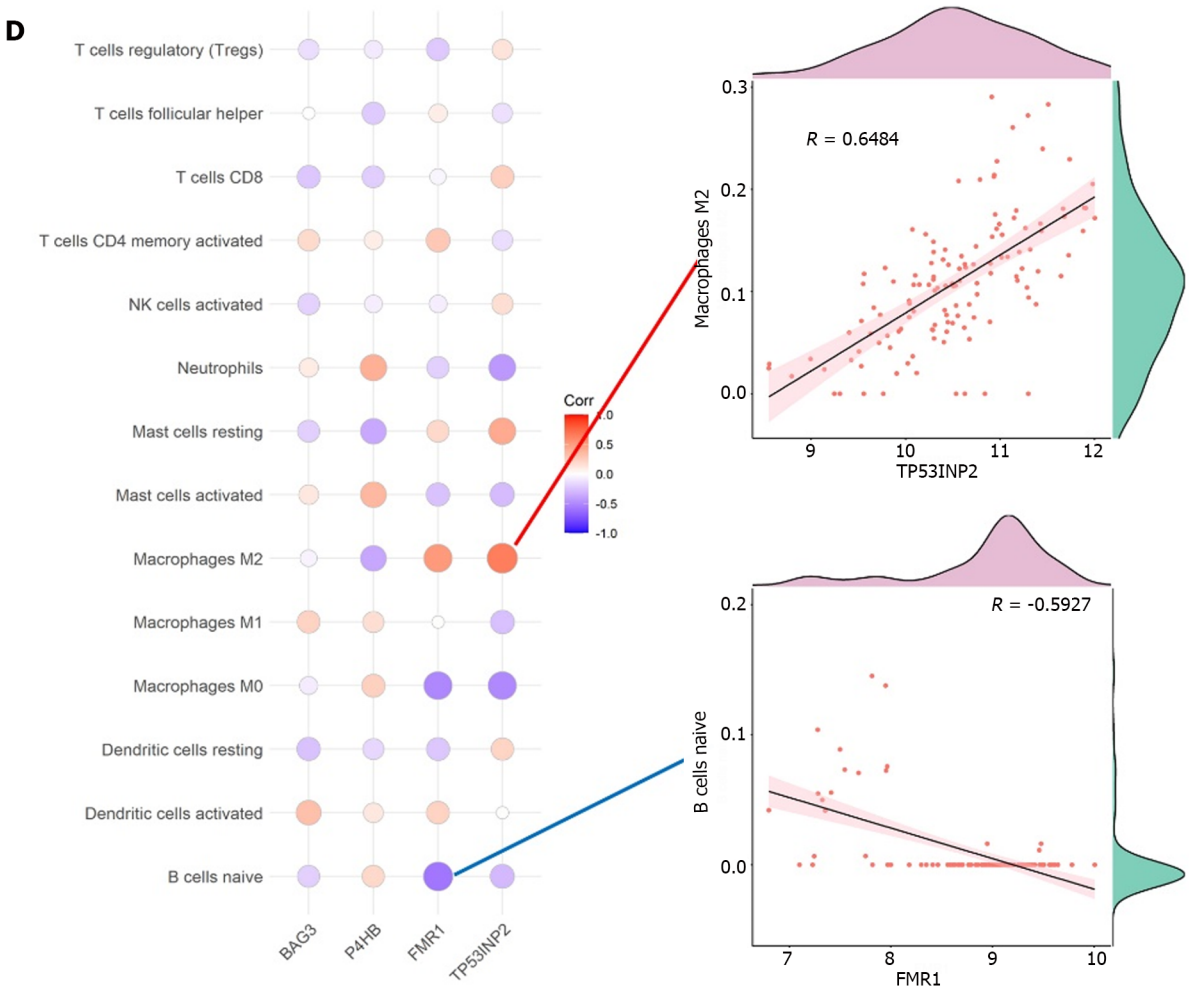


Figure 4 Immuno-infiltration analysis in the ulcerative colitis and normal groups. A: The level of immune infiltration in each sample; B: Heat map of immune cell infiltration; C: Levels of immune cell infiltration between the groups; D: Correlation between characteristic genes and differential immune cells. [a]*P* < 0.05, [b]*P* < 0.01, [c]*P* < 0.001, [d]*P* < 0.001. NS: Not significant.

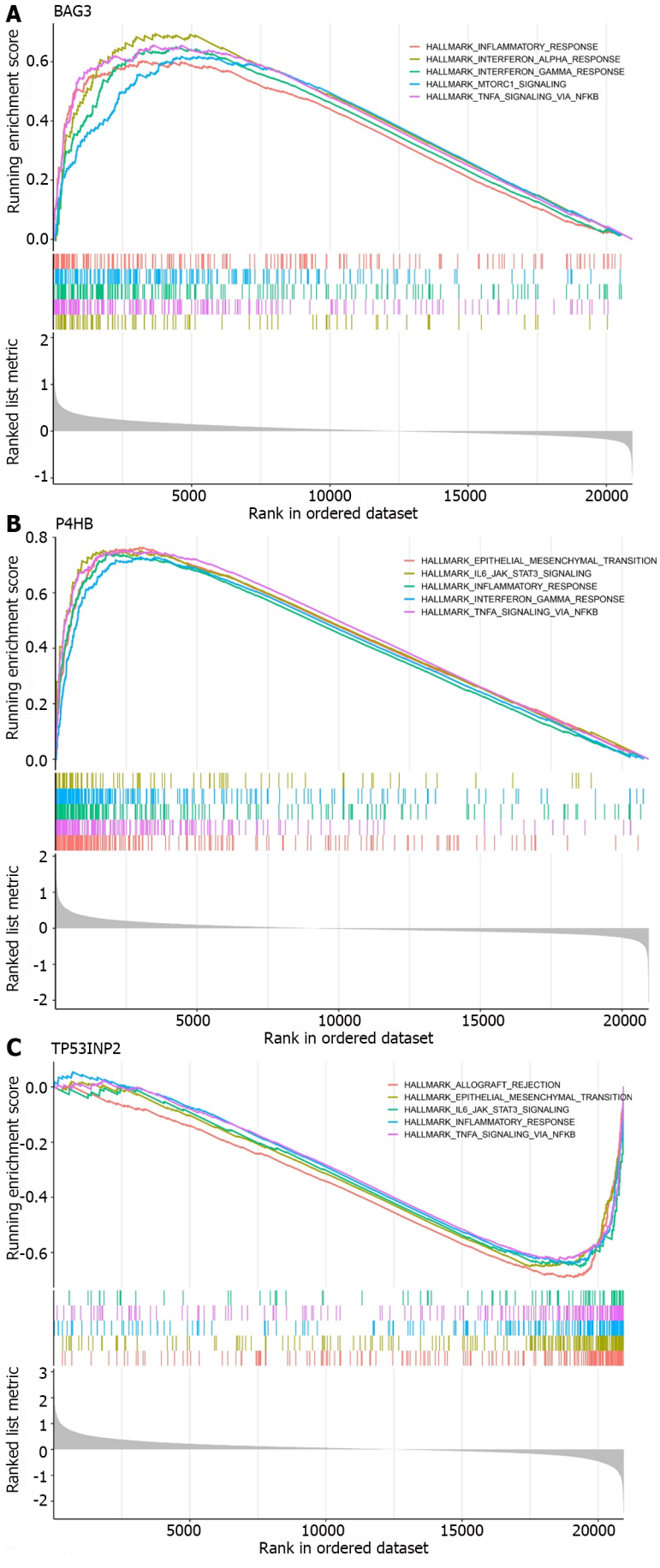
Validation of the expression levels of four characteristic genes in DSS-induced colitis in mice

The control group mice had a good mental state, sensitive reaction, shiny hair, gradually increased body mass and formed faeces; The mice in the DSS group had a poor mental state, slow movement, matted hair, significantly reduced body weight and mucus purulent stool. Compared with the control group, the DAI of the DSS group mice increased significantly on the 7th day of administration (Figure 7A). HE staining showed that the colon tissue structure in the control group mice was complete and orderly arranged, the goblet cells and crypt structure were normal, and there was no congestion, oedema or ulcer. Meanwhile, in the DSS group, the colonic tissue was destroyed, goblet cells and crypts disappeared, a large number of inflammatory cells infiltrated the tissue and large ulcerative lesions were observed (Figure 7B). PCR also revealed significantly higher mRNA levels of BAG3 and P4HB and lower mRNA levels of FMR1 and TP53INP2 in the DSS group compared to the control group (Figure 7C). The flowchart systematically describes our study (Figure 8).

DISCUSSION

The role of m6A modification, especially concerning autophagy regulation, in human diseases such as obesity, heart disease, azoospermia or oligozoospermia, intervertebral disc degeneration and cancer has been extensively studied by scholars. Such studies contribute to the optimisation of treatment strategies for various diseases[9,15,16]. However, research on the mechanism of m^{6}A autophagy interaction in colitis is still lacking.

In our study, four characteristic genes (FMR1, BAG3, P4HB and TP53INP2) were acquired using the machine learning algorithms. FMR1 is related to m6A, while BAG3, P4HB and TP53INP2 are related to autophagy. FMR1, the gene responsible for fragile X syndrome, encodes the fragile X mental retardation protein[17]. BAG proteins compete with Hip for binding to the Hsc70/Hsp70 ATPase domain and promote substrate release. Additionally, diseases associated with BAG3 include myopathy, myofibrillar and cardiomyopathy[18]. P4HB is an important endoplasmic reticulum (ER) molecular chaperone. Traditionally, it regulates the post-translational modification of proteins in the ER, which in turn is


A
BAG3
Running enrichment score
HALLMARK_INFLAMMATORY_RESPONSE
HALLMARK_INTERFERON_ALPHA_RESPONSE
HALLMARK_INTERFERON_GAMMA_RESPONSE
HALLMARK_MTORC1_SIGNALING
HALLMARK_TNFA_SIGNALING_VIA_NFKB
Ranked list metric
Rank in ordered dataset
B
P4HB
Running enrichment score
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION
HALLMARK_IL6_JAK_STAT3_SIGNALING
HALLMARK_INFLAMMATORY_RESPONSE
HALLMARK_INTERFERON_GAMMA_RESPONSE
HALLMARK_TNFA_SIGNALING_VIA_NFKB
Ranked list metric
Rank in ordered dataset
C
TP53INP2
Running enrichment score
HALLMARK_ALLOGRAFT_REJECTION
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION
HALLMARK_IL6_JAK_STAT3_SIGNALING
HALLMARK_INFLAMMATORY_RESPONSE
HALLMARK_TNFA_SIGNALING_VIA_NFKB
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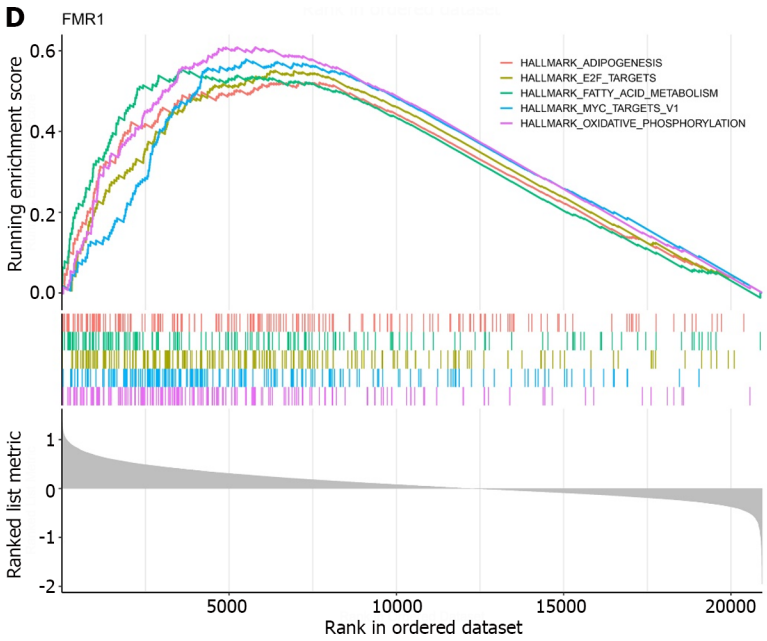

Figure 5 Gene set enrichment analysis of characteristic genes. A: BAG3; B: P4HB; C: TP53INP2; D: FMR1.

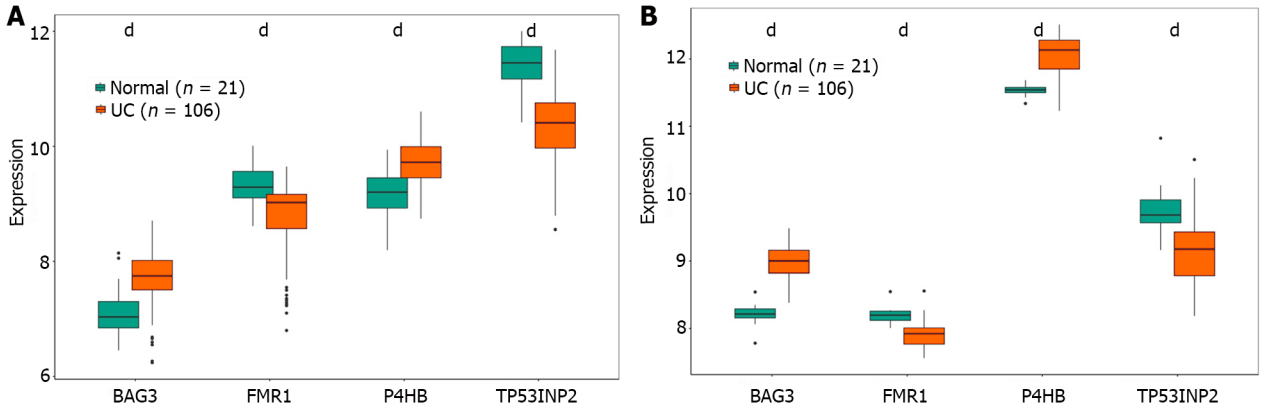

Figure 6 The mRNA levels of characteristic genes. A: Training set: expression of marker genes; B: Validation set: expression of marker genes. $^{d}P < 0.001$.

crucial for cell proliferation, apoptosis and autophagy regulation[19]. The protein encoded by TP53INP2 promotes autophagy and is essential for proper autophagosome formation and processing[20]. Recent studies report that the relationship between these four genes and intestinal diseases is mainly studied in colorectal cancer, with very little attention being paid to colitis.

In this study, through machine learning and animal model verification, the expression of Fmr1 and TP53INP2 was observed to be reduced in colitis. Researchers report that the relative abundance of Proteus, Deironobacteria and Bacteroides in Fmr1 knockout mice was higher than that in the wild-type (WT) mice, whereas that of Firmicutes and Tenericutes was lower in Fmr1 knockout mice than in the WT mice[21]. Therefore, we speculate that Fmr1 could affect the occurrence and development of colitis through the intestinal flora and its metabolites. Studies also report that the downregulation of TP53INP2 inhibits epithelial-to-mesenchymal transition (EMT) *via* the GSK-3β/β-catenin/Snail1 pathway in bladder cancer[22]. We hypothesised that TP53INP2 could inhibit the occurrence of EMT by regulating EMT-related transcription factors, thus blocking the key link required for UC-associated colorectal cancer (CAC) transformation. In the current study, the expression of BAG3 and P4HB was elevated in colitis. Studies have revealed that BAG3 overexpression promoted HCT-116 cell growth, migration and invasion in vitro. Contrastingly, BAG3 knockout inhibited HCT-116 cell growth, migration and invasion[23]. In view of the similar biological characteristics of HCT-116 and HT-29/intestinal epithelial cells, we speculate that BAG3 is involved in the signalling pathway related to cell proliferation, migration, invasion and chemical resistance control in colitis. Moreover, P4HB has been reported to be highly expressed in patients with colorectal cancer and closely related to the degree of cancer differentiation[24]. Thus, we hypothesise that P4HB has potential as a molecular marker in the diagnosis and treatment of human CAC.

GSEA revealed that BAG3, P4HB and TP53INP2 were involved in the NF-κB/TNF-α signalling pathway. The NF-κB signalling pathway plays an important role in the development of UC. The loss of the NF-κB signalling pathway and its regulatory factors lead to pathological changes in the UC intestinal tract, which, acting as positive feedback, further

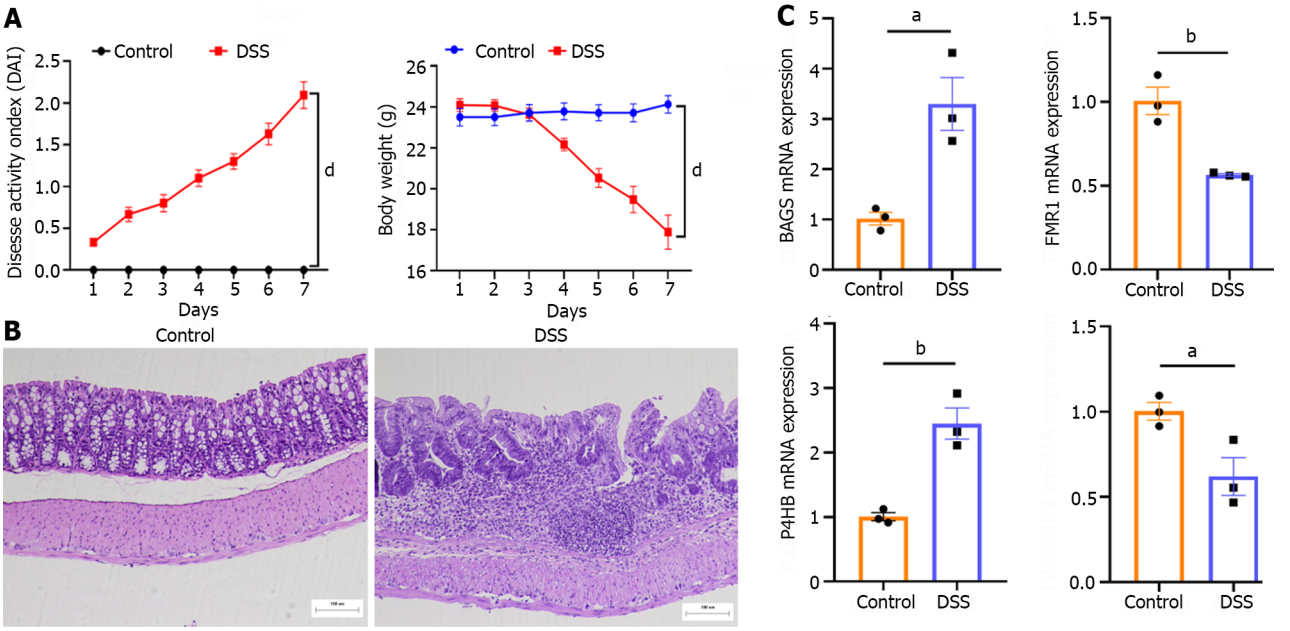

Figure 7 Validation of the animal model. A: Disease activity index scores were recorded daily; B: H&E staining (×100); C: The relative mRNA level of characteristic genes. The relative mRNA level was detected using qPCR in Dextran sulfate sodium-induced colitis mice. Data are shown as the mean ± SEM. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$, $^{d}P < 0.001$. DSS: Dextran sulfate sodium.

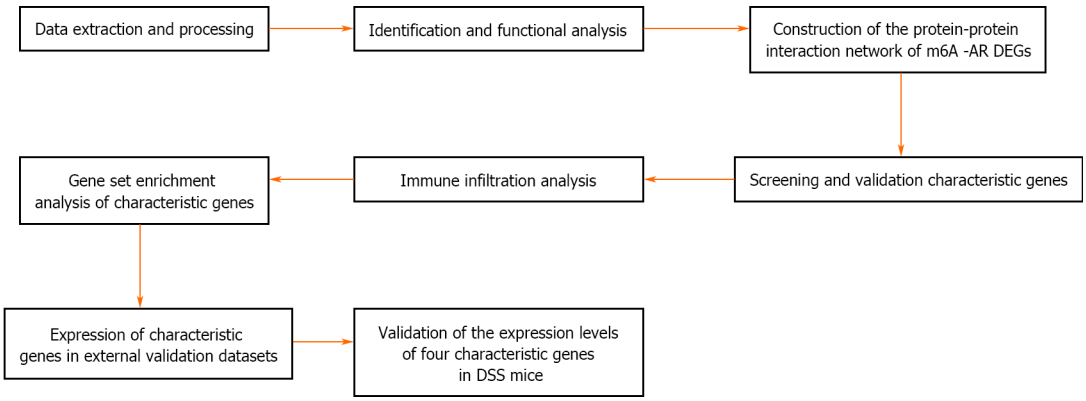

Figure 8 Flowchart of the research. DEGs: Differentially expressed genes; m6A: N6-methyladenosine; DSS: Dextran sulfate sodium.

activates NF-κB and aggravates inflammation. Cytokines such as TNF-α, interleukin (IL)-6 and IL-1β are influenced by NF-κB and regulate immunity and inflammation in different ways[25]. Therefore, BAG3, P4HB and TP53INP2-related NF- κB/TNF-α signalling pathways have curative potential in clinical UC treatment[26].

Immuno-infiltration analysis showed that TP53INP2 had the highest positive correlation with M2 macrophages, while FMR1 had the highest negative correlation with naive B cells. Intestinal macrophages are involved in intestinal immune homeostasis and intestinal inflammation. The imbalance of the classical activated pro-inflammatory phenotype (M1)/alternative activated anti-inflammatory phenotype (M2) macrophage polarization can lead to intestinal inflammation. In UC patients, intestinal inflammation is closely related to the imbalance of intestinal M1/M2 macrophages polarization [27]. Therefore, targeted therapy that promotes macrophage polarisation by regulating TP53INP2 can reconstruct the homeostasis of intestinal immune microenvironment and restore post-inflammatory tissue homeostasis, which is a new focus of UC therapy. Through single-cell RNA sequencing of B cells from three cohorts of patients with UC, researchers have drawn the composition, transcription and clonal map of the intestinal mucosa and circulating B cells and found major perturbations within the mucosal B cell compartment, including an expansion of naive B cells and IgG+ plasma cells with curtailed diversity and maturation. These findings suggest that B cells play an important role in the pathogenesis of UC[28]. Nevertheless, the mechanism of how *FMR1* regulates naive B cells requires further study.

CONCLUSION

In conclusion, our study analysed the diagnostic value of m6A and ARGs in predicting the occurrence of UC. A total of

four key genes (FMR1, BAG3, P4HB and TP53INP2) were identified and verified using animal models, providing a foundation for the clinical diagnosis and treatment of UC. However, m6A and ARGs how to participate in the occurrence and development of UC, as well as the genes identification are as possible markers for assessing UC severity and developing innovative UC targeted therapeutic approaches. The specific regulatory mechanisms of these genes need further experimental research and clinical application research.

ARTICLE HIGHLIGHTS

Research background

Both N6-methyladenosine (m6A) methylation and autophagy are considered relevant to the pathogenesis of ulcerative colitis (UC). However, a systematic exploration of the role of the combination of m6A methylation and autophagy in UC remains to be performed.

Research motivation

In this study, we used publicly available data related to UC and comprehensive bioinformatics methods to elucidate the autophagy-related genes of m6A with a diagnostic value for UC, thereby contributing to the development of treatment options for patients with UC.

Research objectives

To elucidate the autophagy-related genes of m6A with a diagnostic value for UC.

Research methods

The correlation between m6A-related genes and autophagy-related genes (ARGs) was analysed. Finally, gene set enrichment analysis (GSEA) was performed on the characteristic genes. Additionally, the expression levels of four characteristic genes were verified in DSS-induced colitis in mice.

Research results

GSEA indicated that BAG3, P4HB and TP53INP2 were involved in the inflammatory response and TNF-α signalling *via* NF- κB. Furthermore, polymerase chain reaction results showed significantly higher mRNA levels of BAG3 and P4HB and lower mRNA levels of FMR1 and TP53INP2 in the DSS group compared to the control group.

Research conclusions

This study identified four m6A-ARGs that predict the occurrence of UC, thus providing a scientific reference for further studies on the pathogenesis of UC.

Research perspectives

The specific regulatory mechanisms of these genes need further experimental research and clinical application research.

FOOTNOTES

Author contributions: Liu XY and Qian D authored the paper and contributed equally to this work; Dai YC conceived and designed the experiments; Zhang YL, Liu ZX, and Chen YL performed the experiments; Que RY analyzed the data; Cao HY provided reagents/materials/analysis tools; all authors have read and approved the final manuscript.

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Institutional animal care and use committee statement: All animal experiments conformed to the internationally accepted principles for the care and use of laboratory animals (No. PZSHUTCM210611001, the Animal Ethics Committee of the Shanghai University of Traditional Chinese Medicine).

Clinical trial registration statement: This study is registered at Chinese Clinical Trial Registry. The registration identification number is ChiCTR2300068348.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All authors report no conflicts of interest in this work.

Data sharing statement: The following publicly available datasets were analyzed in this study: https://www.ncbi.nlm.nih.gov/, http://www.autophagy.lu/index.html.

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CASE REPORT

Demyelinating neuropathy in patients with hepatitis B virus: A case report

Xiao-Xiao Yan, Jin Huang, Jing Lin

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Abstract

BACKGROUND

Hepatitis B rarely leads to demyelinating neuropathy, despite peripheral neuropathy being the first symptom of hepatitis B infection.

CASE SUMMARY

A 64-year-old man presented with sensorimotor symptoms in multiple peripheral nerves. Serological testing showed that these symptoms were due to hepatitis B. After undergoing treatment involving intravenous immunoglobulin and an antiviral agent, there was a notable improvement in his symptoms.

CONCLUSION

Although hepatitis B virus (HBV) infection is known to affect hepatocytes, it is crucial to recognize the range of additional manifestations linked to this infection. The connection between long-term HBV infection and demyelinating neuropathy has seldom been documented; hence, prompt diagnostic and treatment are essential. The patient's positive reaction to immunoglobulin seems to be associated with production of the antigen-antibody immune complex.

Key Words: Hepatitis B virus infection; Extrahepatic manifestations; Demyelinating neuropathy; Intravenous immunoglobulin; Electroneuromyography; Case report

Core Tip: We report an exceptional case of demyelinating neuropathy in an individual with hepatitis B virus (HBV) infection, emphasizing the importance for clinicians to consistently take this into account when making a diagnosis. The underlying disease process and mechanisms of peripheral neuropathy following HBV infection are still unknown. The patient's favorable reaction to immunoglobulin suggests the potential of long-term immune-induced neuropathy.

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INTRODUCTION

In 2015, the World Health Organization estimated that there were approximately 257 million individuals suffering from chronic hepatitis B (CHB), a liver disease characterized by long-term inflammation, due to continuous infection with the hepatitis B virus (HBV)[1]. The Western Pacific and African regions accounted for 68% of these individuals. Approximately 650000 individuals across the globe succumb annually due to CHB-related complications, including cirrhosis and hepatocellular carcinoma[2,3]. Currently, there are around 70 million individuals in China who have contracted HBV, and approximately 20 to 30 million of them are CHB patients[3], which poses a significant burden on both the families of these patients and the society as a whole. Extrahepatic manifestations, such as serum sickness-like syndrome, polyarthritis, polyarteritis nodosa (PAN), glomerulonephritis, cryoglobulinemia, and various neurological disorders, are occasionally observed in addition to the common manifestations of the affected liver, such as icteric hepatitis, ascites, cirrhosis, and liver cancer[4]. In this article, we describe an elderly gentleman who exhibited demyelinating neuropathy as the initial indication of HBV infection. Treatment with antiviral therapy and intravenous immunoglobulin (IVIG) led to a remarkable recovery. It is important to consider the potential for HBV infection in cases of demyelinating neuropathy, despite its low occurrence rate of 0.04%[5].

CASE PRESENTATION

Chief complaints

A previously healthy 64-year-old man was referred the Department of Neurology at our hospital after presenting with numbness and weakness five months previously.

History of present illness

The patient initially noticed numbness in the lower legs and on the ventral side of the fingertips that gradually progressed upwards to the wrists and ankles on both sides. In addition to numbness, he also experienced soreness and swelling of the muscles. He attended the local hospital for treatment and underwent cervical and lumbar magnetic resonance imaging, which revealed normal cervical and lumbar spine parameters. He was given methyl cobalamin tablets, but this treatment was ineffective. One month ago, he felt weak and was no longer able to walk independently. In the previous week, the patient began to experience nocturnal lower limb twitching, which occurred several times each night.

History of past illness

The patient had no previous medical history.

Personal and family history

The patient had no related family history.

Physical examination

During the neurological examination, it was observed that the proximal muscle strength was 4/5 and distal muscle strength was 4/5 in the limbs. Additionally, his muscle tone was low and the bilateral brachial biceps, triceps, knee, and Achilles tendon reflexes were all decreased. The distal limbs showed the greatest decrease in temperature and pain perception, and both lower limbs exhibited a negative Babinski sign. No evidence of altered consciousness, linguistic impairment, or cranial nerve paralysis was present.

Laboratory examinations

Laboratory findings revealed normal routine blood counts, liver function, kidney function, and blood sugar. The level of Vitamin B12 was within the normal range. An increase of 4 mm/h in erythrocyte sedimentation rate was noted. There was no evidence of anti-nuclear, anti-DNA, anti-Ro antibody, anti-La antibody, or anti-neutrophil cytoplasmic antibodies

(ANCAs), which include proteinase 3 (PR3)-ANCAs and myeloperoxidase (MPO)-ANCAs, and there were no detectable serum cryoglobulins. Immunoelectrophoretic results were negative. Urine levels were as follows: κ light chain < 7.28 mg/L, λ light chain < 4.00 mg/L, and κ/λ light chain ratio 1.82. Hepatitis B surface antigen (HBsAg), hepatitis B core antibody, and hepatitis B e antibody were positive. Test results for hepatitis B surface antibody (HBsAb) and envelope antigen (HBeAg) were negative. Blood HBV DNA level was 6.14E+02 IU/mL. According to cerebrospinal fluid analysis, white blood cell concentration was 2×10^6/L, red blood cell concentration was 0×10^9/L, glucose concentration was 3.61 mmol/L, and protein concentration was 465.78 mg/L. The patient did not have antibodies against human immunodeficiency virus, rubella virus, *Campylobacter jejuni*, *Treponema pallidum*, Epstein-Barr virus, herpes simplex virus, and ganglioside (GD1a, GQ1b, GM1, and GM2).

Imaging examinations

The patient underwent brain and whole spine magnetic resonance imaging, and no abnormalities were found.

MULTIDISCIPLINARY EXPERT CONSULTATION

The patient was further evaluated *via* electroneuromyography, which revealed multiple peripheral neuropathies, suggesting the occurrence of motor and sensory demyelination (Table 1). We suggested that he undergo muscle biopsy for a clear diagnosis, but unfortunately, he refused.

FINAL DIAGNOSIS

Suspected demyelinating neuropathy related to HBV based on the above findings.

TREATMENT

Following the diagnosis of demyelinating neuropathy related to hepatitis B, our initial course of action was to administer lamivudine. To prevent persistence and replication of the virus, the IVIG dose of 400 mg/kg was given for 5 d, as corticosteroid treatment may encourage these processes.

OUTCOME AND FOLLOW-UP

The patient's weakness and numbness improved three weeks after treatment.

DISCUSSION

Around 20% of individuals infected with HBV display extrahepatic symptoms, with 5% experiencing neurological conditions such as peripheral neuropathy and myopathy[6]. In acute or chronic hepatitis, especially when peripheral nerve damage occurs in the advanced stage, after excluding other causes of peripheral nerve damage caused mainly by demyelination, the remaining conditions are classified as hepatic neuropathy. Chronic hepatitis is accompanied by peripheral neuropathy, and the main manifestations are abnormal sensation, weakness, significant decline or disappearance of the tendon reflex, and muscle atrophy. In addition, unilateral or bilateral nerves may be involved, and sphincter dysfunction and meningeal stimulation signs can also appear. There have been reports of different forms of peripheral neuropathy related to HBV, including Guillain-Barré syndrome; PAN; non-PAN vasculitis neuropathy; and chronic neuropathy syndromes, such as chronic polyneuropathy/polyradiculoneuropathy, mononeuritis multiplex, and chronic relapsing demyelinating polyneuropathy[6]. Distinct clinical and pathogenic variances exist among the various genotypes of HBV, potentially leading to diverse clinical presentations, treatment responses, and long-term prognoses based on the viral genotype/subtype. Clinical variations between subcategories and genetic types at different levels of extrahepatic manifestation are becoming more apparent, as indicated by growing evidence[7]. Guillain–Barré syndrome is the most common peripheral neuropathy associated with this viral disease[8,9]. Other polyneuropathies have been reported in CHB, although they are less common than Guillain–Barré syndrome. Multiple peripheral mononeuropathies are even rarer than previously mentioned[9]. Tsukada *et al*[10] reported the initial instance of demyelinating polyneuropathy with HBV in 1987. Subsequently, there have been occasional observations of individuals experiencing peripheral neuropathy, along with increased transaminase levels and liver enlargement. In 2017, Lupescu and Dulamea documented the case of a 57-year-old female who exhibited improvement in both clinical and electromyographic aspects of her demyelinating polyneuropathy following steroid, IVIG and antiviral treatments[11]. Demyelinating neuropathy is a prevalent characteristic often observed in various conditions including leprosy, diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus (also referred to as connective tissue disorders), sarcoidosis, primary systemic vasculitis, and paraneoplastic syndromes[12]. In our patient, chronic multiple demyelinating peripheral neuropathies were the first

Table 1 Nerve conduction study on admission

	Latency (ms)	Amplitude (mv)	Conduction velocity (m/s)
R-Ulnar nerve (m)			
Wrist – ADM	3.65	7.3	
Bl. elbow – wrist	9.38	6.4	33.5
Ab. elbow – Bl elbow	10.7	5.9	78
R-Median (m)			
Wrist – APB	3.92	5.2	
Elbow – Wrist	12	4.8	33.4
R-Tibial (m)			
Ankle – Abd hal	5.9	4.9	
Popliteal fossa – Ankle	17.1	3.0	32.9
R-Peroneal (m)			
Ankle – EDB	7.22	3.3	
Bl. Fib. head – Ankle	18.2	2.5	24.8
Ab. Fib. head - Bl. Fib. head	20.3	2.5	45.2
R-Ulnar nerve (s)			
Wrist – Digit V	2.15	4.7	48.8
Median (s)			
Wrist – Digit II	2.37	18.1	48.5
Superficial peroneal (s)			
Lower leg – Ankle	2.14	6.1	51.4
Sural (s)			
Mid lower leg – Lat alleolus	2.42	6.2	42.1

Ab: Above; Abd hal: Abductor halluces; ADM: Abductor digiti minimi; APB: Abductor pollicis brevis; Bl: Below; EDB: Extensor digitorum brevis; m: Motor study; s: Sensory study.

manifestation of hepatitis B. Hence, it is crucial to emphasize the significance of conducting a thorough assessment of the patient's epidemiological background, liver function, and serological examinations to detect potential HBV infection in individuals suffering from unidentified peripheral neuropathy. Moreover, the patient's liver function was normal, and the degree of neurological damage was inconsistent with the degree of liver function damage. None of the reported cases have exhibited disease exacerbation or severity of demyelinating neuropathy that correlated precisely with the HBV load [12]. The exact cause of demyelinating neuropathy in individuals with HBV infection remains unclear. Studies in this area suggest that the lesion results from the action of the virus itself on nerve fibers or perhaps from deposits of immune complexes on the vasa nervorum of the nerves, leading to vasculitis and consequent ischemia of the nerve fibers[13-15]. Replication of the virus or deposition of immune complexes directly injures the blood vessels, leading to vasculitis. Activation of the complement system initiates inflammation that later leads to endothelial damage. PAN, a condition that primarily affects medium-sized arteries and causes tissue death, is responsible for the majority of fatalities in patients. Significant evidence from the 1970s has demonstrated a robust correlation between the presence of HBV infection and the occurrence of PAN[16]. Testing positive for hepatitis B surface antigen (HBsAg+) can result in vasculitis, commonly appearing as PAN, which often occurs early in the progression of the illness and might be the initial sign of HBV infection. When linked with chronic active Hepatitis B, there is a reasonably prevalent association with demyelinating neuropathy and PAN. Our patient exhibited signs of chronic active Hepatitis B and multifocal sensorimotor mononeuropathy, a condition similar to vasculitis neuropathies such as PAN. The immediate effect of the virus on nerve fibers or the build-up of HBsAg and HBeAg immune complexes on the vasa nervorum may induce neuron damage related to the immune response, and could potentially lead to peripheral neuropathies[17]. Unfortunately, this patient refused muscle biopsy; however, the improvement in his symptoms following immunosuppressive therapy seems to suggest an immune-related pathogenesis. Furthermore, some studies suggest that antiviral medications such as interferon-α2b, lamivudine, or a combination of these substances exhibit efficacy in the treatment of HBV-related demyelinating neuropathy[18]. Scholars recently disclosed the effectiveness of brief corticosteroid treatment, succeeded by lamivudine and plasma exchange, for demyelinating neuropathy associated with hepatitis B[15,19]. In our study, we

successfully treated patients with immunoglobulin by inhibiting HBV replication with lamivudine without exacerbating liver dysfunction. This approach can help patients avoid the confusion of using corticosteroids in the acute stage of hepatitis, while immunomodulatory therapy should be administered to accumulate clinical experience.

CONCLUSION

Patients infected with HBV display demyelinating neuropathy as described in our patient. The fundamental disease process and functioning of peripheral neuropathy after HBV infection remain unclear. Additionally, the positive effect of immunoglobulin suggests the potential existence of chronic neuropathy triggered by the immune system.

FOOTNOTES

Author contributions: Yan XX managed the patient and wrote the manuscript; Huang J participated in data collection and revised the manuscript; Lin J was responsible for clinical management of the patient, and drafted and edited the manuscript; all the authors thoroughly reviewed and gave their approval for the final version of the manuscript.

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CASE REPORT

Successful treatment of *Purpureocillium lilacinum* pulmonary infection with isavuconazole: A case report

Xue-Lin Yang, Jun-Yu Zhang, Jian-Min Ren

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Abstract

BACKGROUND

Purpureocillium lilacinum (*P. lilacinum*) is a saprophytic fungus widespread in soil and vegetation. As a causative agent, it is very rarely detected in humans, most commonly in the skin.

CASE SUMMARY

In this article, we reported the case of a 72-year-old patient with chronic lymphocytic leukemia who was admitted with cough and fever. Computed tomography revealed an infection in the right lower lobe. Bronchoalveolar lavage fluid culture and metagenomic next-generation sequencing were ultimately confirmed to have a pulmonary infection with *P. lilacinum*. She was eventually discharged with good outcomes after treatment with isavuconazole.

CONCLUSION

Pulmonary infection with *P. lilacinum* was exceedingly rare. While currently there are no definitive therapeutic agents, there are reports of high resistance to amphotericin B and fluconazole and good sensitivity to second-generation triazoles. The present report is the first known use of isavuconazole for pulmonary *P. lilacinum* infection. It provides new evidence for the characterization and treatment of clinical *P. lilacinum* lung infections.

Key Words: *Purpureocillium lilacinum*; Pulmonary infection; Isavuconazole; Case report

Core Tip: Pulmonary infection caused by *Purpureocillium lilacinum* (*P. lilacinum*) is exceedingly rare, with uncharacteristic clinical symptoms, signs, and imaging findings. In this case, we reported an older woman with chronic lymphocytic leukemia, long-standing ibrutinib, poor immune function, and fever and cough was admitted to a hematologic department. The patient was diagnosed with *P. lilacinum* pulmonary infection based on bronchoalveolar lavage fluid culture and metagenomic next-generation sequencing. Conventional antifungal agents often have inherent resistance. Isavuconazole was found to have good safety and efficacy. This is the first known use of isavuconazole for pulmonary *P. lilacinum* infection. After treatment with isavuconazole, the clinical symptoms of cough and fever improved, and the patient was discharged from the hospital.

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INTRODUCTION

Purpureocillium lilacinum (*P. lilacinum*) is a saprophytic fungus widely found in soil and vegetation and a common contaminant detected in laboratories and instruments. In 1977, Takayasu *et al*[1] first reported that *P. lilacinum* causes skin infections in humans[1]. However, since then, only a few sporadic cases of infection have been reported worldwide. These cases were found in both immunocompetent and immunocompromised populations, most commonly in the skin but exceedingly rarely in the lungs[2,3]. While there are no standardized treatments for *P. lilacinum* infection, there are reports of high resistance to amphotericin B and fluconazole and good sensitivity to second-generation triazoles[4,5]. Herein, we reported a case of pulmonary infection caused by *P. lilacinum* successfully treated with isavuconazole, and reviewed the relevant literature.

CASE PRESENTATION

Chief complaints

A 72-year-old female with fever and chest tightness coughing sputum for 1 month presented at our emergency department.

History of present illness

The patient had no history of present illness.

History of past illness

She had an 11-month history of chronic lymphocytic leukemia and was treated with long-term, regular ibrutinib antitumor therapy.

Personal and family history

The patient had no notable personal or family history.

Physical examination

Her physical examination was as follows: Clear consciousness, blood pressure 112/63 mmHg (14.896/8.379 kPa), respiratory rate 24/min, heart rate 102/min, body temperature 38.2 °C, fingertip oxygen saturation 98%, and moist rales in the right lung.

Laboratory examinations

White blood cell 10.6 × 10^9/L (Normal range: 3.5 × 10^9/L to 9.5 × 10^9/L), neutrophils percentage 70.2% (Normal range: 40% to 75%), hemoglobin 98 g/L (Normal range: 115 g/L to 150 g/L), platelets 310 × 10^9/L (Normal range: 125 × 10^9/L to 350 × 10^9/L), and C-reactive protein 67 mg/L (Normal range: 0 mg/L to 8 mg/L). Procalcitonin 0.35 ng/mL (Normal range: 0 ng/mL to 0.05 ng/mL). Fungal D-glucan, galactomannan test and aspergillus IgG antibodies were all normal.

Imaging examinations

Computed tomography (CT) revealed an infection in the right lower lobe (Figure 1A and B).

Additional diagnostic work-up

After admission to the hospital, the patient was given oxygen, and because her etiology was unknown, we administered empiric cefoperazone-sulbactam for anti-infection. Three d post-treatment, the patient remained feverish and chest

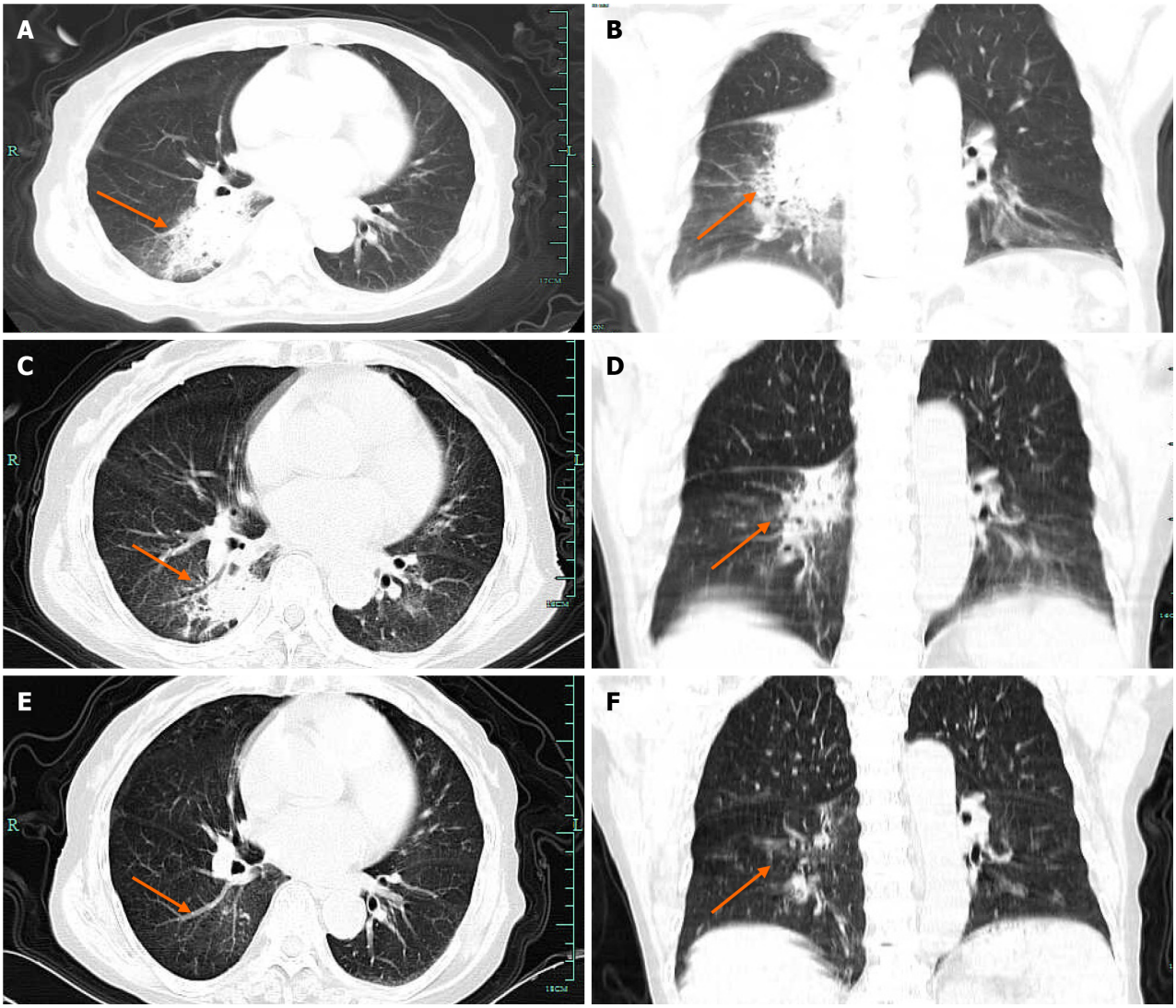

Figure 1 Chest computed tomography on admission and post-treatment. A: Pulmonary consolidation in the posterior segment of the right lower lobe at admission [axial thorax computed tomography (CT) view); B: Mass consolidation in the posterior segment of the right lower lobe at admission (coronal thorax CT view); C: Lesion reduction in pulmonary consolidation in the posterior segment of the right lower lobe after 2 wk of isavuconazole treatment (axial thorax CT view); D: Lesion reduction in pulmonary consolidation in the posterior segment of the right lower lobe after 2 wk of isavuconazole treatment (coronal thorax CT view); E: Significant absorption of pulmonary consolidation in the posterior segment of the right lower lobe at 6 wk of discharge (axial thorax CT view); F: Significant absorption of pulmonary consolidation in the posterior segment of the right lower lobe at 6 wk of discharge (coronal thorax CT view).

tightness remained unresolved. Bronchoscopy was performed to identify the causative agent. On day 7, the colonies were approximately 3.0 cm in diameter, and the purplish colony were concentric (Figure 2A and B). Microscopic examination of the microbiota was performed, and clear, colorless, branching hyphae were observed, and the spores were infarct (Figure 2C). *P. lilacinum* was identified by the Vitek® MS Full Automated Rapid Microbiota Spectrometry System with a confidence interval of 99.9%. *In vitro* drug susceptibility for *P. lilacinum* was as follows: Amphotericin B = 8 μg/mL, fluconazole = 16 μg/mL, voriconazole = 1 μg/mL, and isavuconazolezole = 1 μg/mL. A sample of 1.5-3 mL of bronchoalveolar lavage fluid (BALF) from the patient was submitted for metagenomic next-generation sequencing (mNGS) analysis, which showed 100% homology with ATCC10114 (AY213665.1) from the GenBank database, and was classified as *P. lilacinum*.

FINAL DIAGNOSIS

The patient was diagnosed with *P. lilacinum* pulmonary infection and chronic lymphocytic leukemia based on medical history, physical examination, laboratory tests, imaging, BALF culture, and mNGS.

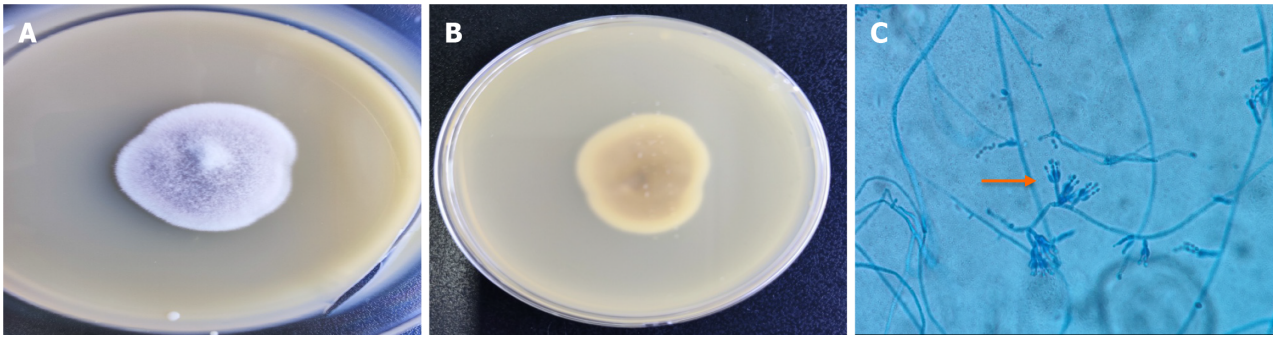

Figure 2 Culture and microscopic examination of the microorganisms. A: Salmonella glucose agar, 28 °C, culture for 7 d, the purplish colony were concentric on the front; B: Yellowish-pale colonies on the back; C: Colorless hyaline branching filaments were observed under light microscopy, and the spores were erect, with a broomy tip and a cone-shaped, fine bony tip at the base of the flask. The spores were mainly oval or near-spherical in shape, and the chains were cylindrical or discrete.

TREATMENT

Based on pathogenic studies and *in vitro* drug sensitivity, we used voriconazole 200 mg tablets every 12 h for antifungal therapy. After 3 d, the patient presented with hallucinations and involuntary tremors of the hands and feet, which were considered adverse events associated with voriconazole. The patient stopped using voriconazole and was given isavuconazole tablets (200 mg every 8 h for the first 48 h, 200 mg once daily after 48 h) followed by antifungal therapy. The hallucinations and tremors of the hands and feet disappeared after 12 h of voriconazole. After 72 h of administration, her body temperature returned to normal, and cough and chest tightness improved after 1 wk.

OUTCOME AND FOLLOW-UP

The patient was discharged from the hospital on day 14, continuing to take isavuconazole for 3 wk, during which time she experienced no significant adverse effects. At one week after discharge, re-examination using chest CT revealed reduced lung lesions (Figure 1C and D). At 6 wk after discharge, chest CT was performed again, and the pulmonary lesions were essentially absorbed (Figure 1E and F).

DISCUSSION

P. lilacinum is a fungus found in a wide range of habitats. In 1974, Samson classified it as a penicillium-like genus based on the characteristic cone-shaped distortion of the top of the flask[6]. Cultural identification of *P. lilacinum* is based on its pale-violet colony color and characteristic flask morphology, and genetic sequencing of the strain may provide a more accurate identification method for clinicians[7]. *P. lilacinum* is rarely found in humans and is generally not considered a pathogenic mold. However, sporadic cases have been reported worldwide since 1977, when it was first described as a skin infection. It predominantly presents as a skin infection, posing the highest threat for immunocompromised patients. Sprute *et al*[8] analyzed 101 cases of invasive *P. lilacinum* infection, found that the youngest patient was 31, and the oldest was 64; male accounted for 61.1%; 31 cases (30.7%) with hematologic and neoplastic disease, 27 (26.7%) with steroid therapy, 26 (25.7%) with solid organ transplantation, and 19 (18.8%) with diabetes mellitus, with the skin being the most common site of infection (36.6%); fever, cough, and dyspnoea were the most common clinical symptoms of pulmonary infection; overall mortality was 21.8%[8].

In the present case, an older woman with chronic lymphocytic leukemia, long-standing ibrutinib, poor immune function, and fever and cough was admitted to a hematologic department and initially considered to be infected with bacteria. She was injected with cefoperazone-sulbactam as an anti-infection therapy, with no good effect.

Identifying *P. lilacinum* is challenging, and its histomorphology is very similar to that of *Aspergillus* and other hyaluro-cephalus pathogens[9]. There are no characteristic imaging findings. In chest CT, nodular infiltrates and cavitary lesions were common findings[8]. In our case, there was a probability of progression from pulmonary consolidation to cavitary lesions without any treatment. To further identify the causative organisms, we cultured BALF on the medium for 7 d, observed the growth of a violet-colored colony on the dishes, and observed the microscopically characteristic infarct morphology of the bottle. Microbiome profiling and BALF mNGS further identified *P. lilacinum*, which provided laboratory evidence for diagnosing the pathogen.

There are only a few clinical cases of *P. lilacinum*, so no standard antifungal regimens exist[10]. Aguilar *et al*[11] showed early on that amphotericin B, miconazole, itraconazole, fluconazole, and flucytosine are less active against penicillium [11]. González performed *in vitro* drug susceptibility assays on 22 strains of *Aspergillus pallidus*, revealing that isavuconazole had a minimum inhibitory concentration of 0.2 to 2 μg/mL, amphotericin B 4 to 16 μg/mL, itraconazole 1 to 16 μg/mL, fluxonazole 16 to 64 μg/mL, voriconazole 0.5 to 4 μg/mL, posaconazole 0.5 to 2 μg/mL, and ravuconazole

0.25 to 2 μg/mL[12]. By analyzing clinical isolates of infected cases, Sprute *et al*[8] showed high resistance to amphotericin B and excellent *in vitro* activity against second-generation triazole[8]. In this case, we also performed *in vitro* drug susceptibility assays on isolates showing poor antifungal activity of amphotericin B and fluconazole, and excellent antifungal activity of voriconazole and isavuconazole, which is consistent with the previous literature. Our patient was administered voriconazole tablets, but on day 3 she developed hallucinations and involuntary tremors of the hands and feet, so the treatment was stopped. Isavuconazole is a second-generation triazole antifungal approved by the United States Food and Drug Administration in 2015 for treating invasive aspergillosis and mold diseases. It inhibits cytochrome woolly steroid 14 alpha-demethylation enzyme (CYP51), disrupts the structure and function of the fungal cell membrane by blocking the synthesis of ergosterol on the fungal cell membrane, has a higher affinity for fungal side chain CYP51 protein in its structural molecules, has a broad antifungal spectrum, and includes fungi resistant to other triazole antifungals[13]. In their study, Maertens *et al*[14] conducted an international multicenter, randomized, double-blind, phase III Secure clinical trial involving patients with a clinical diagnosis of invasive mold disease who were initially treated with isavuconazole and voriconazole, finding similar overall response rates ($P > 0.05$), with adverse drug reaction rates of 42% and 60%, respectively ($P < 0.001$), and lower visual, psychiatric, and liver toxicity associated with isavuconazole than with voriconazole[14]. In the vital study, Thompson *et al*[15] found that 38 patients with rare fungal diseases (including cryptococcosis, 9 cases of paracoccosis, 9 cases of coccidiosis, 7 cases of histoplasmosis, and 3 cases of blastomycosis) were treated with isavuconazole, with an overall response rate of 63.2% and stable disease progression in 21.1%, suggesting that isavuconazole is also an effective drug for rare invasive fungal diseases[15]. Moreover, compared with posaconazole, isavuconazole has a cost-effective option for treating invasive mold diseases in high-risk hematological patients[16]. We could identify only one case of a cutaneous infection caused by *P. lilacinum* used to treat a patient who was successfully cured by PubMed[17]. Huang *et al*[18] conducted a pharmacokinetic study of intravenous isavuconazole in healthy subjects, finding that lung tissue/plasma concentration was 1.438[18]. Caballero-Bermejo *et al*[19] found that isavuconazole was a drug with a tolerable safety profile that achieved adequate concentrations in the lung[19]. The bioavailability of isavuconazole tablets was 98%. Therefore, we switched to oral isavuconazole to continue antifungal therapy. To the best of our knowledge, this is the first known use of isavuconazole for pulmonary *P. lilacinum* infection.

After 12 h of voriconazole discontinuation, the patient's hallucinations and autonomic tremor disappeared, further confirming voriconazole-associated adverse effects. After 1 wk of treatment with isavuconazole, the clinical symptoms of cough and fever improved, and the patient was discharged from the hospital on day 14, continuing to take isavuconazole for 3 wk, during which time she experienced no significant adverse effects. At 6 wk after discharge, chest CT was performed again, and the pulmonary lesions were essentially absorbed.

CONCLUSION

Pulmonary infection caused by *P. lilacinum* is exceedingly rare, with uncharacteristic clinical symptoms, signs, and imaging findings. Pathogenic detection is complex, and conventional antifungal agents often have inherent resistance. In our patient infected with *P. lilacinum*, isavuconazole was found to have good safety and efficacy, but due to the small number of patients, more studies are needed to determine the optimal treatment strategy.

FOOTNOTES

Author contributions: Zhang JY conceived and designed the experiments, was responsible for the revision of the manuscript for important content; Yang XL collected information of case and drafted the manuscript; Ren JM performed the microbiological analyses. All authors critically reviewed and approved the final manuscript.

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CASE REPORT

Cellular angiofibroma arising from the rectocutaneous fistula in an adult: A case report

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Abstract

BACKGROUND

Rectocutaneous fistulae are common. The infection originates within the anal glands and subsequently extends into adjacent regions, ultimately resulting in fistula development. Cellular angiofibroma (CAF), also known as an angiomy-

ofibroblastoma-like tumor, is a rare benign soft tissue neoplasm predominantly observed in the scrotum, perineum, and inguinal area in males and in the vulva in females. We describe the first documented case CAF that developed within a rectocutaneous fistula and manifested as a perineal mass.

CASE SUMMARY

In the outpatient setting, a 52-year-old male patient presented with a 2-year history of a growing perineal mass, accompanied by throbbing pain and minor scrotal abrasion. Physical examination revealed a soft, well-defined, non-tender mass at the left buttock that extended towards the perineum, without a visible opening. The initial assessment identified a soft tissue tumor, and the laboratory data were within normal ranges. Abdominal and pelvic computed tomography (CT) revealed swelling of the abscess cavity that was linked to a rectal cutaneous fistula, with a track-like lesion measuring 6 cm × 0.7 cm in the left perineal region and attached to the left rectum. Rectoscope examination found no significant inner orifices. A left medial gluteal incision revealed a thick-walled mass, which was excised along with the extending tract, and curettage was performed. Histopathological examination confirmed CAF diagnosis. The patient achieved total resolution during follow-up assessments and did not require additional hospitalization.

CONCLUSION

CT imaging supports perineal lesion diagnosis and management. Perineal angiofibromas, even with a cutaneous fistula, can be excised transperineally.

Key Words: Angiofibroma; Perineal mass; Rectocutaneous fistula; Anorectal fistula; Anal fistula; Case report

Core Tip: Although uncommon, certain typical clinical conditions, such as rectal cutaneous fistulas, may manifest in complex presentations, as demonstrated in this patient. Notably, recurrence and complications such as incontinence are frequently associated with complex fistulas and incomplete mapping. Therefore, establishing a definitive diagnosis through a precise mapping of the fistula is imperative before surgical intervention. Computed tomography imaging is useful for detecting, understanding and managing perineal lesions. Perineal angiofibromas can be removed *via* transperineal excision, even if linked to a rectal cutaneous fistula. In such complex cases, a personalized and careful diagnostic approach is crucial.

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INTRODUCTION

Cellular angiofibroma (CAF), also known as an angiomyofibroblastoma (AMF)-like tumor, is a rare benign soft tissue neoplasm that is predominantly observed in the scrotum, perineum, and inguinal area in males and the vulva in females. This description was first published by Nucci *et al*[1] in 1997. Microscopically, CAFs are distinguished by small- to medium-sized vessels with hyaline fibrosis and bland spindle cells[2]. The diagnosis of CAF can be challenging, particularly in cases outside the genital region, where more common pathologies may initially take precedence. Furthermore, its pathological attributes are similar to those of other mesenchymal tumors. Thus, immunohistochemistry is instrumental in separating CAF from other mesenchymal tumors, including those with the potential for higher aggressiveness[3,4].

Precise diagnosis of perianal fistulas poses an ongoing difficulty for medical professionals. Most often, perianal abscesses begin with an infection of the anal gland. Obstructing these glands can result in stagnation, excessive bacterial growth, and abscess formation within the intersphincteric groove[5]. Multiple drainage pathways exist for these abscesses, the most typical of which involve either downward extension into the anoderm or lateral progression involving the external sphincter muscle and extending into the ischiorectal fossa. Less prevalent dissemination patterns include expansion into the supralevator space and advancement within the submucosal plane. After abscess drainage, whether through surgical intervention or spontaneous resolution, there is the potential for septic foci to persist, and the draining tract may undergo epithelialization, giving rise to the development of a chronic anorectal fistula. Approximately 60% of abscesses eventually result in the formation of a fistula[6].

To date, no description of a CAF derived from a rectal-cutaneous fistula has been reported. Here, we describe the case of a 52-year-old man with a CAF that arose from a rectocutaneous fistulous tract that extended to the perineal region.

CASE PRESENTATION

Chief complaints

A perineal mass, present for 2 years, that had gradually increased in size over time, causing discomfort.

History of present illness

A 52-year-old Asian man visited the outpatient department for discomfort associated with a perineal mass that he had first noticed 2 years prior. Initially, the patient experienced pain but did not seek medical assistance because the recurrent condition had a negligible impact on his daily routine. However, the swelling gradually increased, leading to throbbing pain and minor scrotal abrasion.

History of past illness

The patient had a medical history of hypertension and dyslipidemia, which were managed with oral medication. He also had a surgical history of ureteroscopic lithotripsy 4 years prior and conventional hemorrhoidectomy 10 years prior. The patient's medical history revealed no evidence of underlying abdominal malignancy, inflammatory bowel disease, abdominal trauma, or other gastrointestinal disorders.

Personal and family history

No family history of abdominal neoplasms or inflammatory bowel disease was noted, and the patient exhibited regular social functioning and self-care abilities.

Physical examination

Vital signs, including blood pressure and body temperature, were within the normal ranges. Physical examination revealed a soft, well-defined, non-tender mass at the left buttock tracking towards the patient's perineum, without a visible opening. The preliminary diagnosis indicated a soft tissue tumor.

Laboratory examinations

Laboratory data, including white blood cell count, hemoglobin, neutrophils, lymphocytes, and electrolytes such as sodium and potassium, were within the normal range.

Imaging examinations

Computed tomography (CT) of the abdomen and pelvis revealed a swelling of the abscess cavity connected to a rectal cutaneous fistula. A track-like lesion (approximately 6 cm × 0.7 cm) was observed between the internal and external anal sphincters (Figure 1A). The superior aspect of the lesion was positioned within the intersphincteric plane, and the lower part extended into the perineum (Figure 1B). There was no evidence of invasion of the levator ani muscle or muscular plane of the gluteus, and the small intestine and mesentery appeared normal.

FINAL DIAGNOSIS

The definitive diagnosis was CAF.

TREATMENT

After bowel preparation using an enema, the patient was transferred to the operating room and placed in the prone position under epidural anesthesia. A protruding mass was identified at the 1 o'clock position. An incision was made *via* the left medial gluteal approach, and a thick-walled mass was encountered (Figure 2A). The mass was excised, and the identified tract was found to extend medially. The lesion was found to be 5.4 cm × 3.2 cm × 1.8 cm in size, well circumscribed, and connected to a track-like tissue (Figure 2B). The tract was assessed *via* digital examination, and no apparent link to the rectum was identified. The tract was then partially excised and curetted, and the skin was closed over a Penrose drain (Figure 2C). Histopathological examination of the specimen confirmed findings consistent with CAF. Grossly, the specimens were gray and elastic (Figure 3). Microscopically, the section showed tumors with well-circumscribed borders that were primarily composed of consistently uniform, short, and spindle-shaped cells within a fibrous stroma. The stroma was characterized by the presence of short bundles of delicate collagen fibers and numerous small-to medium-sized thick-walled vessels with hyaline and fibrotic vascular walls. The spindle cell component was moderately-to-highly cellular and was randomly distributed throughout the lesion, occasionally in a fascicular arrangement. The tumor cells were immunohistochemically positive for smooth muscle actin, focally positive for estrogen receptor and progesterone receptor, and negative for S100, cluster of differentiation 34, and desmin.

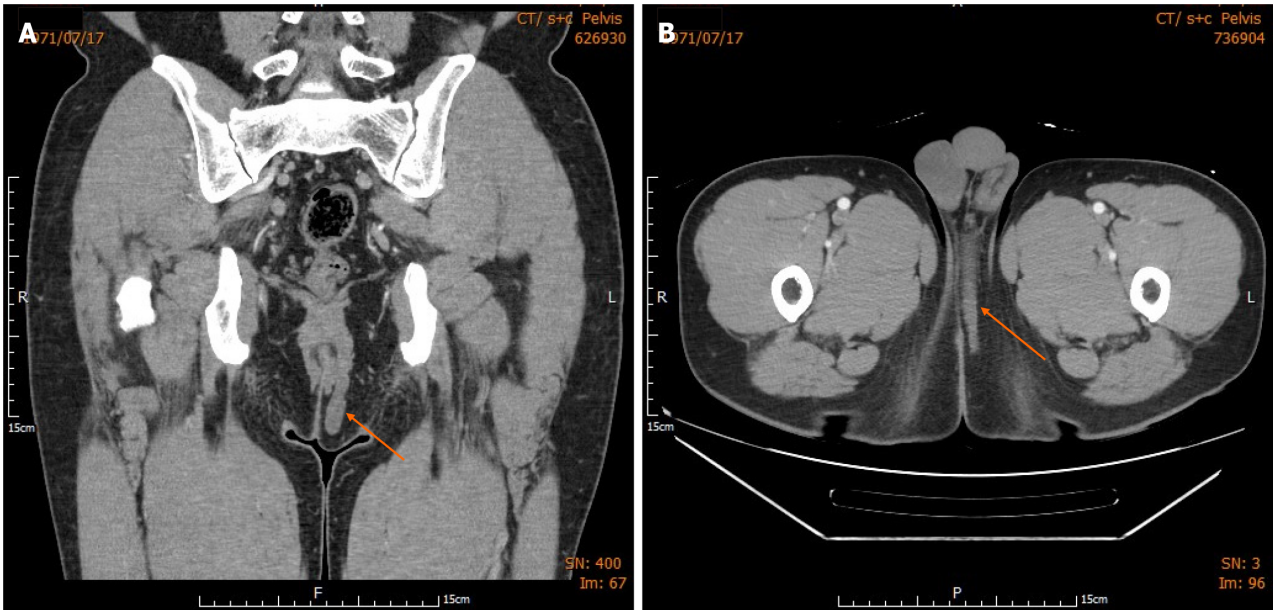

Figure 1 Abdominal and pelvic computed tomography. A: A track-like lesion, approximately 6 cm × 0.7 cm in size (orange arrow) is visible, which appears to originate from between the internal and external anal sphincters, with the superior part of the lesion lying in the intersphicteric plan; B: The lower part of the lesion (orange arrow) bulged into the perineum.

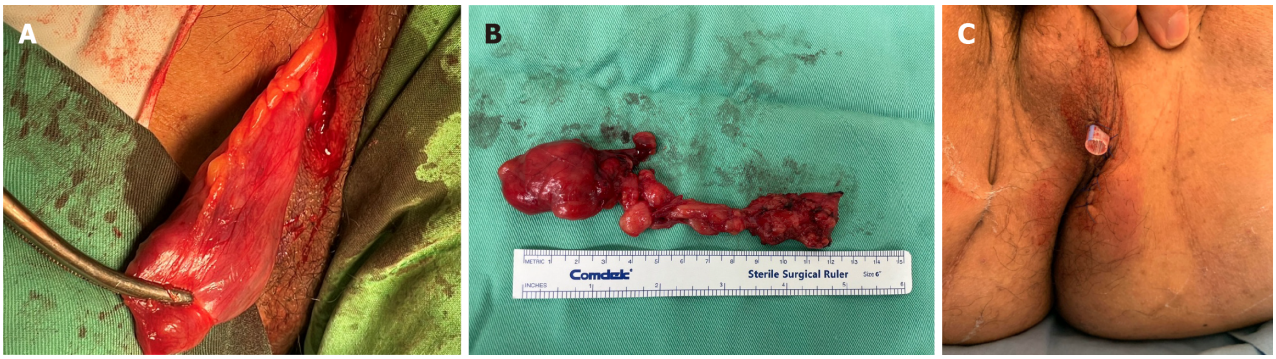

Figure 2 Surgical findings. A: A thick-walled cavity was discovered, and the communicating tract was identified going medially; B: The thick-walled mass with tract-like lesion measured approximately 12 cm in length; C: The skin was closed over a Penrose drain.

OUTCOME AND FOLLOW-UP

The patient had no complications postoperatively and was discharged on the 1st postoperative day. He was instructed to continue with routine dressings during the upcoming period, and throughout the 6-mo follow-up period, complete resolution of the fistulous tract was observed. The patient expressed satisfaction with the treatment outcome and no further hospitalization was necessary.

DISCUSSION

We describe the first documented case of a CAF arising from a rectocutaneous fistula that presented as a perineal mass. CAFs are benign mesenchymal tumors that feature spindle cells and conspicuous stromal blood vessels. This condition most frequently occurs in the inguinoscrotal or vulvovaginal regions, and the tumors exhibit the highest frequency in women during the fifth decade of life, whereas men are typically affected in their seventh decade[7]. The differential diagnosis of this neoplasm is broad and encompasses epithelioid leiomyoma, CAF, aggressive angiomyxoma, and AMF. In a series of 51 patients, extragenital CAF was discovered in locations that include the vulva-vagina, inguinal-scrota, retroperitoneum, and urethra, and the rectal-cutaneous fistula stie has not been reported previously[8]. In our study, the unusual tumor site posed considerable diagnostic challenges during the preoperative evaluation and management of the patient.

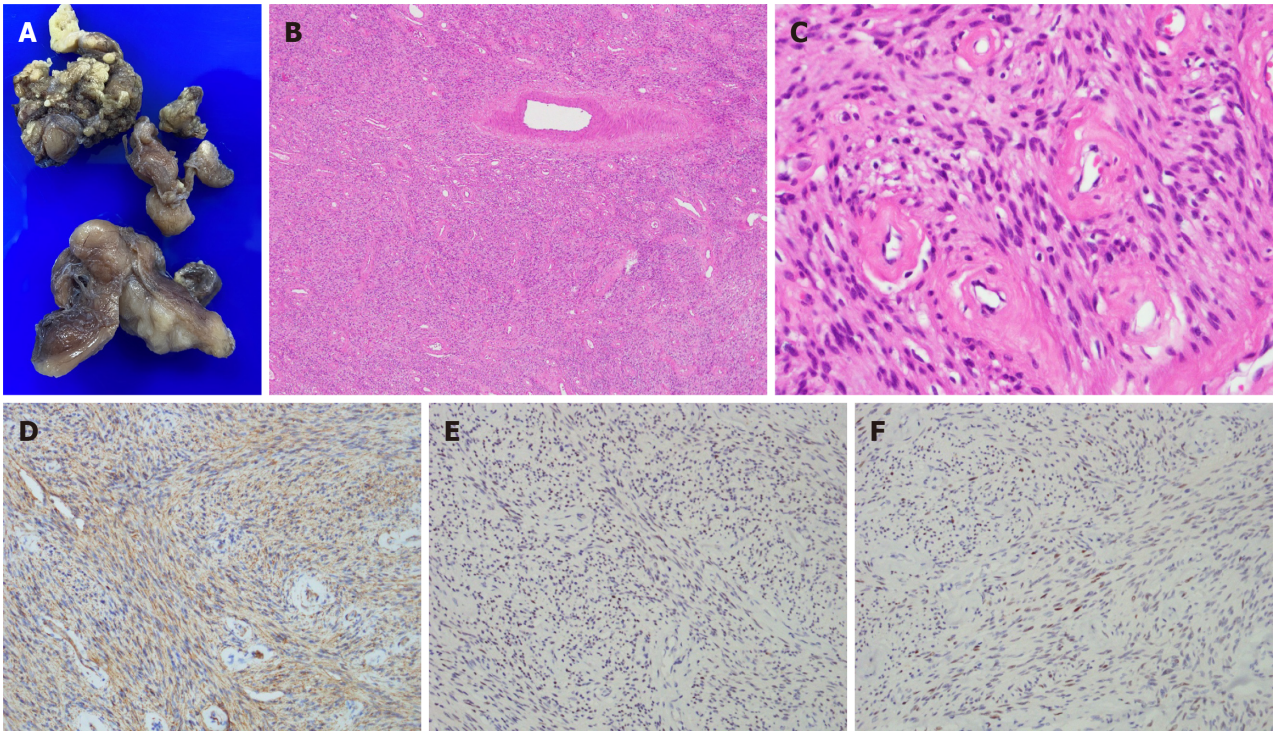

Figure 3 Pathological findings. A: Grossly, the excised tumors were gray and elastic; B: Cellular angiofibroma displayed numerous thick-walled blood vessels with wall hyalinization (hematoxylin and eosin [H&E] 40 ×); C: The stroma contained small uniform short spindle-shaped cells with fusiform nuclei and pale indistinct cytoplasm (H&E 400 ×); D: Immunohistochemistry was positive for smooth muscle actin; E: Immunohistochemistry of the estrogen receptor showed focal positivity; F: Immunohistochemistry of the progesterone receptor showed focal positivity.

The presence of a rectal cutaneous fistula reflects the chronic state of an ongoing perianal infection. It commonly presents as a granulating channel that develops between the anorectal and perianal regions or perineum. The onset of most fistulas is attributed to anorectal abscesses, and fistula development often occurs when an abscess drains spontaneously. Anal fistulas are predominantly caused by infected anal glands in more than 90% of patients that create pathways for the infection to traverse the anal lumen into the deep sphincter muscles, leading to chronic continuous perianal infection. The infection can gain access to the wall of the anal canal by passing through a fissure or another type of wound. Once established, fecal content usually maintains the patency of the infected tract[9]. A typical fistula comprises a passageway with both a primary (internal) entrance and a secondary (external) exit.

Rectal cutaneous fistulas are characterized by the continuous or sporadic release of purulent, mucous, or bloody discharge. When there is an intersphincteric extension or mechanical obstruction due to swelling, patients may have difficulty sitting and encounter hindrances during defecation[10]. It is usually transformed by perianorectal abscesses and is closely associated with perianal trauma, tuberculosis, malignancy, Crohn's disease, and radiation proctitis. Classification of the fistula route and its relationship to the anal sphincters has been established by CT or magnetic resonance imaging (MRI), which depict different anatomical locations. The classification system introduced by Parks *et al*[11] in 1976, which sorts anorectal fistulas into intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric categories, is the most commonly used and endorsed. This classification accurately describes the anatomical track of the fistula and is useful for predicting the complexity of the operative procedure to treat the fistula.

Radiologists have introduced the following alternative grading system for evaluating the outcomes of anorectal fistulae, known as the St. James's University Hospital classification, which incorporates axial plane landmarks, abscesses, and secondary extensions: 0, normal appearance; 1, simple linear intersphincteric fistula; 2, intersphincteric fistula with intersphincteric abscess or secondary fistulous tract; 3, trans-sphincteric fistula; 4, trans-sphincteric fistula with abscess or secondary track within the ischioanal or ischiorectal fossa; and 5, supralevator and translevator disease. Grades 1 and 2 typically lead to favorable outcomes, whereas less favorable results are commonly associated with grades 3–5, which often necessitates reoperation due to recurrence[12,13].

Our patient had experienced a perianal mass for a duration of 2 years before seeking medical attention, indicating that the formation of the fistulous tract and abscess likely predated this timeframe. Despite the resolution of the abscess, the fistulous tract remained intact. Most likely, the CAF emerged over time within the previous abscess cavity, with the internal entry of the fistulous tract positioned in the anal canal. The pathogenesis of rectal cutaneous fistulae is well established; however, the origin of the CAFs remains unclear. Several hypotheses have been proposed, including the possibility of monoallelic deletion of retinoblastoma 1 and forkhead box 1, both of which are located on chromosome 13q14, a region strongly implicated in disease pathogenesis[14]. As for the potential reasons behind CAF growth within a rectocutaneous fistula, we postulate that the presence of this benign mesenchymal tumor in such a specific anatomical location may be attributed to the chronic inflammation associated with the fistulous tract. Chronic inflammation is known to create a microenvironment that is conducive to tumorigenesis and promote cellular changes and the development of

neoplastic lesions[14]. Further research is needed to elucidate the precise mechanisms that link chronic inflammation, rectocutaneous fistula, and CAF development.

In the present case, the initial impression on physical examination was a soft tissue mass over the perineum. A rectal-cutaneous fistula was not diagnosed until CT was performed, and CT is often performed as a first-line examination to locate the perineal mass and define its anatomical relationship[15]. In addition to CT, endosonography and MRI can serve as diagnostic tools for perianal tumors and rectal cutaneous fistulas[16]. In the present case, the path of the fistulous tract within the perianal region was identified on the left side, traversed the intersphincteric area, and extended inferiorly into the perineum. Considering that the tract was a rectal-cutaneous fistula accompanied by a soft tissue tumor, total excision of the mass with marsupialization was performed. Surgery was initiated through a transperineal incision and tumor excision was performed without compromising rectal integrity. The procedure was performed successfully using a minimally invasive technique that aimed to achieve permanent closure of the fistula tract without functional impairment. While the surgeon may consider flatus incontinence a minor issue, it can be a profound embarrassment for the patient [12].

Here, we present the case of a patient who was diagnosed with the coexistence of a perianal fistula and CAF, with clear margins observed after surgical resection. Notably, CAFs are generally characterized by a benign clinical course and exhibit a minimal risk of recurrence at the resection site. Local excision with negative margins is the current standard treatment[17]. It necessitates careful consideration of CAF's growth location, thereby tailoring the surgical approach to the specific anatomical site involved. In the context of a retrospective study of patients with a vulvovaginal CAF[18], urinary catheterization was employed during the excision procedure to ensure the safety of the patients and prevent urethral injury. When dealing with CAF growth within a rectocutaneous fistula, unlike vulvovaginal CAF, it is imperative to utilize pre-operative imaging examinations and intraoperative physical examination to ensure the preservation of the sphincter muscles when ligating the fistula tract. In our study, the tract was completely resected, with no noted impairment of the sphincter function in the postoperative course.

CONCLUSION

Although uncommon, certain typical clinical conditions, such as rectal cutaneous fistulas, can appear in complex ways, as in the case presented here. Before surgery, it is essential to confirm the diagnosis and outline the fistula accurately. Complex fistulae and incomplete mapping often result in recurrence or incontinence. CT imaging is useful for spotting and understanding perineal lesions and aiding treatment planning. Perineal angiofibromas can be removed *via* transperineal excision, even if they are linked to a rectal cutaneous fistula. The findings of our study indicates that, for complex cases like this one, a personalized approach and careful diagnostic setup are crucial. The accumulation of similar cases and larger-scale studies may help identify the best treatment approach.

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FOOTNOTES

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CASE REPORT

Jaffe-Campanacci syndrome resulted in amputation: A case report

Jun Jiang, Min Liu

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Abstract

BACKGROUND

Jaffe-Campanacci syndrome (JCS) is a very rare syndrome. The treatment of JCS is more conservative, and most authors recommend that no surgery should be done in asymptomatic patients. The conventional concept holds that the natural course of non-ossifying fibromas (NOFs) grows with the development of bones, and the osteolytic region gradually stops expanding and self-healing through bone ossifying around the lesion and ossification within the lesion. But in this case, the bone lesions were potentially biologically aggressive, which led to severe limb deformities and pain.

CASE SUMMARY

We present the case of a 5-year-old girl with JCS presenting with not only NOF sand café-au-lait macules, but also showed features not mentioned before, severe limb pain, and at last resulted in amputation. She was admitted to our hospital after presenting with claudication and mild pain over her right thigh, which worsened when stretching or being touched. Skin examination revealed multiple café-au-lait macules on the neck, arm, axilla, and torso, including the nipples and perineum. Radiographs revealed multiple lytic lesions in the proximal part of the right humerus, distal part of the right clavicle, proximal and distal parts of the right femur, and proximal parts of the right tibia and fibula. Curettage and biopsy were performed on the distal part of the right femur. At the age of 7, the girl was re-admitted to our hospital for a pathological fracture in the middle in the right femur and underwent Intralesional excision, internal fixation, bone grafting, and spica casting. At the age of 10, the girl came to our hospital again for severe pain of the right leg. Amputation from the middle level of the right femur was performed. We present the case of a 5-year-old girl with JCS presenting with not only NOFs and café-au-lait macules, but also showed features not mentioned before, severe limb pain, and at last resulted in amputation. She was admitted to our hospital after presenting with claudication and mild pain over her right thigh, which worsened when stretching or being touched. Skin examination revealed multiple café-au-lait macules on the neck, arm, armpit, and torso, including the nipples and perineum. Radiographs revealed multiple lytic lesions in the

proximal part of the right humerus, distal part of the right clavicle, proximal and distal parts of the right femur, and proximal parts of the right tibia and fibula. Curettage and biopsy were performed on the distal part of the right femur. At the age of 7, the girl was re-admitted to our hospital for a pathological fracture in the middle in the right femur and underwent Intralesional excision, internal fixation, bone grafting, and spica casting. At the age of 10, the girl came to our hospital again for severe pain of the right leg. Amputation from the middle level of the right femur was performed.

CONCLUSION
In our opinion, education on preventing pathological fractures and explaining the consequent serious consequences to the parents is a matter of prime significance. At the same time, prophylactic treatment (restricted exercise, support, or surgery) is also considerable for JSC.

Key Words: Jaffe-Campanacci syndrome; Multiple non-ossifying fibromas; Café-au-lait macule; Amputation; Case report

Core Tip: Jaffe-Campanacci syndrome (JCS) is exceedingly rare. In this case, a 10-year-old girl with JCS presented with not only non-ossifying fibromas and café-au-lait macules, but also showed features not mentioned before, severe limb pain, and at last resulted in amputation. This case is a big failure with a tragic ending and has revelatory educational value to all orthopaedic surgeons. We aim to share our failures in treatment and remind other doctors that not every JSC grows with bone development and can be self-healing. We highly recommend education on preventing pathological fractures and explaining the consequent serious consequences to the parents is a matter of prime significance. At the same time, prophylactic treatment (restricted exercise, support, or surgery) is also considerable for JSC.

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INTRODUCTION

Jaffe-Campanacci syndrome (JCS) is a very rare syndrome that was first described by Jaffe in 1959[1]. In 1983, Campanacci *et al*[2] reported 10 similar cases. The term "Jaffe-Campanacci syndrome" was first used in an article by Mirra *et al*[3] in 1982. To date, 22 cases of JCS have been reported in English literature (6 of 10 cases reported by Campanacci *et al*[2]), all of which were sporadic cases. Presently, most scholars describe it as an ill-defined syndrome associated with non-ossifying fibromas (NOFs), skin manifestations (café-au-lait macules), and other extraskeletal anomalies. Some scholars consider axillary freckles to be an important feature of JCS[4-6]. The café-au-lait macules are usually in the shape of the "coast of California". In most cases, JSC patients were treated conservatively, if pathological fracture occurs, surgery would be necessary.

CASE PRESENTATION

Chief complaints

A 10-year-old Chinese girl was admitted to our hospital for severe pain accompanied by shortening and deformity of the right leg.

History of present illness

Five years ago, the patient (5-year-old) came to our hospital after presenting with claudication and mild pain over her right thigh, which worsened when stretching or being touched. Radiographs revealed multiple lytic lesions in the proximal part of the right humerus, distal part of the right clavicle, proximal and distal parts of the right femur, and proximal parts of the right tibia and fibula (Figure 1). Curettage and biopsy were performed on the distal part of the right femur. Histopathological examination showed spindle-shaped fibroblastic and collagenous stromal tissue, characteristic of the NOF (Figure 2), then the diagnosis of JCS was made. Conservative therapy was applied with suggestions of observation, reduction of mobility, and follow-up. Three years ago, at the age of 7, the patient was re-admitted to our hospital for a pathological fracture in the middle of the right femur. Intralesional excision, internal fixation, bone grafting, and spica casting were performed (Figure 3). During the operation, brown granulomas-like tissues were found in the cortex and marrow of the femur and were extending into the metaphysis of the distal femur. The plaster was removed one month after surgery and the patient began to walk three months postoperatively.

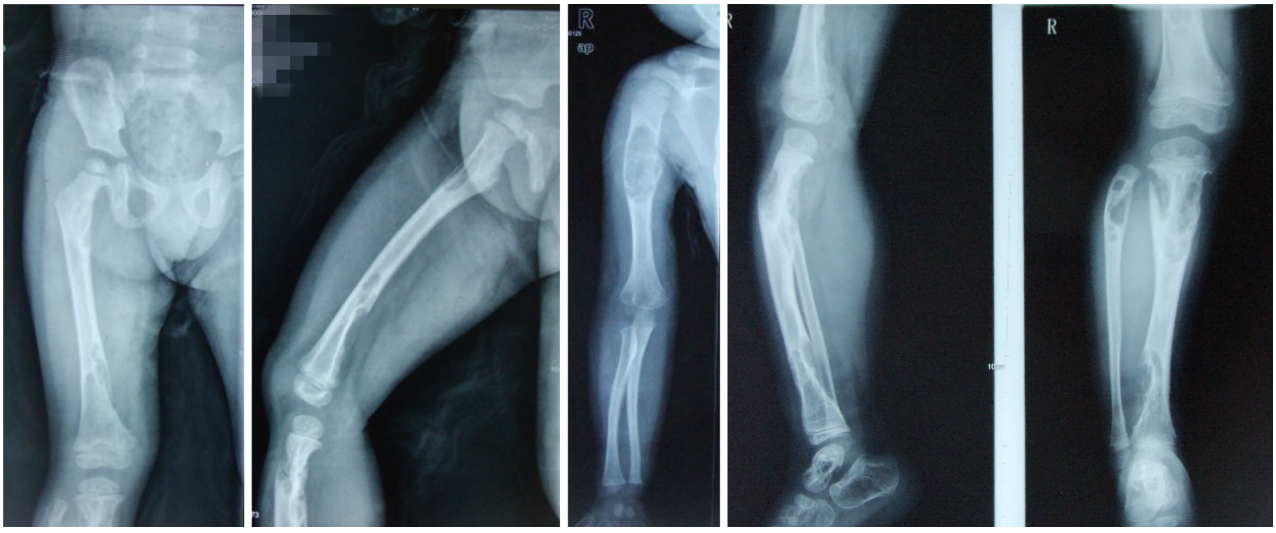

Figure 1 Radiographs at first hospitalization at the age of 5.

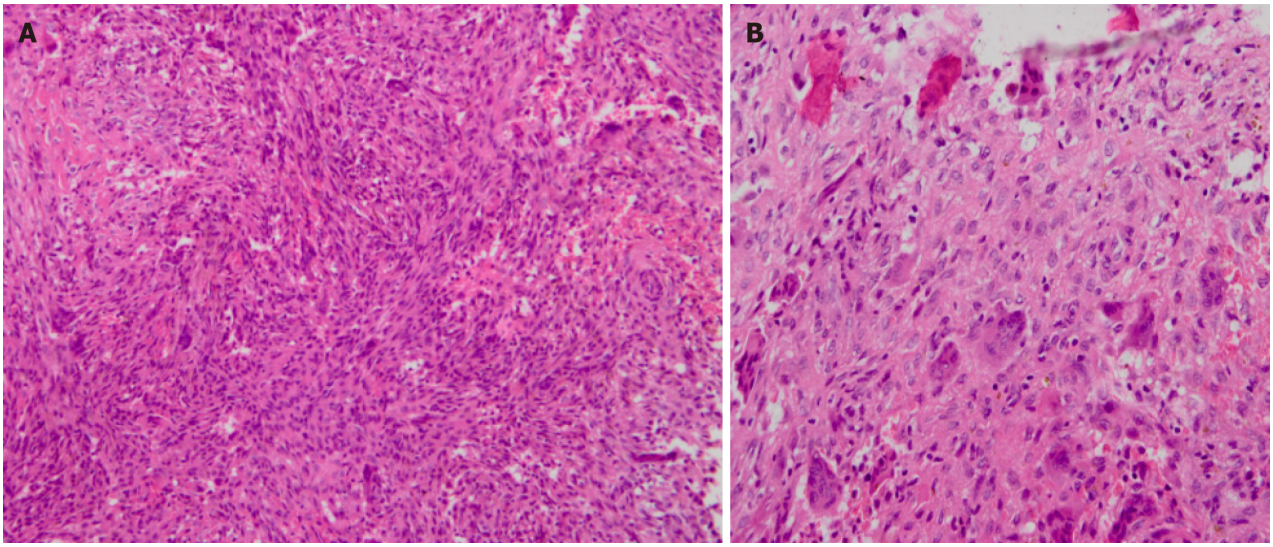

Figure 2 Histological findings. A: × 200; B: × 400. Histopathological examination showed spindle-shaped fibroblastic and collagenous stromal tissue, characteristic of non-ossifying fibroma, then diagnosis of Jaffe-Campanacci syndrome was made. Conservative therapy was applied with suggestions of observation, reduction of mobility and follow-up.

Personal and family history

Family history did not reveal any familial disease, neurofibromatosis, or bone lesions.

Physical examination

The right leg was 20 cm shorter than the left leg, with a severe curved deformity of the thigh and crus (Figure 4). During palpation, there was severe pain from the middle part of the right thigh to the upper part of the calf. The right knee joint remained in a flexed position and could not be extended or flexed. The muscles of the right lower limb were atrophied. Skin examination revealed multiple café-au-lait macules on the neck, arm, armpit, and torso, including the nipples and perineum. The patient showed no pain or itching associated with the macules. The area of the lesions covered the neck, arm, armpit, and torso including the nipple and the perineum, and had a "Coast of Maine" shape with ragged, irregular outlines. Brown granular nodules eres noted in the middle of the lesions (Figure 5).

Laboratory examinations

Laboratory testing revealed no abnormal findings. The whole exome gene test found tuberous sclerosis complex (TSC) 1 (exon7) on the chr9:135797354 had a missense mutation [NM_000368.4: c.515T>C (p. Val172Ala)] in peripheral blood.

Imaging examinations

The lytic lesions of the right femur, tibia, and fibula were larger than before, both femur and tibia were severely curved.

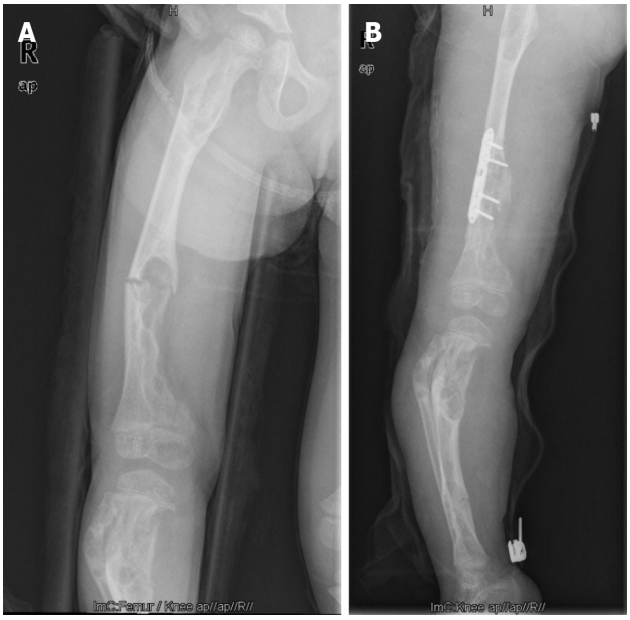

Figure 3 Patient at the age of 7: X-rays before and after surgery. A: X-rays before surgery; B: X-rays after surgery.

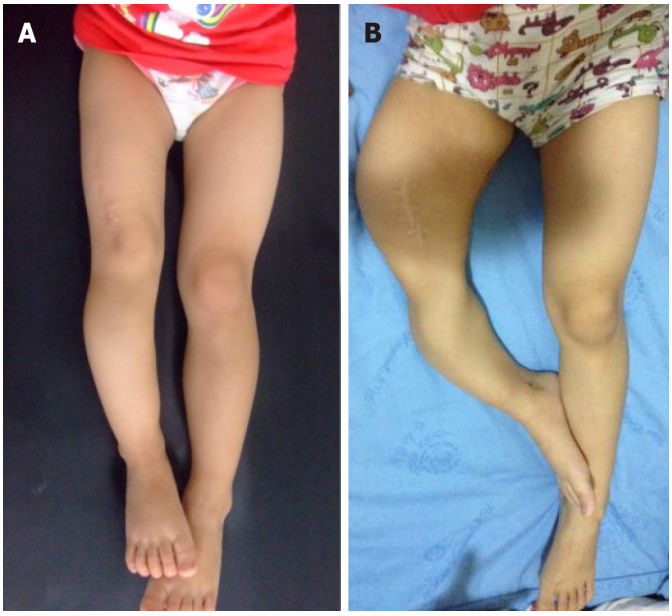

Figure 4 Changes in the appearance of both lower limbs. A: Patient at age 5, after curettage and biopsy of the distal part of the right femur: The right leg is about 5 cm shorter than the left leg; B: Patient at age 10, before amputation: The right leg is obviously shorter than the left side and shows severe deformity of the thigh and shank.

The whole tibia was affected by the lesion with a large cortical defect in the lower part of the tibia (Figure 6).

FINAL DIAGNOSIS

Considering the results of imaging and histopathological examination we arrived at a final diagnosis of JSC.

TREATMENT

Amputation from the middle level of the right femur was performed (Figure 7).

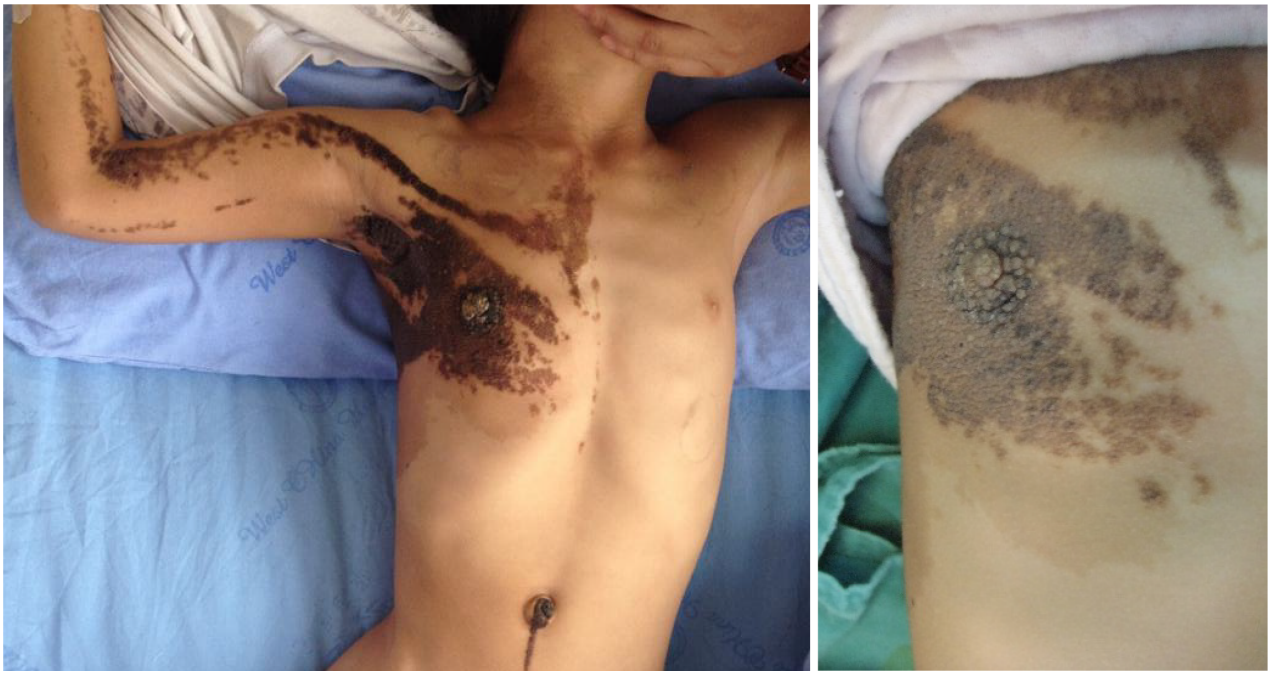

Figure 5 Multiple café-au-lait macules were noted on the child's body.

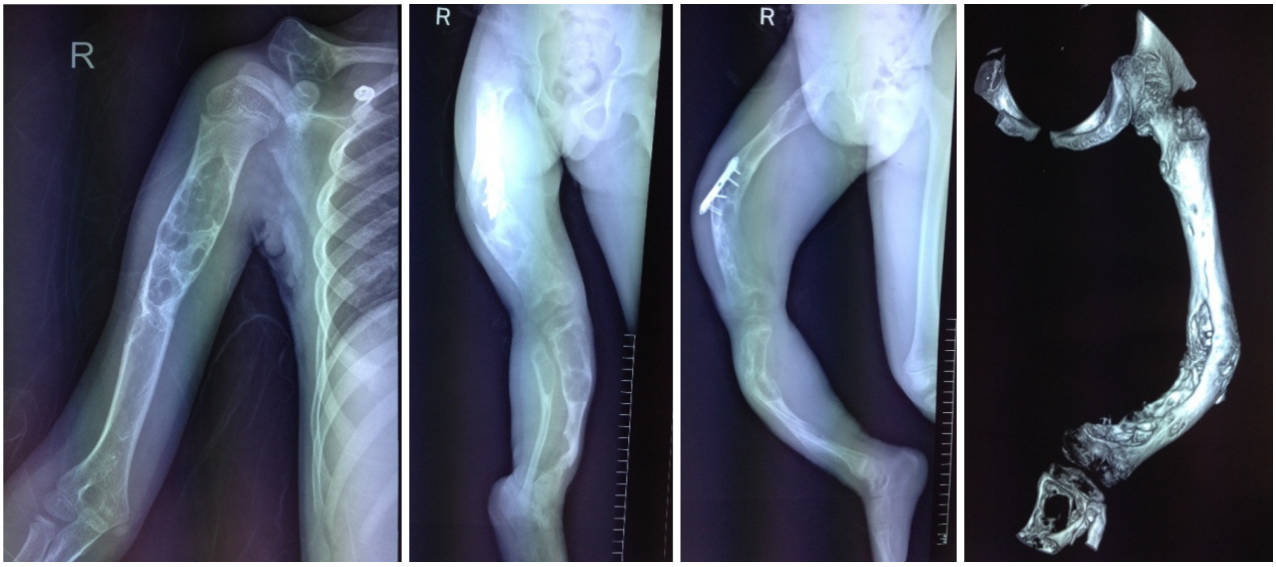

Figure 6 Radiographs of the right humerus, right clavicle, right femur, right tibia, and fibula before amputation.

OUTCOME AND FOLLOW-UP

The wound on the right thigh healed well 2-month after surgery with no pain reoccurring, and the girl started rehabilitation. During the following 3-year follow-up, the area of the lesions did not expand with no pain or itching. She could walk and run well with the help of artificial limb.

DISCUSSION

Presently, most scholars describe JCS as an ill-defined syndrome associated with NOFs, skin manifestations (café-au-lait macules), and extraskeletal anomalies, which include mental retardation, hypogonadism, cryptorchidism, ocular anomalies, or cardiovascular malformations some. It is still controversial whether JCS is a special type of type 1 neurofibromatosis or a separate syndrome. Mirra's group suggested that JSC might clinically be considered an abortive form (forme frusta) of neurofibromatosis[3]. Colby and Saul suggested that JCS may be a manifestation of Neurofibromatosis type 1 (*NF1*) mutations because they studied four patients who fulfilled the diagnostic criteria for both *NF1* and JCS,

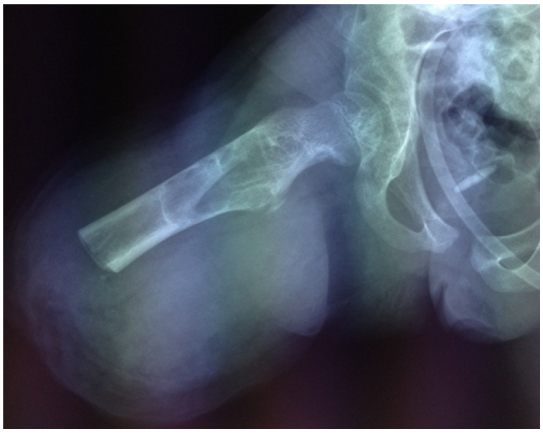

Figure 7 X-ray of the right femur 1 d after amputation.

which led them to think that these two syndromes may be potentially allelic[7]. This hypothesis has not been confirmed because no genetic analysis of JCS patients has been performed before 1990 in which the *NF1* gene was identified[7,8]. In research by Stewart *et al*[8], the majority of patients with café-au-lait macules and NOFs or giant cell lesions were found to harbor a pathogenic germline *NF1* mutation, suggesting that many JCS cases may have *NF1*[8]. In this case, we found a missense mutation in tuberous sclerosis complex 1, which can cause lymphangioleiomyomatosis (LAM) or TSC. LAM is a rare, progressive, and systemic disease that typically results in cystic lung destruction. It predominantly affects women, especially during childbearing years. The term sporadic LAM is used for patients with LAM not associated with TSC, while TSC-LAM refers to LAM that is associated with TSC. However, the patient did not have any clinical manifestations of these diseases nor any matutions in *NF1* SPRED1 or guanine nucleotide binding protein 1 (exon8).

In all 22 cases have been reported in English literature, most patients were under the age of 18 and males were more than females (13 males, 9 females) (Supplementary Table 1). Three previous cases have been reported in East Asia, and, thus, the present case is the fourth[9-11]. It is interesting to find that the bone lesions and café-au-lait macules of this and another case from East Asia were unilateral—especially the abdominal café-au-lait macules which were bounded by the midline on the right and did not cross to the other side (Figure 5). The café-au-lait macules were in the shape of the "coast of Maine", rather than the "coast of California". In this case, brown granular nodules occurred in the middle of the café-au-lait macules, which was different from those described in the previous literature of JCS. The lesion feature of *NF1* commonly presents as a painless skin-colored or violaceous papule, nodule, or subcutaneous mass, which is also different from this case. These features are distinct from those reported in Caucasian patients. Localized skin lesion histopathological examination was suggested, but the parents refused to do any more surgeries but the leg.

Most JCS patients are asymptomatic, the most typical extraskeletal anomalies are café-au-lait macules, some patients have axillar freckling, *i.e*., clusters of freckle-like light brown macules with a diameter of 1 mm to 3 mm located in the armpits or other parts of the trunk. Another unusual manifestation was limb pain. The child felt mild pain after activity, which worsened gradually and extended from the thigh to the crus. The right leg became shorter and shorter with femoral and tibial flexion deformity, which seriously affected mobility and daily life. Serious pain was not reported in previous cases, the reason and mechanism are still uncertain. But it seems to be caused by the bone lesions, for the pain in the right thigh had greatly relieved after the intralesional excision surgery and became more serious as the bone lesions deteriorated. During the treatment, an arachnoid cyst was found in the occipital area of the head, which was not mentioned in previous literature.

No consensus has been reached for the treatment for JSC. In most cases, JSC patients were treated conservatively, for the simple reason as Campanacii *et al*[2] found, the natural course of NOFs grows with bone development, the osteolytic region gradually stops expanding, and there will be self-healing through bone ossification around the lesion and ossification within the lesion[2]. The reason why this case is characterized by pain, and it became more and more serious with the progress of the bone lesions is uncertain. However, the lesions in this case were potentially biologically aggressive, consistent with the case described by Blau *et al*[12].

If pathological the fracture occurs, curettage, grafting, and internal fixation would be necessary. Colby and Saul[7] supposed this could be because large polyostotic area lesions cause weight-bearing bones (*e.g*., proximal femur, proximal tibia) to become thin and brittle. When pathological fractures occur, operation is necessary[7]. As differentiation of JSC from other osteolytic lesions is sometimes difficult, some authors also recommend a two-stage operation[6]. Biopsy surgery should be performed first and then Definitive surgery followed. Of all the 22 cases of JSC reported in the English literature, 59.1% (13/22) had pathological fractures, which is much higher than the incidence of NOFs pathological fractures. The girl in the present case is the first report of amputation in JCS. There are various reasons for amputation. Firstly, the progressive aggravation of the lesions leads to severe limb deformities. After curettage, grafting, and internal fixation with a conventional plate, the lesions of the right femur and tibia were enlarged with a large defect in the lower part of the tibia, and the tibia was bent and deformed with severe shortening. As the progression of the disease, there was no way to regain either alignment or length of the leg. Secondly, the pain in the right leg is from beginning to end. When the girl had performed Intralesional excision, internal fixation, and bone grafting surgery, the pain was relieved for half a year, but then became more and more serious and gradually extended to the right crus. Before amputation, the girl had to

ease the pain by drugs every day.

There are limited reports about the long-term prognosis. The short-term prognosis of JCS with conservative treatment is good except high incidence of pathological fractures. Patients with pathological fractures gradually healed after surgery, and mobility was largely unaffected. Although there have been no reports of limb malformations in JCS, limb malformation caused by NOFs has been reported[13]. Proper intervention (restricted exercise, support, or surgery) may reduce the rate of long-term disability[7]. Given the present case, we highly recommend preventive measures for patients (especially overweight patients) with simultaneous femoral and tibial lesions who have a high risk of limb deformity. Given the close relationship between JSC and *NF1*, some researchers have suggested that patients diagnosed with *NF1* should undergo bone examination to exclude NOFs or even JCS to prevent secondary pathological fractures[4]. However, the skin lesions of this case are different from those in other cases of JSC. Meanwhile, both the bone lesions and the pain were continuously deteriorating, leading to a poor prognosis. All these suggested the lesions in this case were potentially aggressive.

CONCLUSION

Our case showed features of JCS not mentioned before. The bone lesions and café-au-lait macules of this case were unilateral—especially the abdominal café-au-lait macules which were bounded by the midline on the right and never crossed to the other side. Another unusual manifestation was severe limb pain. Both the bone lesions and the pain were continuously deteriorating, leading to a poor prognosis. All these suggested the lesions in this case were potentially aggressive. In our opinion, education on preventing pathological fractures and explaining the consequent serious consequences to the parents is a matter of prime significance. At the same time, prophylactic treatment (restricted exercise, support, or surgery) is also considerable for JSC.

FOOTNOTES

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CASE REPORT

Paradoxical herniation associated with hyperbaric oxygen therapy after decompressive craniectomy: A case report

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Abstract

BACKGROUND

Whether hyperbaric oxygen therapy (HBOT) can cause paradoxical herniation is still unclear.

CASE SUMMARY

A 65-year-old patient who was comatose due to brain trauma underwent decompressive craniotomy and gradually regained consciousness after surgery. HBOT was administered 22 d after surgery due to speech impairment. Paradoxical herniation appeared on the second day after treatment, and the patient's condition worsened after receiving mannitol treatment at the rehabilitation hospital. After timely skull repair, the paradoxical herniation was resolved, and the patient regained consciousness and had a good recovery as observed at the follow-up visit.

CONCLUSION

Paradoxical herniation is rare and may be caused by HBOT. However, the underlying mechanism is unknown, and the understanding of this phenomenon is insufficient. The use of mannitol may worsen this condition. Timely skull repair can treat paradoxical herniation and prevent serious complications.

Key Words: Decompressive craniectomy; Hyperbaric oxygen therapy; Mannitol; Para-

doxical herniation; Case report

Core Tip: Paradoxical herniation may be caused by high-pressure oxygen therapy after decompressive craniectomy has not been reported. Paradoxical herniation has been misdiagnosed by the neurosurgery department of subordinate hospitals and provincial neurological rehabilitation hospitals for many times, thus delaying treatment. This report is to improve the understanding of paradoxical herniation.

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INTRODUCTION

Decompression with a bone flap is an effective rescue measure for alleviating various types of malignant intracranial hypertension. After cerebral edema subsides, the skull loses mechanical support, and the force generated by atmospheric pressure directly acts on the skull defect site. This causes the flap to sag after collapsing downward and inward, leading to a series of neurological declines. The mechanism by which paradoxical herniation occurs remains unclear because it is relatively rare. Moreover, many doctors do not have a comprehensive understanding of this disease, which can lead to misdiagnosis, missed diagnosis, or even deterioration of the patient's condition and, in severe cases, death. We encountered a rare patient with paradoxical herniation caused by hyperbaric oxygen therapy (HBOT) that was misdiagnosed. Here we report such case to improve the understanding of this disease.

CASE PRESENTATION

Chief complaints

A 65-year-old male patient was in a coma for more than a month due to a high fall.

History of present illness

A 65-year-old male patient presented to Zhangping City Hospital in Fujian Province on May 2, 2021 (Figure 1A) with loss of consciousness for 20 min following a fall from a high height. Cranial computed tomography (CT) revealed a bilateral acute temporal subdural hematoma and contusion in the right frontotemporal lobe. The patient was admitted to the hospital and underwent physical examination. The Glasgow Coma Scale score of the patient was 7 (E1, V2, M4), and he was slightly unconscious, irritable, and unable to answer and cooperate during examination. The bilateral pupils were equally round and large, 0.2 cm in diameter, and slow to respond to light. Lacerations were observed in the left temporal area with obvious local swelling. Bright red bloody fluid was observed in the left external auditory canal and bilateral nasal cavity, with slight resistance in the neck. Lacerations were present in the left thorax, waist, and left anterior abdominal region, with slightly greater muscle tension. The Barnberg sign and Ke's sign were negative. In the Emergency Department, "right craniotomy + intracranial hematoma removal + bone decompression + secondary artificial dural repair" was performed (Figure 1B). After the operation, fluid rehydration therapy, hemostatic agents, nutritional support, brain tissue assessment, infection prevention treatment, stomach protection measures, electrolyte balance therapy, and sedation and analgesia were administered. After the operation (Figure 1C), the patient's condition gradually improved, but he was unable to speak. On May 24, 2021 (Figure 1D), "hyperbaric oxygen" (inside the cabin, gauge pressure 0.1 mPa, oxygen inhalation for 30 min, rest for 10 min (air inhalation), and oxygen inhalation for 30 min) was administered. The next day (May 25, 2021, Figure 1E), the bone window collapse was obvious; however, local doctors considered it to be normal and thus continued two courses of hyperbaric oxygen treatment. The duration of each treatment course was 10 d, and the degree of bone window collapse did not significantly improve. The patient's family considered that the treatment response was poor due to his speech disturbance, dysphagia, and occasional dizziness. On June 14, 2021, the patient was transferred to a higher-level hospital for rehabilitation treatment, and on June 15, 202, he was transferred to the Rehabilitation Hospital Affiliated with Fujian University of Chinese Medicine. On the day after admission, cranial CT examination revealed paradoxical herniation (Figure 1F). An attempt to lower cranial pressure using mannitol resulted in drowsiness. On June 17, 2021 (Figure 1G), craniocerebral CT revealed worsened paradoxical herniation, and further treatment was not effective. Five days later (June 22, 2021), a craniocerebral CT review revealed no improvement, and consultation was requested due to continued drowsiness. The patient was referred to our hospital on June 25, 2021, at which point the effects of fluid rehydration were unsatisfactory. A review of the craniocerebral CT images revealed that the paradoxical herniation was still present (June 27, 2021; Figure 1H and I). Cranioplasty was performed on July 1, 2021

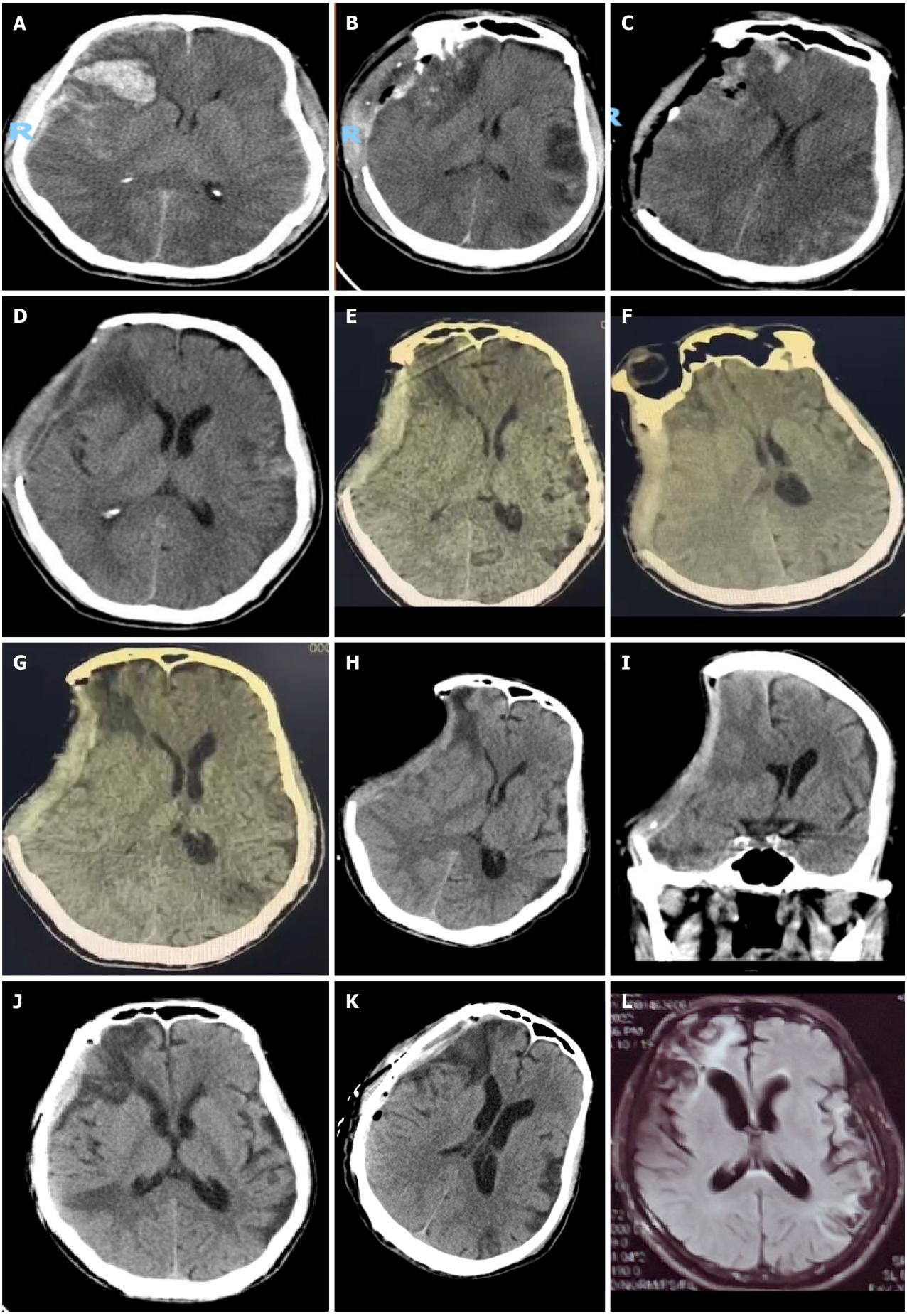

Figure 1 Computed tomography findings during patient diagnosis and treatment. A: Preoperative cranial computed tomography (CT) image on May

2, 2021; B: First postoperative cranial CT image (May 2, 2021); C: Cranial CT image obtained 1 wk after the first surgery (May 8, 2021); D: Cranial CT image before hyperbaric oxygen therapy (HBOT) (May 24, 2021); E: Cranial CT image on the second day of HBOT (May 25, 2021); F: Cranial CT image on the tenth day of HBOT (June 15, 2021); G: Cranial CT image before mannitol treatment (June 17, 2021); H: Second preoperative cranial CT image (axial) (June 27, 2021); I: Second preoperative cranial CT image (coronal) (June 27, 2021); J: Cranial CT before the second surgery (July 2, 2021); K: Cranial CT at 20 d after the second surgery (July 22, 2021); L: One-year postoperative cranial MR image (June 17, 2022).

(Figure 1J), and the patient was no longer drowsy on the second day after surgery. The stitches were removed, and the patient was discharged from the hospital one week later.

History of past illness
The patient had a medical history of pulmonary tuberculosis.

Personal and family history
The patient denied any family history of malignant tumors or other genetic conditions.

Physical examination
The vital signs of the patient were as follows: Body temperature, 36.9 °C; heart rate, 68/min; respiratory rate, 20/min; and blood pressure, 123/83 mmHg.

Laboratory examinations
Laboratory examinations showed no abnormalities.

Imaging examinations
Cranial CT showed the presence of paradoxical herniation on the next day of HBOT initiation (May 25, 2021, Figure 1E), abnormal aggravation of the cerebral hernia on June 17, 2021 after receiving mannitol treatment (Figure 1G), and the disappearance of paradoxical herniation following cranioplasty on July 1, 2021 (Figure 1J).

FINAL DIAGNOSIS
Paradoxical herniation associated with HBOT.

TREATMENT
After the patient's skull was repaired, the paradoxical herniation disappeared.

OUTCOME AND FOLLOW-UP
At the postoperative follow-up visit, the patient was mentally clear. Repeat magnetic resonance imaging showed that the paradoxical herniation did not reappear. The patient's speech gradually improved (Figure 1).

DISCUSSION
Paradoxical herniation, also known as paradoxical herniation syndrome or acute progressive hypotension syndrome, was first described by Schwab *et al*[1] in 1998 as the result of the absence of a portion of the skull after craniotomy. Cerebrospinal fluid (CSF) flow produces a siphoning effect, and atmospheric pressure directly acts on the cerebral cortex and causes intracranial venous reflux, ultimately leading to flap collapse. Thus, surgery-induced dynamic changes in CSF that cause an intracranial infection or require mannitol dehydration after decompression of the bone flap may lead to brain tissue displacement and brain hernia. Although the pathophysiological mechanism of paradoxical herniation remains unclear, the sum of the changes in intracranial pressure, cerebral blood flow dynamics, and CSF dynamics after bone flap removal can be evaluated using brain compliance ($\Delta V/\Delta P$). All factors causing increased cerebral compliance reduce CSF pulsation, resulting in the abovementioned CSF dynamics disorders[2-4]. It has often been reported that excessive drainage reduces the pressure gradient and creates bilateral imbalances, ultimately leading to paradoxical herniation[5-9].

HBOT-induced paradoxical herniation has not been reported in the literature. However, whether it affects CSF circulation is unknown. Early use of HBOT is conducive to the rehabilitation of patients after decompressive craniotomy. Its main mechanism of action is to increase the oxygen supply to the lesion area in the brain, reduce blood oxygen tension, increase oxygen dispersion, facilitate the establishment of collateral circulation, reverse the inhibition of brain cells, and

prevent further decline in brain cell function[10]. However, the establishment of collateral circulation increases CSF absorption, which decreases the amount of CSF. HBOT helps to improve the absorption function of the cerebral surface and arachnoid granulations to establish a balance between CSF secretion and absorption. However, in this case, the patient received HBOT after decompressive craniectomy surgery, during which time excessive dehydration was not achieved and cranial pressure was not reduced; this led to paradoxical herniation on the second day. In a normal cranial cavity[11], brain pulsation is closely related to changes in intracranial arterial and venous pulsation; however, bone flap decompression may have an impact on this process. Atmospheric pressure may act on the defective cranial cavity, resulting in a sunken bone window flap and a compressed intracranial cortex, which may lead to neurological function damage, insufficient cerebrospinal fluid volume, and flap sinking syndrome. If the atmospheric pressure increases significantly, the volume of CSF becomes insufficient, resulting in the formation of a paradoxical herniation. Siphoning due to skull defects may lead to excessive drainage of CSF[1], which reduces the intracranial pressure and the "fluid cushion" effect of CSF. Direct compression caused by high atmospheric pressure causes the cranial contents to shift to the normal tissue side, resulting in symptoms of neuropathy. The dural space may be partially deformed or displaced by high air pressure, thus increasing the size of the cerebral cortex and the intracranial venous return flow. This results in the dynamic siphoning effect of CSF, which may also lead to insufficient CSF volume and the occurrence of paradoxical herniation[8,12]. Bender *et al*[13] suggested that due to the loss of protective support provided by a bone flap as a unilateral decompressor, atmospheric pressure and flap gravity directly act on the flap, the elastic modulus of which is much smaller than that of the skull, resulting in flap collapse. This further diminishes the integrity of the already collapsing flap, causing scalp depression. In addition, surgical damage to the scalp and surrounding tissues leads to the formation of adhesions between the scalp and surrounding tissues and scar formation. With increasing depression, the volume of the cranial cavity gradually decreases, and paradoxical herniation occurs[14,15].

Ignoring the nature of the high compliance and low cranial pressure associated with disordered CSF dynamics, attempting to drain CSF, or using dehydrating agents to change its abnormal distribution will further exacerbate disordered CSF dynamics, destroy the homeostasis of the central nervous system, and seriously worsen nerve function. Because doctors, including neurosurgeons[14] and neurorehabilitation doctors, have some deficiencies in understanding this phenomenon, mannitol dehydration treatment is often administered immediately after the discovery of a cerebral hernia. This method of treatment has been a standard protocol for a long time but results in worsening of both paradoxical herniation and consciousness disorders, thereby affecting patient rehabilitation.

Intracranial pressure can be effectively reduced by placing the patient in the low-head and high-foot supine position [15], discontinuing drugs that promote dehydration, increasing the intravenous fluid supply, eliminating all factors leading to CSF loss (lumbar cisternal drainage, ventriculoperitoneal shingles, and cerebrospinal fluid rhinorrhea and otorrhea), and restoring skull integrity as soon as possible. Restoring the integrity of the skull is not only the aim of treatment for paradoxical herniation[12,13,15] but also a means to improve the blood supply to the brain on the skull defect side in patients with paradoxical herniation and to aid in the recovery of nerve function.

In summary, paradoxical herniation is a rare complication after decompressive craniotomy, but its pathological mechanism is unknown. HBOT may cause paradoxical herniation after decompressive craniotomy. However, due to the limitations of single cases, further studies are needed to confirm the exact role of HBOT in the pathogenesis of paradoxical herniation. To improve the in-depth understanding of paradoxical herniation, early diagnosis and timely detection are necessary to ensure timely implementation of effective treatment measures, such as skull repair. Moreover, effective treatment measures are beneficial for repairing the peripheral nerves of lesions and improving patient prognosis.

CONCLUSION

HBOT may cause paradoxical herniation after decompressive craniotomy. Early diagnosis and timely detection are necessary to ensure timely implementation of effective treatment measures, such as skull repair.

FOOTNOTES

Author contributions: Ye ZX, Fu XX, Wu YZ, Lin L, Xie LQ, Hu YL, and Zhou Y designed the research study; Ye ZX, Fu XX, Wu YZ, and Lin L performed the research; You ZG analyzed the data; Lin H analyzed the data and wrote the manuscript.

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CASE REPORT

Subdural effusion associated with COVID-19 encephalopathy: A case report

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Abstract

BACKGROUND

The precise mechanism by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) impacts the central nervous system remains unclear, with manifestations spanning from mild symptoms (*e.g.*, olfactory and gustatory deficits, hallucinations, and headache) to severe complications (*e.g.*, stroke, seizures, encephalitis, and neurally demyelinating lesions). The occurrence of single-pass subdural effusion, as described below, is extremely rare.

CASE SUMMARY

A 56-year-old male patient presented with left-sided limb weakness and slurred speech as predominant clinical symptoms. Through comprehensive imaging and diagnostic assessments, he was diagnosed with cerebral infarction complicated by hemorrhagic transformation affecting the right frontal, temporal, and parietal regions. In addition, an intracranial infection with SARS-CoV-2 was identified during the rehabilitation process; consequently, an idiopathic subdural effusion developed. Remarkably, the subdural effusion underwent absorption within 6 d, with no recurrence observed during the 3-month follow-up.

CONCLUSION

Subdural effusion is a potentially rare intracranial complication associated with SARS-CoV-2 infection.

Key Words: Cerebral infarction; Hemorrhagic transformation; Subdural effusion; COVID-19 encephalopathy; Novel coronavirus infection; Brain fog; Case report

Core Tip: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may transmit *via* the retrograde axonal pathway, bloodstream, or direct penetration through the blood-brain barrier, exerting its effects on angiotensin-converting enzyme-2 receptors. This intricate interaction can cause neurological complications, including subdural effusion, which is very rare. Clinical vigilance is advised for cranial imaging in individuals with SARS-CoV-2 infection to enhance diagnostic precision. Considering its unique characteristics, subdural effusion, a seldom reported complication, warrants attention.

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INTRODUCTION

Subdural effusion or subdural hydrocele commonly stems from craniocerebral trauma, postcranial surgery, or cerebral atrophy. Typically presenting unilaterally or bilaterally in the frontotemporal region, symptoms include headache, dizziness, cognitive alterations, and mood changes. Its slow absorption may progress to chronic subdural hematoma, with treatment options ranging from medications to surgical interventions such as bone flap craniotomy, subdural effusion capsule wall stripping, abdominal shunt, and external drainage[1-4]. This report presents a unique case of subdural effusion that formed after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection but was remarkably resolved within 6 d, showcasing a rare and expeditious resolution.

CASE PRESENTATION

Chief complaints

A 56-year-old male presented with a sudden onset of left-sided limb weakness for over 20 d.

History of present illness

On November 25, 2021, the patient experienced a sudden onset of left-sided limb weakness accompanied by slurred speech. After a comprehensive examination, he was diagnosed with cerebral infarction with hemorrhagic transformation affecting the right frontal, temporal, and parietal lobes. He was then treated for his cranial hemorrhage symptoms. Throughout the hospitalization period, he exhibited fever, dyspnea, and generalized muscular aches and pains. The patient's temperature fluctuated at 38.0 °C, accompanied by headache, hallucinations, and incoherent speech.

History of past illness

He had primary hypertension for 4 years, with a maximum blood pressure of 188/106 mmHg. The patient was on long-term oral medication with sacubitril/valsartan sodium tablets (100 mg) once a day.

Personal and family history

The patient denied any personal or family history of related diseases.

Physical examination

The patient was unresponsive, a shallow left nasolabial groove, slurred speech, difficulty swallowing fluids (leading to choking), slight neck resistance, a positive Kernig's sign, and muscle strength graded at 0, 2, and 5 in the left-upper, left-lower, and right limbs, respectively, were observed. Reduced muscle tone in the left upper limb, decreased pharyngeal reflexes, and a positive Babinski's sign on the left side were also observed. The remaining systematic examination did not reveal any positive signs.

Laboratory examinations

The patient's laboratory examination results were as follows: Platelet count, 462 × 10^9/L (reference range: 100-300/L); sodium level, 125 mmol/L (reference range: 135-145 mmol/L); positive throat swab test result for coronavirus disease 2019 (COVID-19); C-reactive protein level, 44.18 mg/L (reference range: 0-10 mg/L); and blood gas analysis, 60 mmHg (reference range: 83-108 mmHg). Furthermore, inflammatory factors were elevated, with interleukin (IL)-2, IL-6, IL-10, and tumor necrosis factor alpha (TNF-α) at 878.54, 62.83, 136.15, and 111.14 U/mL (reference range: 160-625, 0-7, 0-9.5, and 0-8.5 U/mL), respectively. Lumbar puncture revealed a cerebrospinal fluid pressure of 150 mmH_2O (reference range: 80-180 mmH_2O). The cerebrospinal fluid analysis for SARS-CoV-2 showed specific gene Ct values: N gene Ct value of

35.5429 and ORF1ab gene Ct value of 30.3402 (reference range: > 40 for both). Routine biochemistry of cerebrospinal fluid revealed no abnormalities. Cultures and a full set of viral screenings did not detect pathogens such as bacteria, fungi, parasites, *Mycobacterium tuberculosis* complex, Mycoplasma, or Chlamydia. Moreover, cerebrospinal fluid and serum specimens were negative for autoimmune encephalitis antibodies, paraneoplastic syndrome autoantibody profile semiquantitative test, and ganglioside antibody profile. Coagulation function and procalcitonin levels also showed no abnormalities. Electroencephalogram results showed bilateral symmetrical diffuse slow waves.

Imaging examinations

Cranial magnetic resonance imaging (MRI) revealed a typical infarction in the right frontal, temporal, and parietal lobes, along with brain atrophy indications. On magnetic resonance angiography, the right internal carotid artery and middle cerebral artery were largely undetected, and the walls of the left internal carotid artery, left middle cerebral artery M1 segment, and bilateral posterior cerebral arteries exhibited abnormalities (Figure 1A and B). On December 28, 2021, a repeat cranial computed tomography (CT) scan revealed infarction with hemorrhagic transformation in the right frontal, temporal, parietal, and basal ganglia areas, and chest CT showed scattered patchy shadows in the lungs (Figure 1C). On March 15, 2022, cranial MRI revealed new subdural effusion in the right frontal, temporal, and parietal areas (Figure 1D), with subsequent absorption of the subdural effusions on March 21 (Figure 1E).

FINAL DIAGNOSIS

The patient was diagnosed with the following: (1) Cerebral infarction with hemorrhagic transformation on the right frontal, temporal, and parietal lobes (atherosclerotic large artery type); (2) Cerebral atrophy; (3) Primary hypertension, grade 3 (extremely high-risk group); (4) Pneumonia associated with COVID-19; (5) COVID-19 encephalitis; (6) Subdural effusion; and (7) Hyponatremia.

TREATMENT

The patient received the following: Aspirin enteric-coated tablet (100 mg) orally once a day, rosuvastatin calcium tablet (10 mg) orally at night, butylphthalide soft capsule (0.2 g) orally thrice a day, sacubitril/valsartan sodium tablet (100 mg) orally once a day, and early comprehensive rehabilitation training. He was also prescribed nemavirit (300 mg)/ritonavir (100 mg) tablet orally every 12 h for 5 d, methylprednisolone sodium succinate injection (40 mg) intravenously once a day, and acetylglutamide injection (0.6 g) intravenously once a day.

OUTCOME AND FOLLOW-UP

At 3 months after discharge, we noted that the patient's left-sided limb weakness had improved, and he had clear speech and mild headache that did not disrupt his sleep or daily activities (Figure 1F). The patient's condition has remained stable without any noteworthy concerns.

DISCUSSION

Subdural effusions encompass regressive, stable, progressive, and evolving types, with craniocerebral trauma being the predominant cause. The stable and evolving types are more common among older adults, often progressing slowly and occasionally evolving into chronic subdural hematomas necessitating surgical intervention when conservative approaches fail. Conversely, regressive types are more prevalent in young individuals, showcasing optimal healing outcomes, and progressive types, which are found more commonly in pediatrics, exhibit severe symptoms, neurological deficits, and the highest mortality rate[5]. In the case of our elderly male patient, the subdural effusion spontaneously resolved in only 6 d, aligning with the typical characteristics of regressive subdural effusion.

We analyzed the potential causes of subdural effusion. First, SARS-CoV-2 has a neuroinvasive and neurophilic nature, as seen in the associations of subdural effusion with other viruses, such as enterovirus 71, herpes simplex virus type 1, and Epstein-Barr virus[6]. However, currently, only one case of subdural effusion associated with SARS-CoV-2 has been reported[7]. Involvement in the central nervous system (CNS) by the virus primarily occurs through direct invasion, inflammatory response activation, and autoimmune response induction. Excessive immune activation leads to the intracranial infiltration of inflammatory cells and upregulation of proinflammatory factors such as IL-1α, IL-6, and TNF-α, resulting in a "cytokine inflammatory storm". The virus enters the CNS through the interstitial space between endothelial cells and affects the angiotensin-converting enzyme-2 receptor, causing brain tissue damage and cerebrospinal fluid extravasation[8-12]. Second, blood-brain barrier permeability may be altered. The complex mechanism of cerebral infarction with hemorrhagic transformation involves the release of oxygen-free radicals, inflammatory factors, and cytokines and the degradation of collagen and laminin by brain cell extracellular matrix metalloproteins. This event affects the structural integrity of endothelial cells, basement membranes, and the perivascular pedicle of astrocytes. The

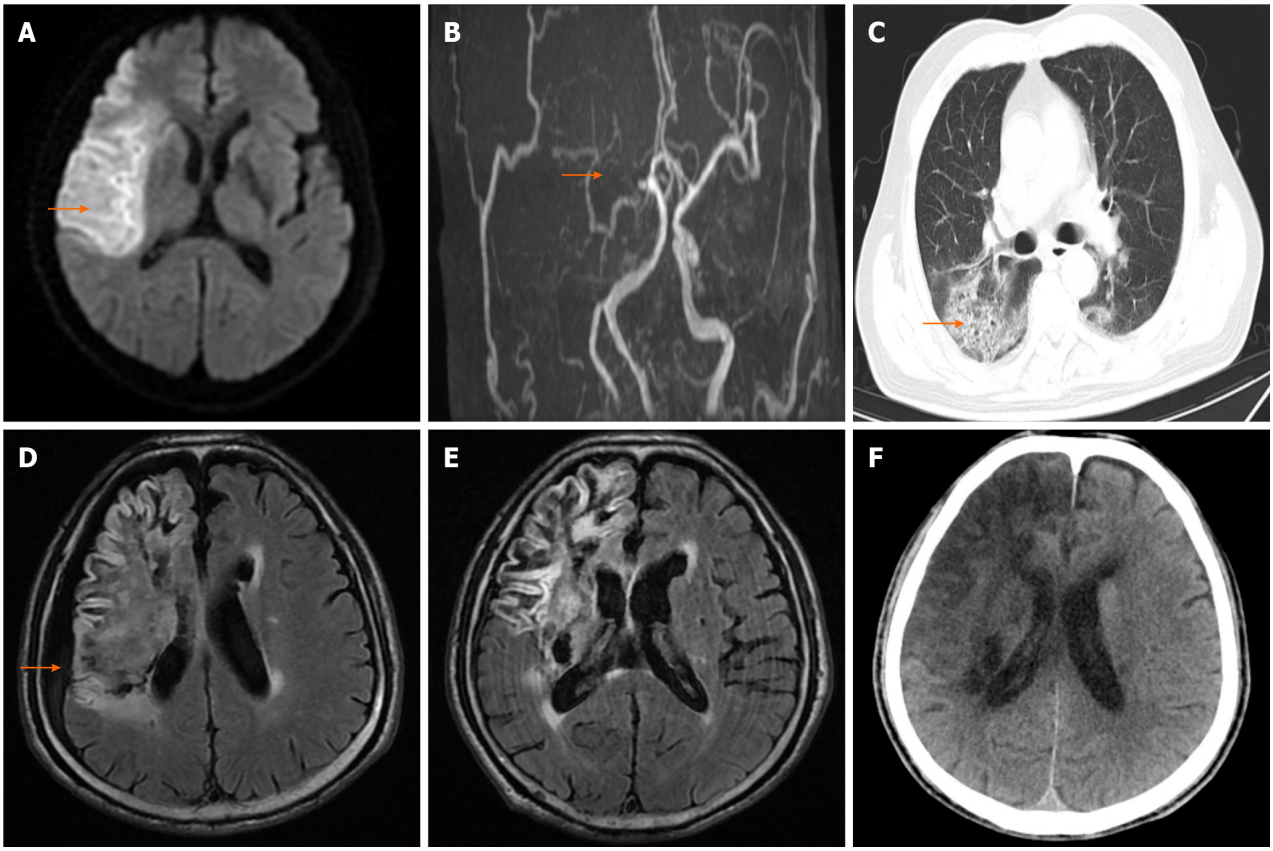

Figure 1 Cranial magnetic resonance imaging. A: Cranial magnetic resonance imaging (MRI) revealed distinct, patchy, nodular long T2 signal shadows in the right frontal, temporal, and parietal lobes; B: Head and neck MRI displayed non-visualization of the right internal carotid and middle cerebral arteries, particularly noting superficial shadows in the right internal carotid siphon, the middle cerebral artery M1 segment, and the right anterior cerebral artery A1 segment (indicated by arrow); C: Chest computed tomography showed scattered patchy shadows in the lungs; D: Cranial MRI displayed new subdural effusion in the right frontal, temporal, and parietal regions; E: Cranial MRI displayed marked absorption of subdural effusion in the right frontal, temporal, and parietal regions at 6 d after its appearance; F: Head computed tomography displayed the scar of cerebral infarction with hemorrhagic transformation in the right frontal, temporal, and parietal lobes at 3 months after discharge.

patient's right cerebral hemispheric parenchyma displayed edema, and MRI revealed fragmented protein deposition in the lesion, further implying blood-brain barrier disruption. Third, brain atrophy could be a potential cause. Cranial CT and MRI revealed ventricular enlargement, cerebral pool enlargement, cerebral sulcus and fissure deepening, and brain tissue volume reduction. Brain atrophy coupled with compensatory dilation of the subdural space was considered to be a factor leading to subdural effusion.

In summary, the mechanisms by which SARS-CoV-2 affects the CNS are insufficiently understood. This virus may use various routes of transmission, ranging from retrograde axonal pathways to bloodstream transmission and direct transmission through the blood-brain barrier. Clinical manifestations may range from mild symptoms (*e.g.*, olfactory and taste deficits) to severe ones (*e.g.*, stroke, seizures, encephalitis, and neurally demyelinating lesions)[13-15]. Subdural effusion has been proposed as a potentially rare feature of SARS-CoV-2 infection. Hence, early evaluation of brain imaging in infected patients is crucial to promptly detect neurological involvement, with timely screening and intervention playing a critical role in reducing subsequent morbidity and mortality.

CONCLUSION

Subdural effusion is a potentially rare intracranial complication associated with SARS-CoV-2 infection.

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FOOTNOTES

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CASE REPORT

Cemented vertebra and adjacent vertebra refractured in a chronic kidney disease-mineral and bone disorder patient: A case report

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Abstract

BACKGROUND

Although percutaneous vertebral augmentation (PVA) is a commonly used procedure for treating vertebral compression fracture (VCF), the risk of vertebral refracture should be considered. Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a systemic disease of mineral and bone metabolism. It is associated with an increased risk of fracture. Few studies have reported the use of PVA in patients with CKD-MBD. We herein report a rare case wherein the cemented vertebra and the adjacent vertebra refractured simultaneously in a CKD-MBD patient after PVA.

CASE SUMMARY

A 74-year-old man suffered from low back pain after taking a fall about 3 wk ago. According to physical examination, imaging and laboratory findings, diagnoses of T12 VCF, CKD-MBD, and chronic kidney disease stage 5 were established. He then received percutaneous vertebroplasty at T12 vertebra. Fourteen weeks later, he presented with T12 and L1 vertebral refractures caused by lumbar sprain. Once again, he was given PVA which was optimized for the refractured vertebrae. Although the short-term postoperative effect was satisfactory, he reported chronic low back pain again at the 3-month follow-up.

CONCLUSION

It is necessary that patients with CKD-MBD who have received PVA are aware of the adverse effects of CKD-MBD. It may increase the risk of vertebral refracture. Furthermore, the PVA surgical technique needs to be optimized according to the condition of the patient. The medium- and long-term effects of PVA remain uncertain in patients with CKD-MBD.

Key Words: Chronic kidney disease-mineral and bone disorder; Percutaneous vertebral augmentation; Vertebral compression fracture; Vertebral refracture; Cemented vertebra; Adjacent vertebra; Case report

Core Tip: This is a rare case wherein the cemented vertebra and the adjacent vertebra refractured simultaneously in a chronic kidney disease-mineral and bone disorder (CKD-MBD) patient after percutaneous vertebral augmentation (PVA). He was given PVA once more, which was optimized for the refractured vertebrae. While, the medium- and long-term effects were not satisfactory. It is necessary that patients with CKD-MBD who have received PVA are aware of the adverse effects of CKD-MBD.

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INTRODUCTION

Percutaneous vertebral augmentation (PVA), including percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP), is widely recognized as a suitable procedure for vertebral compression fracture (VCF). However, vertebral refracture is a common concern after PVA. Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a systemic disorder of mineral and bone metabolism caused by CKD and is associated with an increased risk of hip and vertebral fractures[1,2]. The vertebral fracture is relatively common in patients with CKD-MBD. A previous study has shown that PVA can relieve pain and disability in these patients[3], whereas few studies have reported the refracture of the vertebrae. Here, we report a rare case of simultaneous fracture of a cemented vertebra and an adjacent vertebra in a patient with CKD-MBD after PVA.

CASE PRESENTATION

Chief complaints

The patient was a 74-year-old man who experienced persistent low back pain after taking a fall about 3 wk ago.

History of present illness

The patient took a fall 3 wk ago, and then, he suffered from persistent and drastic lower back pain, and he was barely able to stand and walk.

History of past illness

The patient was diagnosed as having CKD stage 5 in 2006, and since then, he has undergone hemodialysis three times a week and was prescribed oral calcium (1000 mg/d) and calcitriol (0.5 μg/d). The causative disease of CKD was not clear. He was diagnosed with urothelium carcinoma in 2012 and received surgical treatment.

Personal and family history

The patient and his family had no history of fragility fracture, and he had no history of chronic low back pain.

Physical examination

Tenderness was found at the thoracolumbar vertebrae, but there were no neurological signs or symptoms. His body mass index was 16.7 kg/m^2.

Laboratory examinations

Laboratory examination (Table 1) revealed bone metabolism abnormalities in the patient.

Imaging examinations

The computed tomography (CT) and magnetic resonance imaging revealed T12 VCF (Figure 1A-C). The L1-L4 bone mineral density (BMD) was 0.922 (T score: -1.3), and the femoral neck BMD was 0.579 (T score: -3.1).

FINAL DIAGNOSIS

According to the history, physical examination, laboratory and imaging examinations, he was diagnosed as having T12 VCF, CKD-MBD, and CKD stage 5. The secondary causes like hyperparathyroidism, osteomalacia, and malignant tumors

Table 1 Results of laboratory examinations for the two admissions

	Serum calcium (mmol/L)	Serum phosphorus (mmol/L)	Parathyroid hormone (pg/mL)	Vitamin D (ng/mL)	Alkaline phosphatase (U/L)
1st admission	2.45	2.74	562.2	9.25	53
2nd admission	2.16	1.71	557.4	8.57	60

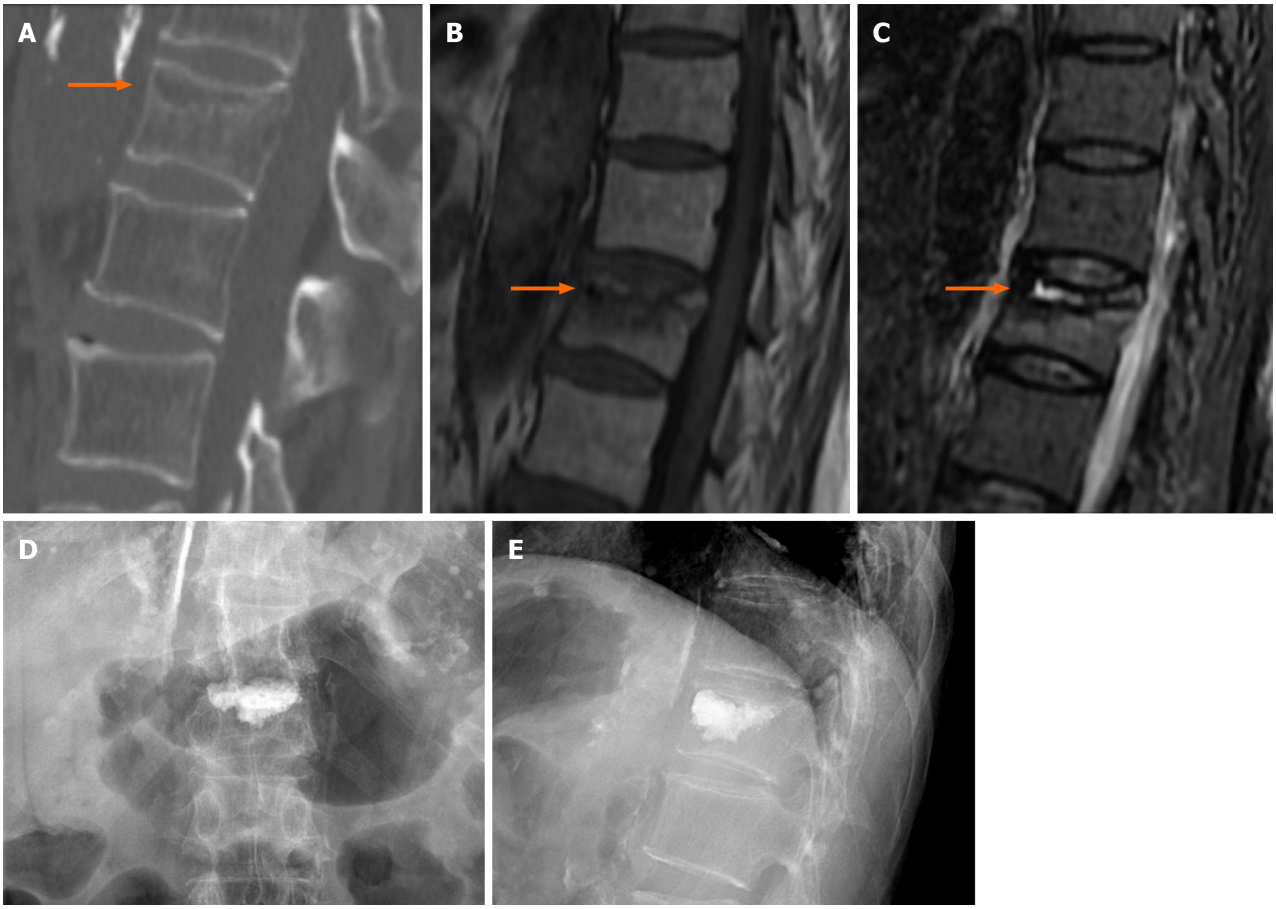

Figure 1 Pre- and post-operative images of T12 vertebral compression fracture. A: preoperative sagittal computed tomography; B: preoperative T1-weighted magnetic resonance imaging (MRI); C: preoperative T2-weighted fat-suppressed MRI; D: postoperative anteroposterior radiograph; E: postoperative lateral radiograph. Orange arrow: The intravertebral cleft in the vertebra.

were excluded.

TREATMENT

He underwent hemodialysis and was prescribed oral medicine as usual. After full preoperative testing and preparation, the patient received T12 PVP (left pedicle approach, cement injection: 3 mL). Typically, the standard procedures of PVP and PKP are the surgical treatment for VCF in patients with CKD-MBD. However, in this case, to fill the intravertebral cleft (IVC; Figure 1, orange arrow) with cement, we penetrated the cleft as precisely as possible during the operation. Postoperatively, the X-ray (Figure 1D and E) revealed that the IVC was filled with the cement without any leakage.

OUTCOME AND FOLLOW-UP

The pain was alleviated significantly on the first postoperative day: The visual analog scale (VAS) score had decreased from 9 to 2, the Oswestry disability index (ODI) score had decreased from 72.5 to 47.5, and he was discharged 3 d later.

During 14th week postoperatively, low back pain occurred again after a lumbar sprain, but he showed no neurological signs or symptoms. CT and bone scan showed T12 and L1 VCFs (Figure 2A-C, thin arrow), the IVC around the injected cement (Figure 2, orange arrow), and the rupture of the posterior vertebral wall (Figure 2, white arrow). The results of the laboratory examination were similar to the previous findings (Table 1). This time, he was diagnosed as having L1 VCF, T12 cemented vertebral refracture, CKD-MBD, and CKD stage 5. After clinical assessment and discussion, we decided to operate again with a further optimized and improved method.

L1 PKP (left pedicle approach, cement injection: 4 mL) was performed as usual, whereas the T12 vertebra was punctured bilaterally (PVP, cement injection: 4 mL). On the left side, a hole in the previous bone cement was drilled using a fine drill, and then, the newly mixed bone cement was injected into the hole and vertebra. The procedure was as usual on the right side. The postoperative X-ray (Figure 2D and E) showed a little cement leakage (Figure 2, bold arrow) in the T12 segment. No neurological signs or symptoms were identified postoperatively. The next day, he could stand and walk with a brace. The VAS score had decreased from 9 to 3, and the ODI score had decreased from 95 to 57.5. He was satisfied with the treatment and discharged 4 d later.

At 1-month follow-up, the VAS score was 2 and ODI was 27.5. The patient complained of chronic low back pain at the 3-month telephonic follow-up, and his VAS score and ODI were found to be 5 and 47.5, respectively. However, owing to loss of follow-up, his imaging examination scheduled to be done at 3-month follow-up could not be performed.

DISCUSSION

Cemented vertebral refracture rarely co-occurs with the adjacent vertebral refracture after PVA in patients with CKD-MBD. The incidence rate of cemented vertebral refracture is reportedly 0.56%–12.5%[4], and its risk factors include age, low BMD, the IVC, high anterior vertebral height restoration, high Cobb angle restoration, and low cement dose in the previous operation[5]. Furthermore, the rate of adjacent vertebral refracture is reportedly 9.9%–16.2%[6-9], and its risk factors include intradiscal cement leakage[6], low BMD, female[10], exceeded cement injection[10], preoperative segmental kyphosis >30°[8], and rheumatoid arthritis and cardiovascular disease[8]. Few studies have reported simultaneous refracture of cemented vertebrae and adjacent vertebrae.

In this case, low BMD and low cement dose in the previous operation may be the factors related to the dual refracture. The minimum volume of cement recommended in the thoracolumbar vertebra is 4–6 mL[11]; however, only 3 mL of the cement was injected in the first operation. In our patient, abnormalities in bone turnover and mineralization caused by CKD-MBD led to low BMD, and we believe this was the most predominant factor resulting in T12 and L1 vertebra refracture. Previous studies have reported that the IVC is the presentation of ischemic vertebral osteonecrosis complicated with fracture nonunion and pseudoarthrosis[12], the histomorphological feature of which is delayed callus mineralization [13].

In the T12 vertebra, IVCs were found both times he was admitted to the hospital. For the first visit at the 3rd week after injury, the abnormality in mineralization and the fracture nonunion caused the formation of the IVC, and its imaging findings were typical[13,14]. At the time of refracture, the IVC formed around the cement again because of abnormal bone mineralization. A large IVC reduced or nullified the strengthening effect of the cement, and the cement even made the vertebra more unstable, thus leading to a fracture even after a minor traumatic injury.

For the L1 vertebra, the low BMD and biomechanical changes of the adjacent vertebra[15] together resulted in the refracture. Thus, the refractures of the vertebrae in this case were both related to the abnormal bone mineralization and low BMD caused by CKD-MBD.

The distribution of cement and filling with cement in the IVC may reportedly influence the clinical outcome[16,17]. In the first operation, we did our best to ensure that the IVC was full of cement and there was sufficient cement distribution. According to the CT findings (Figure 2A and B) acquired after the refracture, although the IVC was completely filled with the cement, the cement was not distributed well. Meanwhile, a larger IVC formed in T12 vertebra, which was accompanied by rupture of the posterior vertebral wall. The surgical technique was optimized to bond the old and the new cement with each other; the IVC was filled with the cement, and more cement was injected into the vertebra. In this way, cement was diffusely distributed, and the stability of the vertebra was enhanced.

The findings of Mo *et al*[18] and Li *et al*[19] establish that cement distribution is associated with the degree of postoperative pain relief. Based on their findings, our patient should have experienced a satisfactory treatment effect; however, he presented with low back pain at 3 months postoperatively. We speculated that the increased stiffness of the cemented vertebrae led to a minimal fracture in the osteoporotic adjacent vertebrae. This implies that medium- and long-term efficacy of PVA may be uncertain in patients with CKD-MBD. Unfortunately, we could not find results of long-term follow-up of these patients in the literature.

Taken together, we consider the following factors to have contributed to the refractures: low BMD, abnormal bone turnover, and abnormal bone mineralization caused by CKD-MBD. These led to the formation of IVCs and may explain why the efficacy was not satisfactory at the last follow-up. The limitation of the case was that bone turnover markers were not tested at the time of admission.

CONCLUSION

For the PVA treatment in patients with CKD-MBD, it is necessary to be aware of the adverse effects of CKD-MBD. It may increase the risk of vertebral refracture. PVA surgical technique needed to be optimized according to the condition of the

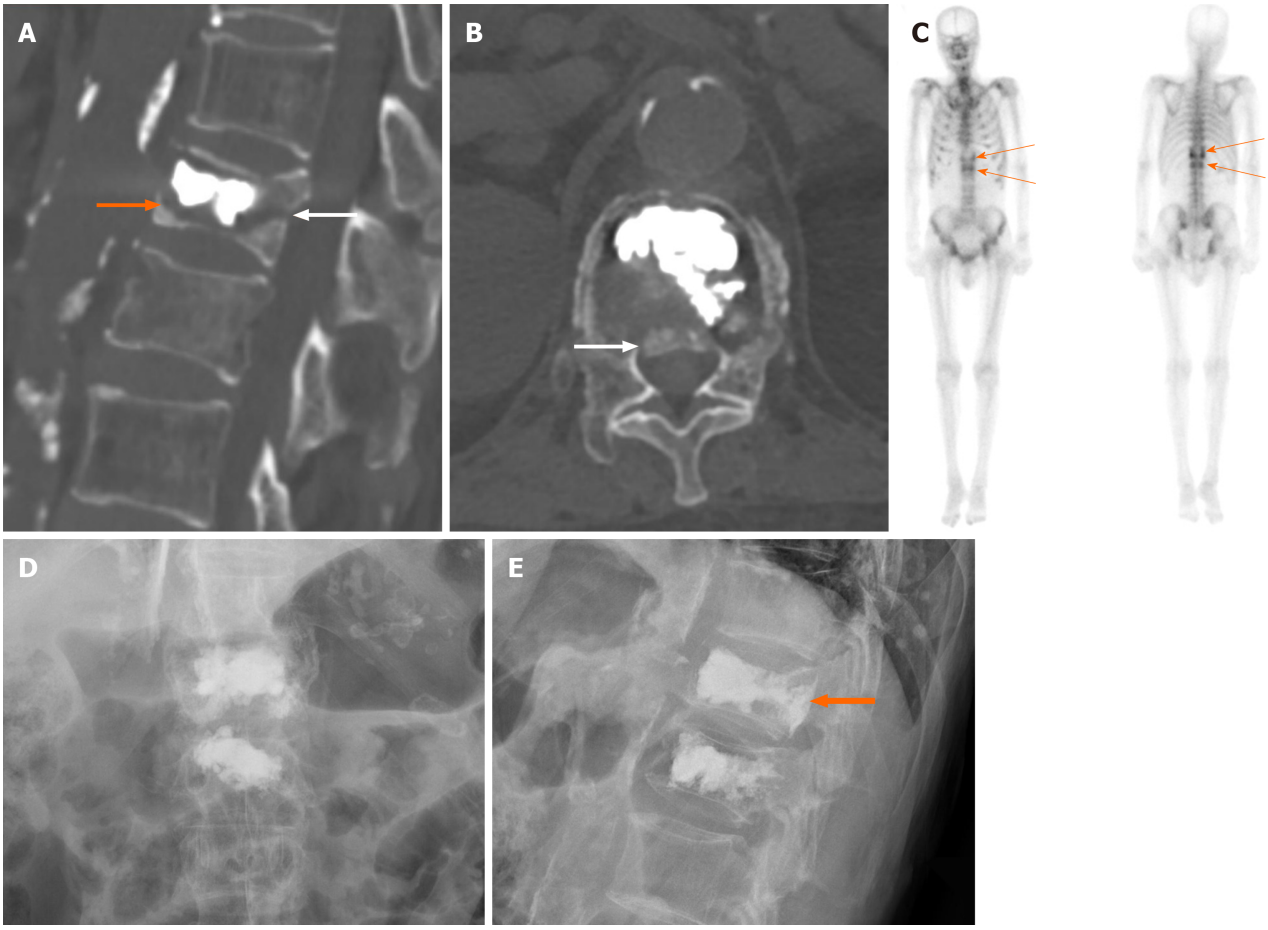

Figure 2 Cemented vertebral refracture and adjacent vertebral refracture after percutaneous vertebral augmentation. A: preoperative sagittal computed tomography (CT); B: preoperative axial CT; C: bone scan; D: postoperative anteroposterior radiograph; E: postoperative lateral radiograph. Orange arrow: the intravertebral cleft in the vertebra; White arrow: the rupture of the posterior vertebral wall; Thin arrow: The fracture of T12 and L1 vertebrae; Bold arrow: Cement leakage in T12 vertebra.

patient. The medium- and long-term treatment effects of PVA may still be uncertain in patients with CKD-MBD.

FOOTNOTES

Author contributions: Yuan YM and Li YM contributed to the conceptualization and project administration; Zhang TD, Cao S, Ren HY investigated the case and data; Zhang TD, Cao S contributed to the visualization; Zhang TD wrote the manuscript; Yuan YM, Cao S reviewed and edited the manuscript; All authors have read and approve the final manuscript.

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CASE REPORT

Idiopathic mesenteric phlebosclerosis missed by a radiologist at initial diagnosis: A case report

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Abstract

BACKGROUND

Idiopathic mesenteric phlebosclerosis (IMP) is a rare type of ischemic colitis characterized by thickening of the wall of the right hemicolon and calcification, sclerosis, and fibrosis of mesenteric veins. The diagnosis of IMP is based on typical clinical features and imaging findings. We report a case of IMP that was initially missed by the radiologist.

CASE SUMMARY

A 77-year-old woman was admitted to the hospital due to chronic diarrhea for over 2 months. She had been consuming Chinese patent medicines (CPM) containing fructus gardeniae for more than 15 years. Colonoscopy revealed an edematous mucosa, bluish-purple discoloration, erosions, and ulcerations throughout the colorectal area. Abdominal computed tomography (CT) showed diffuse mural thickening of the entire colorectum, with tortuous thread-like calcifications in the right hemicolon, left hemicolon, and rectum. Most of the calcifications were located in the mesenteric vein. The diagnosis of IMP was established based on medical history, colonoscopy, CT findings, and histopathological examination. The patient was treated conservatively with papaverine and rifaximin, and CPM was stopped. Her diarrhea symptoms improved, indicating the effectiveness of the treatment. Over the next several years, she took opium alkaloids for an extended period and did not require hospitalization for the

aforementioned gastrointestinal disorder.

CONCLUSION
IMP is a rare gastrointestinal disease affecting Asian populations, possibly related to long-term herbal medicine intake. Accurate imaging analysis is crucial for diagnosis, but insufficient understanding of the disease can lead to misdiagnosis or missed diagnosis. Treatment strategies should be personalized.

Key Words: Idiopathic mesenteric phlebosclerosis; Computed tomography; Colonoscopy; Chinese patent medicines; Fructus gardeniae; Case report

Core Tip: Idiopathic mesenteric phlebosclerosis (IMP) is a rare type of ischemic colitis characterized by thickening of the wall of the right hemicolon and calcification, sclerosis, and fibrosis of mesenteric veins. The diagnosis is based on typical clinical features and abdominal imaging. We report a case of IMP that was initially missed by the radiologist. Finally, IMP was diagnosed by a clinically experienced endoscopist.

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INTRODUCTION

Idiopathic mesenteric phlebosclerosis (IMP) is a rare form of ischemic colitis characterized by thickening of the wall of the right hemicolon and calcification, sclerosis, and fibrosis of mesenteric veins[1]. This clinical entity was first described by Yao *et al*[2] in 1989, and it was proposed to be named as IMP in 2003[3]. In the early stages of the disease, patients may be asymptomatic or have atypical symptoms. As the disease progresses, patients may present with abdominal pain, abnormal stool, or intestinal obstruction[4]. The diagnosis of IMP is based on the characteristic clinical features and abdominal imaging findings[5]. However, we encountered a case of IMP that was initially missed by the radiologist.

CASE PRESENTATION

Chief complaints

A 77-year-old woman was admitted to the hospital with chronic diarrhea for more than 2 months.

History of present illness

Symptoms started more than 2 months before presentation with chronic diarrhea.

History of past illness

The patient had a history of taking Chinese patent medicines (CPM) containing fructus gardeniae for more than 15 years for treatment of constipation. Four years back, she was diagnosed with chronic obstructive pulmonary disease. There was no history of infectious diseases (such as hepatitis or tuberculosis), hypertension, coronary heart disease, or diabetes.

Personal and family history

There was no family history of malignant tumors.

Physical examination

On physical examination, there was severe edema in the patient's lower legs and her abdomen was distended and mildly tender.

Laboratory examinations

Initial laboratory investigations showed hypoalbuminemia (albumin: 30.8 g/L), electrolyte imbalance (K^+: 2.38 mmol/L; Na^+: 128.4 μmol/L; Cl^-: 90.8 mmol/L), and anemia (hemoglobin: 78 g/L). Other laboratory indices were normal. Polymerase chain reaction for *Mycobacterium tuberculosis*, Epstein-Barr virus-encoded RNA, cytomegalovirus (CMV)-BD, and CMV-KT were all negative. The enzyme immunoassay for *Clostridium difficile* toxins A and B were also negative. The stool bacterium culture was negative.

Imaging examinations

Carotid color Doppler flow imaging showed carotid atherosclerosis plaque. Abdominal sonography showed the presence of ascites. The initial abdominal computed tomography (CT) scan did not clearly depict numerous thread-like calcifications within the right-side mesenteric veins and their branches. These calcifications appeared denser in intramural tributaries, marginal veins, and vena recti peripherally. Colonoscopy revealed an edematous mucosa with bluish-purple discoloration, erosions, and ulcerations throughout the colorectal region (Figure 1). Histopathological examination showed mild inflammation and granulomatous reactions (Figure 2).

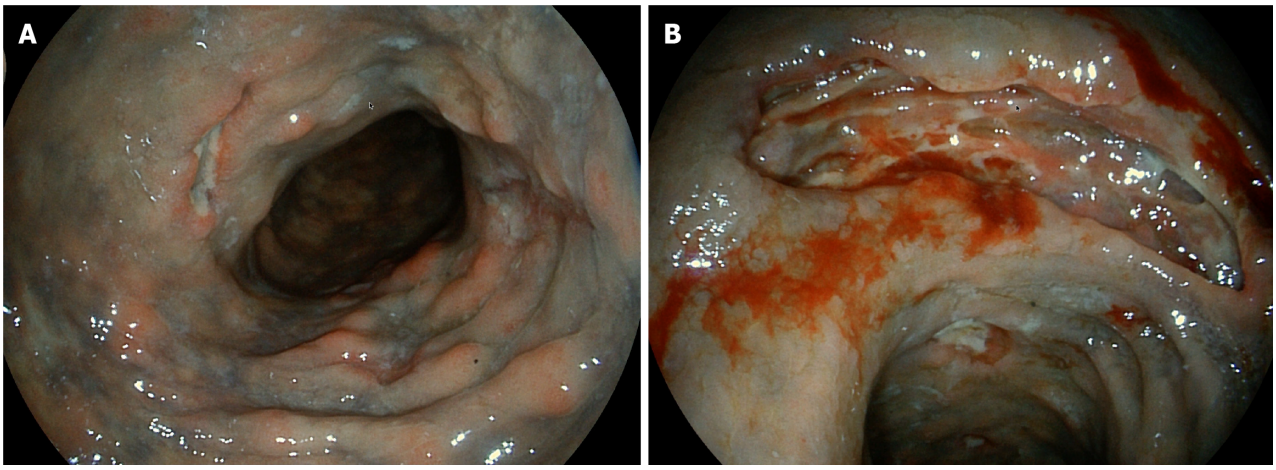

Figure 1 Colonoscopy findings. A: Bluish purple mucosa with multiple ulcers in the ascending colon; B: A deep ulcer in the rectum.

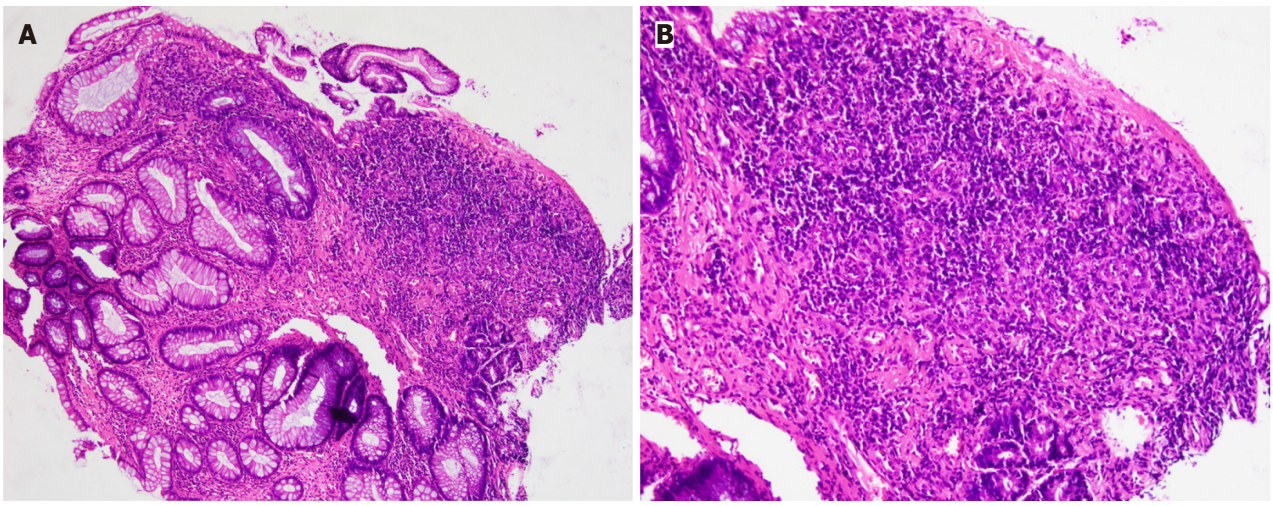

Figure 2 Histological examination. A and B: Mild inflammation and granulomatous reaction were observed.

MULTIDISCIPLINARY EXPERT CONSULTATION

After reevaluating the abdominal CT images in conjunction with colonoscopy findings, a tentative diagnosis of IMP was considered. Further observation of the abdominal CT images exhibited diffuse mural thickening of the entire colon and rectum, with tortuous thread-like calcifications in the right hemicolon, left hemicolon, and rectum. Notably, most of these calcifications were located within the mesenteric vein (Figure 3). Arterial calcification usually occurs in the major arteries. However, it exhibits an irregular and patchy appearance, and usually there are no large areas of point-like fine linear calcifications. Our patient had a plaque in the abdominal aorta and showed stratified calcification in the intestinal wall (Figure 4A and B). The number of point-like intensifications in the arterial and venous phases in similar areas at the same level varied. There was more punctate reinforcement in the arterial phase than in the venous phase, and the punctate reinforcement in the venous phase indicates the foci of calcification (Figure 4C and D). Mesenteric venous calcification points, usually compared to the same level of the venous phase, can be found in the relatively dense occurrence of punctate and linear enhanced areas. In contrast to the arterial phase, the point of disappearance and the position of linear enhancement in the venous phase are usually near the calcification point, and some of the linear enhancement sites become point-like locations, suggesting that there may be arterial enhancement near the calcification point at the same time, which makes the imaging turn linear. It becomes punctate calcification only after the venous phase, relatively in a

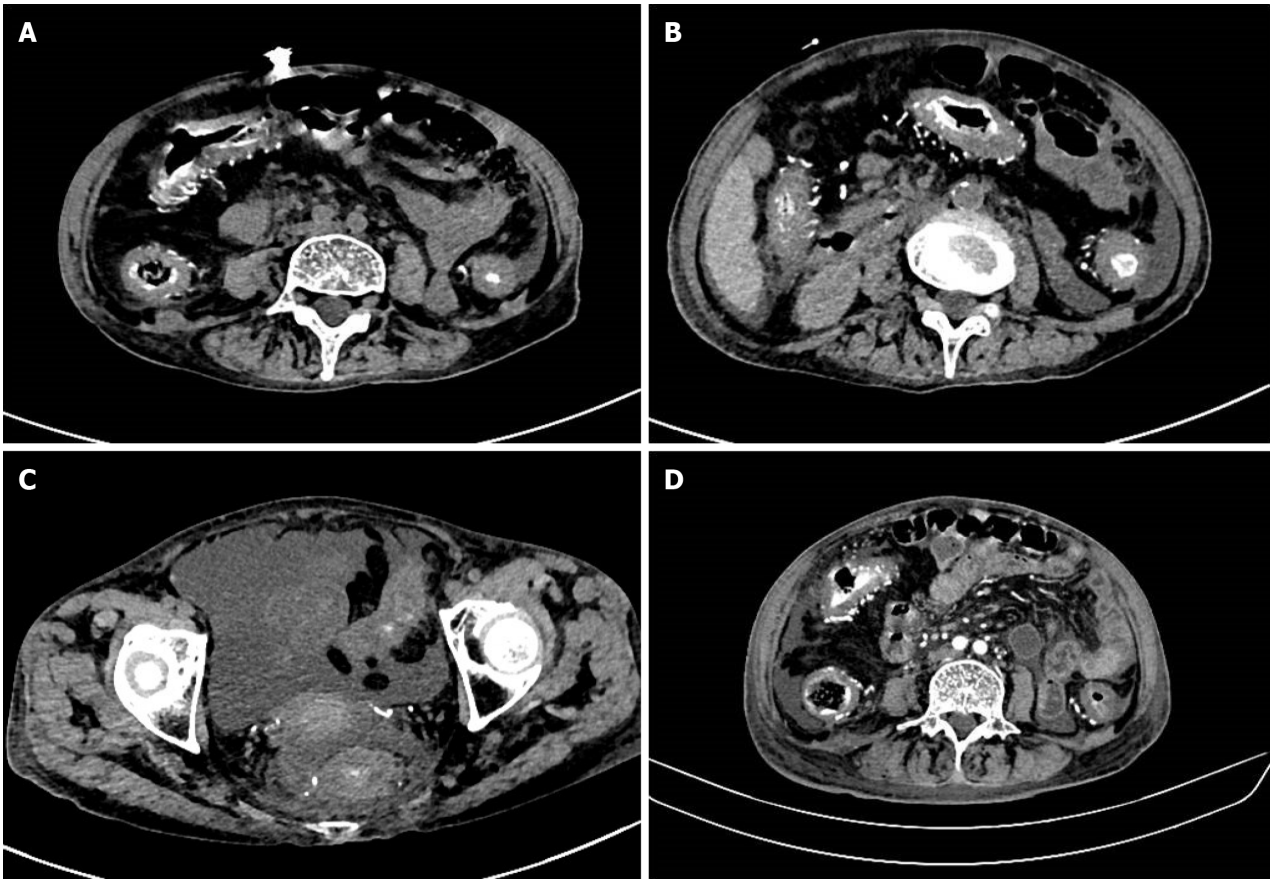

Figure 3 Plain abdominal computed tomography. A-C: Diffuse mural thickening of the total colorectum and tortuous thread-like calcification were observed in the right hemicolon, left hemicolon, and rectum; D: Multiphase, contrast-enhanced computed tomography showed that most calcifications are located in the mesenteric vein.

nearby concomitant position, similar to the relative position of the arteriovenous mesentery. In the arterial phase, the vanishing points in the venous phase will appear randomly, and there will be no similar concomitant relationship between the vanishing points and the calcification points in the same area, and there will be no possibility of linear calcification becoming punctate calcification.

FINAL DIAGNOSIS

A diagnosis of IMP was established based on the patient's medical history, colonoscopy and CT findings.

TREATMENT

The patient was immediately advised to discontinue the use of CPM. Intravenous papaverine (30 mg twice a day) was administered for 3 d, but there was no significant improvement in diarrhea. Although fecal occult blood test was positive and fecal flora was normal, the levels of C-reactive protein (25.03 mg/L) and procalcitonin (0.13 ng/mL) were raised. Therefore, oral rifaximin 0.2 g three times a day was initiated to cover potential intestinal infection. The patient's diarrhea significantly improved, with 1-2 bowel movements per day and improved stool consistency. After discharge, oral rifaximin was continued for 2 wk, while oral papaverine 30 mg is being continued till date, without any side effects.

OUTCOME AND FOLLOW-UP

Nearly 5 years after discharge, the patient has not been readmitted to the hospital for the above disease.

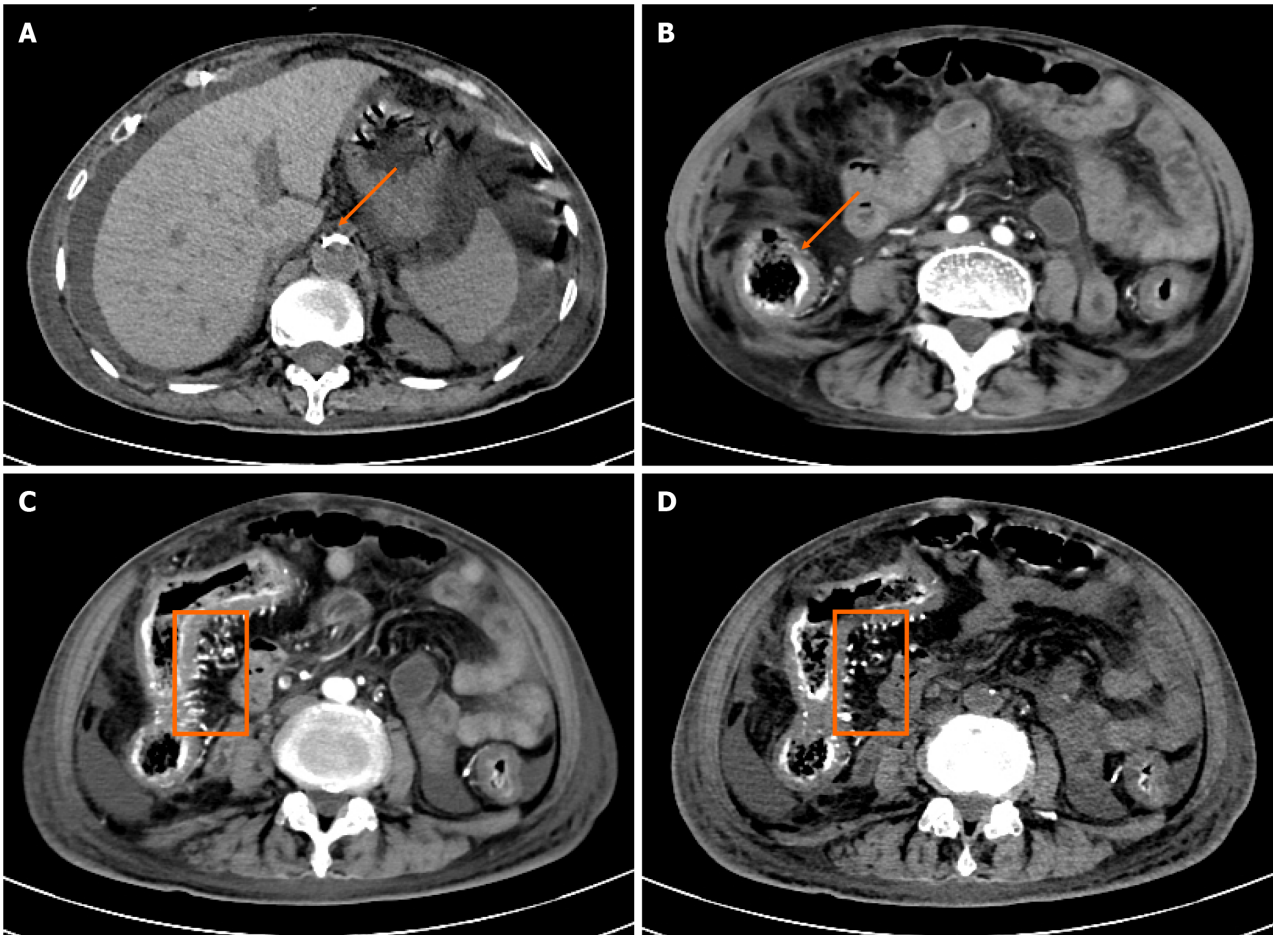

Figure 4 Contrast-enhanced abdominal computed tomography. A: Calcification of the abdominal aorta (arrow); B: Stratified calcification of the intestinal wall (arrow); C and D: The number of point intensifications in the arterial and venous phases in similar areas at the same level were seen to vary (box). There is more punctate reinforcement in the arterial phase than in the venous phase, and the punctate reinforcement in the venous phase is the calcification point.

DISCUSSION

IMP is a rare chronic disease characterized by non-thrombotic, non-inflammatory stenosis or occlusion of the mesenteric veins[6]. It primarily affects the right hemicolon, often involving the proximal colon, and may extend to the terminal ileum or the distal colon[7]. According to a literature review, IMP is more prevalent in middle-aged and elderly men [median age at onset: 61 years (range, 22-87 years)][8]. Guo *et al*[9] observed that the majority of patients were Asians, predominantly from Japan, Taiwan, and mainland China. The exact etiology and pathogenesis of IMP remain elusive but long-term exposure to toxins and biochemical substances may play a role[10]. Nearly all reported cases of IMP had a history of prolonged use of medicinal herbs containing geniposide, such as oldenlandia herbacea, plantaginis semen, eucommiae cortex, herba paederiae scandentis, radix scrophulariae, and fructus gardeniae[11]. Notably, licorice has also been reported as a possible causative agent of IMP[11]. Our patient was a 77-year-old Chinese woman who had a history of taking CPM containing fructus gardeniae for over 15 years, consistent with previous literature reports, and ultimately developed IMP.

Some scholars have proposed that geniposide can be transformed into genipin in the intestinal tract through hydrolysis under the influence of various microenvironmental factors such as the intestinal flora, amino acids, and sulfuric acid. The absorbed genipin then reacts with proteins in the mesenteric vein plasma[6,8]. Additionally, the gradual submucosal accumulation of collagen leads to intimal hyperplasia, venous wall thickening, and fibrosis, resulting in a condition known as "mummification"[6,12]. This process leads to obstruction of venous lumen, impedes venous return, and induces intestinal wall thickening, edema, gliosis, and sclerosis[8,12]. However, geniposide undergoes hydrolysis only after entering the colon and is then transformed to its metabolite, genipin. Genipin then permeates the enterocyte membrane under the influence of various colon microenvironments[6]. This explains why the characteristic lesion sites of IMP are the right-sided colon and transverse colon, which can spread to the entire colorectal area as the disease progresses.

In the early stage, many patients with IMP (10%-27.7%) are asymptomatic[8,13-15]. However, as the disease progresses, patients may present with nonspecific symptoms such as abdominal pain, diarrhea, constipation, nausea, vomiting, abdominal distension, fever, and bloody stool[8,15]. These symptoms complicate the diagnosis of IMP, necessitating the use of abdominal CT and colonoscopy for diagnostic purposes, with histopathological examination ultimately confirming the diagnosis[8]. The typical abdominal CT findings are colonic wall thickening and diffuse calcifications in small

mesenteric veins and their intramural branches[16]. Although the right-sided colon is more commonly involved, the entire colon may be involved in severe cases[16]. The typical colonoscopy findings are a blue or bluish-purple mucosa, which may also display hyperemia, edema, erosion, or ulceration[6]. Histopathologically, IMP is characterized by venous wall thickening, fibrosis, and calcification, venous narrowing, atrophy, and submucosal fibrosis with intrinsic myometrium thickening[10]. Our patient presented with chronic diarrhea. Abdominal CT showed diffuse mural thickening of the entire colorectum and tortuous thread-like calcifications in the right and left hemicolon and rectum, with most calcifications located in the mesenteric veins. Colonoscopy revealed lesions involving the entire colorectal region. Histopathological examination revealed mild inflammation and granulomatous changes. These findings were consistent with the diagnosis of IMP.

As there are currently no standardized treatment guidelines or specific therapeutic agents for IMP, discontinuation of herbal medicine is considered the first-line therapy for early-stage IMP, which, when combined with proper treatment, generally leads to a favorable prognosis[17,18]. According to a large-scale nationwide survey, discontinuation of herbal medicines led to alleviation of symptoms in 84.3% of patients, with none of the cases requiring surgery post-discontinuation[13]. However, the choice between conservative and surgical treatment in patients with IMP is challenging. Surgical treatment will be necessary in case of severe complications, such as colonic obstruction, necrosis, perforation, or massive intestinal bleeding[19]. Sze *et al*[20] reported a 45-year-old Chinese woman with IMP who had stopped consuming Chinese herbs for 3 years and still had recurrent episodes of abdominal pain and flatulence. She eventually had to be treated surgically for intestinal obstruction. However, the presence of poor circulation may mean that colon surgery is not an appropriate treatment, and it must be chosen with care[6]. Our patient received conservative treatment with papaverine and rifaximin and discontinued using CPM. This led to improvement in diarrhea. The patient has been followed for 5 years without any readmissions related to the aforementioned conditions.

CONCLUSION

IMP is a rare intestinal disease that is more prevalent among Asians. The pathogenesis of IMP remains unclear, but it may be associated with the long-term intake of medicinal herbs. While it is crucial to analyze the imaging features on CT or colonoscopy, a lack of awareness about the disease can easily lead to missed or misdiagnoses. The treatment strategy for IMP should be individualized to achieve the best possible outcome.

FOOTNOTES

Co-first authors: Min Wang and Yu-Xia Wan.

Author contributions: Wang M, Wan YX, Liao JW, and Xiong F designed the research study; Wang M and Wan YX drafted the manuscript and provided the images; Liao JW and Xiong F performed the review; Wang M and Wan YX contributed equally to this work as co-first authors; all authors have read and approved the final manuscript.

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CASE REPORT

Gallbladder carcinosarcoma with a poor prognosis: A case report

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Abstract

BACKGROUND

Carcinosarcoma of the gallbladder is a rare malignant tumor with a very poor prognosis. To date, only approximately 100 patients have been reported in the English literature. The prognosis of this tumor type is poor, the preoperative diagnosis is difficult, and there is a possibility of a misdiagnosis. We present an unsuccessful case of carcinosarcoma of the gallbladder with a preoperative misdiagnosis and rapid early postoperative recurrence. Therefore, we have a deeper understanding of the poor prognosis of gallbladder carcinosarcoma (GBC) patients.

CASE SUMMARY

The patient is a 65-year-old male. He was admitted to the hospital because of right upper abdomen distending pain and discomfort for half a month. Abdominal magnetic resonance imaging revealed a polycystic mass in the right lobe of the liver and the fossa of the gallbladder. After admission, the patient was diagnosed with a liver abscess, which was treated by abscess puncture drainage. Obviously, this treatment was unsuccessful. Hepatectomy and cholecystectomy were performed one month after the puncture. Postoperative pathologic examination revealed carcinosarcoma of the gallbladder, and the resected specimen contained two tumor components. One month after surgery, the patient's tumor recurred in situ and started to compress the duodenum, resulting in duodenal obstruction and bleeding. The treatment was not effective. The patient died of gastrointestinal hemorrhage and hypovolemic shock.

CONCLUSION
Carcinosarcoma of the gallbladder is a rare malignant tumor that is easily misdiagnosed preoperatively and has a poor prognosis.

Key Words: Gallbladder disease; Carcinosarcoma; Misdiagnosis; Poor prognosis; Pathological diagnosis; Recurrence; Case report

Core Tip: Herein, we report a patient with carcinosarcoma of the gallbladder who was diagnosed with a liver abscess before surgery due to radiographic polycystic features of the liver. Then, the wrong treatment was administered. After surgical removal of the tumor, the tumor rapidly recurred locally and caused obstruction and bleeding of the digestive tract, leading to the patient's death. We need to learn some lessons from this case.

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INTRODUCTION

Gallbladder carcinosarcoma is an extremely rare malignant tumor that contains both mesodermal and epithelial tumor components[1]. The clinical presentation of this condition is nonspecific, making it challenging to diagnose preoperatively, and the overall prognosis is unfavorable[2]. In 2023, a patient with highly malignant gallbladder carcinosarcoma was admitted to our department, and unfortunately, the patient's prognosis was very poor. The details of the case are presented below.

CASE PRESENTATION

Chief complaints

Abdominal pain for two weeks.

History of present illness

In January 2023, we admitted a 65-year-old male patient to our hospital who presented with a history of abdominal pain for two weeks. The patient reported experiencing right upper abdominal pain and discomfort, characterized by intermittent distending pain, along with mild fatigue and weight loss. Notably, the patient denied any symptoms of jaundice, fever, nausea, vomiting, or diarrhea.

History of past illness

The patient denied any history of hepatitis B or gallstones.

Personal and family history

The patient denied a family history of similar episodes of illness.

Physical examination

The patient's body temperature was measured at 36.5 °C, and no obvious signs of jaundice were observed in the skin or sclera. Tenderness was noted in the right upper abdomen, with no evidence of muscle tension or rebound pain. No palpable masses were detected, but a suspicious positive Murphy sign was noted.

Laboratory examinations

The routine blood test results were as follows: WBC 13.9 × 10^9/L, neutrophils granulocyte percentage 85.5%; RBC 2.86 × 10^{12}/L; Hb 8.0 g/L; PLT 423 × 10^9/L; CRP 105.71 mg/L; liver function: ALT 23 μ/mL; AST 38 μ/mL; AKP 388 μ/mL; r-GGT 469 μ/mL; TBLD 4.7 μmol/L, ALB 37.5 g/L; tumor marker: CA19-9 59.86 μ/mL; CA125 43.97 μ/mL; CEA 2.13 ng/mL; and AFP 7.4 ng/mL.

Imaging examinations

Abdominal computed tomography (CT) revealed clumps with slightly reduced density in the right lobe of the liver and the gallbladder fossa. There was also an area of uneven density, along with localized high-density shadows, with a larger cross-section measuring approximately 10.1 cm × 7.5 cm. An enhanced scan indicated irregular enhancement, suggesting the potential presence of suppurative cholecystitis involving the liver and the formation of a liver abscess (Figure 1).

Admission diagnosis

Liver abscess. Followed by abscess puncture drainage guided by color ultrasound. Approximately 100 mL of milky pus was drained, and less drainage followed. One month later, a follow-up abdominal CT scan revealed that the mass consisted mostly of solid tissue, with a small amount of cystic components (Figure 2). A biopsy of the mass was performed through puncture. The findings suggested a soft tissue sarcoma.

FINAL DIAGNOSIS

The preoperative diagnosis was abdominal soft tissue sarcoma stage IIb (GxT2NxM0, AJCC tumor stage 9th edition). Postoperative pathological diagnosis was "gallbladder carcinoma sarcoma".

TREATMENT

Gallbladder tumor resection was performed under general anesthesia. Intraoperatively, a small amount of light yellow ascites was observed in the abdominal cavity, and the gallbladder was adhered to the surrounding omentum. A palpable soft tissue mass was identified within the gallbladder. The tumor was found to be invading liver segments 5 and 4. Upon removal of the specimen, a section revealed that the gallbladder was filled with soft, fish-like tissue measuring approximately 8 cm × 7 cm × 5 cm. The tumor had invaded the right margin of the liver portal and the right hepatic pedicle. Gallbladder contained new fish-like tissue. Necrosis and bleeding were observed in the lesion (Figure 3).

Postoperative pathological report

The findings indicate a malignant gallbladder tumor involving the entire layer and adjacent liver. Extensive necrosis and vascular thrombus are present. Immunohistochemical staining demonstrates positive expression of CK(AE1/AE3) and CK19 in epithelial cells, negative expression of CK7, positive expression of SATB2 in interstitial cells, and positive expression of TLE1 in the lesion (Figure 4).

OUTCOME AND FOLLOW-UP

The patient experienced a smooth recovery after surgery. However, one month postsurgery, he was readmitted to the hospital due to recurrent vomiting and abdominal distension. A CT examination of the upper abdomen revealed a 9 cm × 8 cm × 8 cm mass invading the right upper abdomen, causing duodenal obstruction. Local recurrence of gallbladder carcinosarcoma with duodenal invasion was suspected (Figure 5).

To alleviate his gastrointestinal symptoms, a gastric tube was inserted to decompress the gastrointestinal tract, successfully draining approximately 500 mL of gastric fluid per day. Unfortunately, the patient declined further surgical intervention. Within seven days of readmission, a significant amount of blood was drained through the gastric tube, and the patient started to pass bloody stools. An attempted interventional embolization and hemostasis procedure was unsuccessful. Subsequently, there was another significant discharge of bright red blood through the gastric tube the following day, accompanied by the continued presence of blood in the stool. At the request of the patient and his family, no further interventions or blood transfusions were pursued. Tragically, the patient passed away two days later due to gastrointestinal bleeding and resulting hypovolemic shock.

DISCUSSION

Gallbladder carcinosarcoma is an exceptionally rare malignant tumor of the gallbladder that accounts for only approximately 1.7% of all gallbladder malignancies[1]. Most reported cases in the literature are sporadic, with a total of approximately 100 documented cases. In 1907, Landsteiner[3] reported the first recorded case of gallbladder carcinosarcoma. This tumor is distinguished by the presence of two malignant tumor components: epithelial tumor tissue and stromal sarcoma tissue.

Carcinosarcoma can also occur in other organs, including the uterus, gastrointestinal tract, lungs, pancreas, thyroid, and kidneys. Although the exact cause of this disease is not well understood, a study by Dacic *et al*[4] suggested that the coexistence of two distinct tumor cell types in carcinosarcoma may be attributed to the varied differentiation pathways of tumor totipotent stem cells.

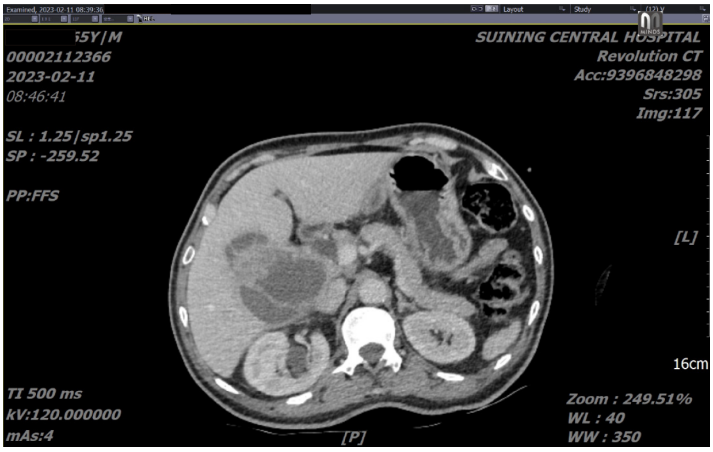

Figure 1 Enhanced computed tomography scan revealed a polycystic mass of 10.1 cm × 7.5 cm in size in the right liver and gallbladder fossa with a thick and enhanced cyst wall. Gallbladder was not obvious. No evidence of gallstones were seen.

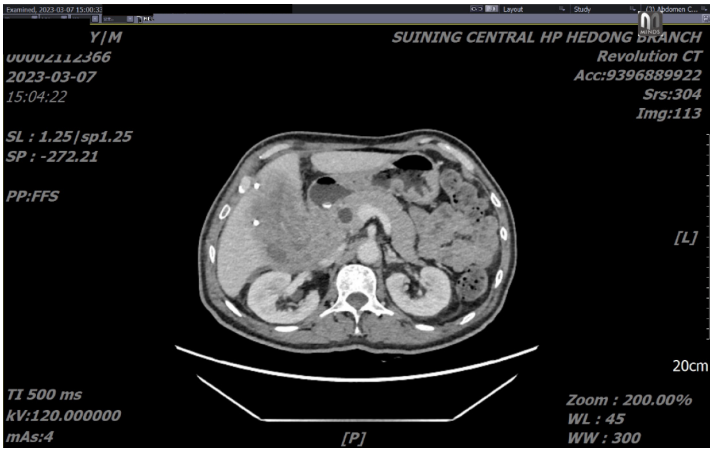

Figure 2 A month later, computed tomography reexamination revealed that the liver mass had not shrunk significantly and had become a fully solid mass. The common bile duct is not dilated by the pressure.

Gallbladder carcinosarcoma is more frequently diagnosed in women than in men and accounts for approximately 72.4% of cases. The average age of onset was 66 years. The most commonly reported clinical manifestations include abdominal pain (76%), weight loss (29%), nausea and vomiting (25%), fever (17%), jaundice (10%), and abdominal distension (4%). Notably, a significant majority of patients had a prolonged history of gallstones (83%). Abnormal liver function is observed in 47.5% of patients, with CA19-9 (15.5%) being the most commonly elevated tumor marker[5].

In the case of this particular patient, the primary clinical symptoms were mild to moderate distending pain in the right upper abdomen and a slight increase in CA19-9, despite a lack of gallstones being detected.

The reported literature on gallbladder carcinosarcoma shows wide variation in tumor imaging sizes, ranging from 25 cm × 35 cm to 1.5 cm × 1 cm, with an average diameter of approximately 8.1 cm[6]. For the patient in our study, the initial maximum tumor diameter was approximately 9 cm × 8 cm.

Regarding magnetic resonance imaging (MRI) and CT findings, most studies describe solid space-occupying lesions within the gallbladder, with some cases demonstrating invasion of the liver and surrounding organs. Unfortunately, imaging findings often lack specific characteristics that can aid in diagnosis and differentiation. In this particular study, the initial MRI findings showed multiple liver cysts, leading to a misdiagnosis of a liver abscess, which was subsequently treated with puncture drainage. Intriguingly, a similar situation was reported by Khurram[7]. The underlying reasons for this resemblance and whether it reflects any unique tissue biochemical reactions during the growth of gallbladder carcinosarcoma in patients have not been determined. Notably, no similar incidents have been documented in the other cases reported in the literature.

Gallbladder carcinosarcoma exhibits a diverse array of compositions, manifesting in various forms, such as leiomyosarcoma, osteosarcoma, chondrosarcoma, synovial sarcoma, rhabdomyosarcoma, angiosarcoma, fibrosarcoma, *etc*[8-10]. In the case of this patient, positive expression of TLE1 and SATB2 indicated the presence of synovial sarcoma and osteosarcoma as the two sarcomatous components. On the other hand, the presence of keratin (CK and CK19) primarily serves as the main diagnostic basis for epithelial adenocarcinoma. It is essential for the diagnosis of carcinosarcoma that both tissue components are concurrently present.

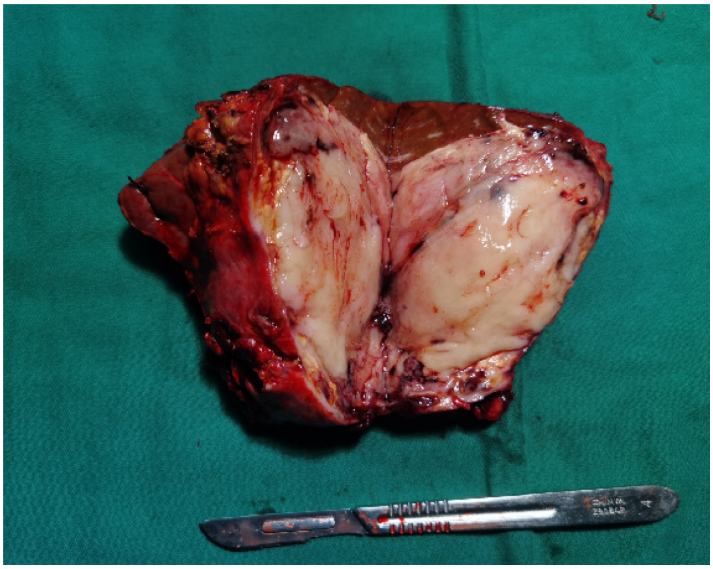

Figure 3 The resected specimen was a nodular mass with a size of about 9 cm × 8 cm × 6.5 cm. The section is grayish white, solid tissue, soft texture, and adhesion to the surrounding tissue. The gallbladder was invaded into the liver. The gallbladder contained new fish-like tissue. Necrosis and bleeding were seen in the lesion.

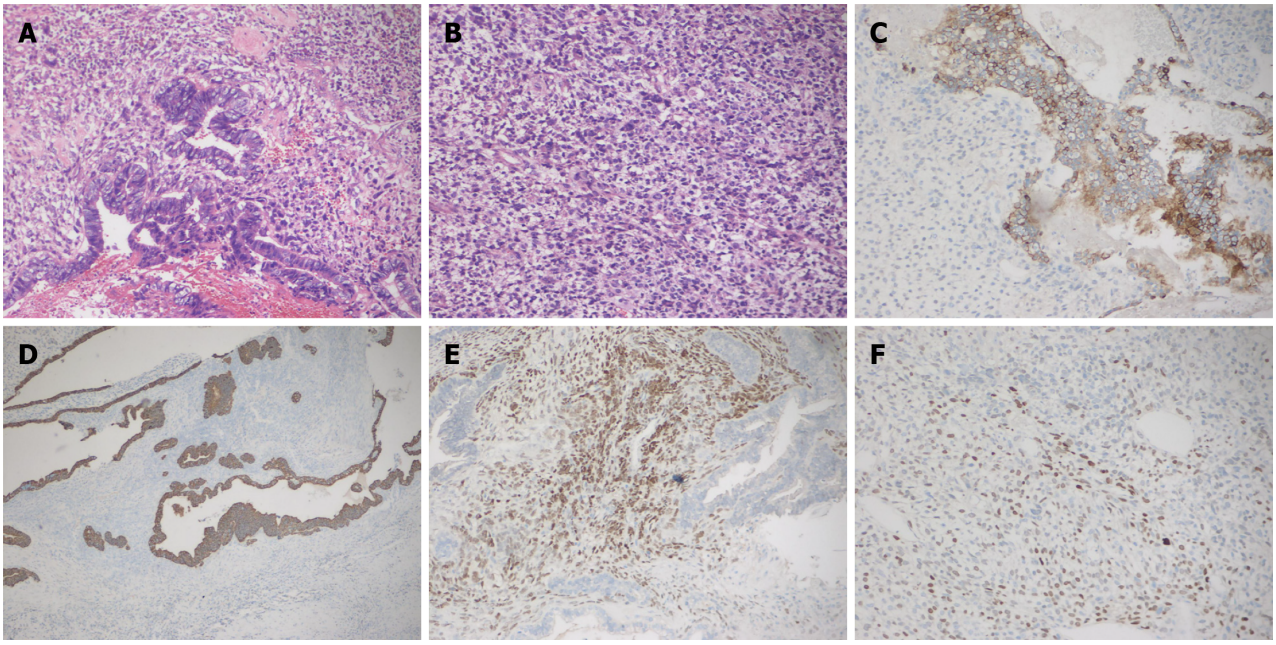

Figure 4 Pathological features of carcinosarcoma of gallbladder. A: High power view of the gallbladder wall show intramucosal adenocarcinoma [hematoxylin and eosin (H&E) stain, 40 ×]; B: High power view show high-grade spindle cell sarcoma (H&E, 40 ×); C: Cytokeratin (CK) (HIC, 40 ×) staining show strong membranous positivity in the intramucosal adenocarcinoma; D: CK-19 (HIC, 10 ×) staining show strong membranous positivity in the intramucosal adenocarcimoma; E: Transducin-like enhancer protein 1 (HIC, 40 ×) staining show strong sarcomatous component positivity in the gallbladder neoplasm; F: Special AT-rich sequence-binding protein 2 (HIC, 40 ×) staining show osteoblastic component positivity in the gallbladder neoplasm.

Gallbladder carcinosarcoma exhibits biological behavior more akin to that of sarcomas and is characterized by rapid growth and insensitivity to both radiation and chemotherapy. Achieving R0 resection through surgical removal is considered the most promising treatment for ensuring long-term survival. However, the patient outcomes generally remain poor. For instance, in a study of 26 patients with gallbladder carcinosarcoma conducted by Huguet *et al*[11], only 3 individuals survived beyond one year. Ajiki *et al*[12] reported in the literature that few patients survive beyond 20 months, regardless of the treatment undertaken. Unfortunately, in the patient who underwent surgical resection, rapid tumor growth, recurrence, and complications arose from organ invasion. These circumstances further underscore the unfavorable prognosis associated with this malignant tumor.

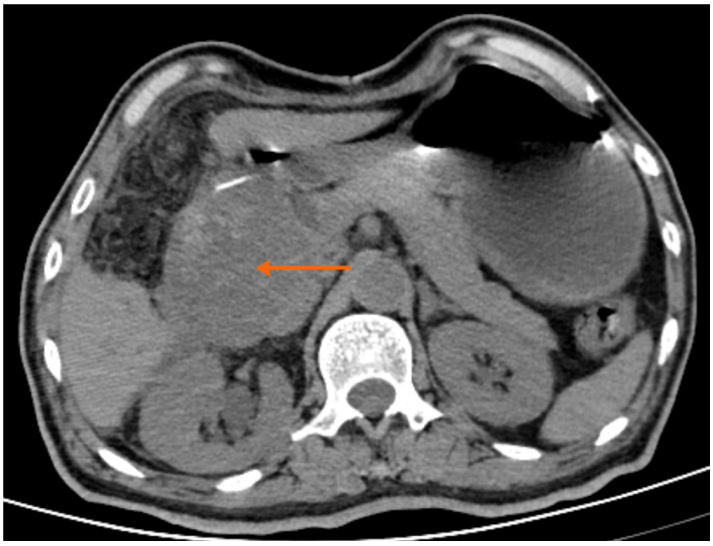

Figure 5 One month after surgery, the patient had recurrent episodes of nausea and vomiting. Vomiting more stomach contents. Abdominal computed tomography (CT) scan (the patient refused to undergo enhanced CT) revealed a 9 cm × 8 cm × 8 cm mass in the anterior duodenum (indicated by the red arrow), leading to duodenal obstruction. Local recurrence of the tumor is suspected.

CONCLUSION

This case report found gallbladder carcinosarcoma is a very rare disease, and its clinical manifestations, laboratory tests and imaging examinations are not specific. As a result, it is easy to be misdiagnosed before operation. Moreover, the prognosis of this disease is extremely poor, and it is prone to relapse even after surgical resection.

FOOTNOTES

Author contributions: Dai Y designed the study, performed the surgery, and managed the patients; Meng M provided the oncology data; Luo QZ provided the pathological data and analysis; Liu YJ, Xiao F, and Wang CH managed the patients and signed the treatment and study consent forms; All authors have read and approve the final manuscript.

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CASE REPORT

Unique method for removal of knotted lumbar epidural catheter: A case report

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Abstract

BACKGROUND

Combined spinal-epidural (CSE) anesthesia is the preferred anesthesia method for cesarean delivery. The use of an epidural catheter is essential for administering additional drugs intraoperatively and managing postoperative pain. However, the insertion of epidural catheters is associated with various complications, such as total spinal anesthesia, symptoms indicative of spinal nerve root irritation, and challenges in epidural catheter removal.

CASE SUMMARY

We present a case report of a challenging epidural catheter removal due to knotting. The lumbar computed tomography scan results revealed that the catheter formed a tight knot in the epidural space. We used a novel extubation method and successfully removed the catheter.

CONCLUSION

The operator can use opposite forces to "spiral" apart the spinal joints by positioning the patient's body in a specific position. The findings indicate that, when combined with imaging examination results, this method is effective for the removal of epidural catheters.

Key Words: Epidural catheter; Knotting; Challenging extubation; Case report

Core Tip: Lumbar computed tomography imaging showed that the reinforced catheter formed a tight knot in the epidural space. The patient's body was placed in a specific position, and the doctor's hands were respectively at the right scapula and the right hip joint of the patient, and the force in the opposite direction was used to "spiral" the spinal joint, and the catheter was successfully removed.

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INTRODUCTION

Challenging removal of the epidural catheter is among the complications associated with continuous epidural anesthesia. This challenge is attributed to the compression of the catheter in the narrow intervertebral space or the formation of loops, tangles, or knots within the epidural space. The occurrence of catheter knotting, which leads to challenging removal, is extremely rare[1].

CASE PRESENTATION

Chief complaints

A 30-year-old female patient (38 wk pregnant, single pregnancy) underwent cesarean section. After the surgery, the anesthesiologist found it difficult to remove the epidural catheter.

History of present illness

The pregnant patient was placed in a right lateral tilt position. The midline puncture through the L2-3 intervertebral space was executed, but the medical staff encountered resistance after several needle direction adjustments. An alternate paramedian puncture technique was used, resulting in reduced resistance. A sensation of ligamentum flavum penetration was experienced at a depth of approximately 7 cm. A negative pressure test confirmed the entry of the epidural puncture needle into the epidural space. Subsequently, a spinal needle was inserted through the epidural needle, resulting in a sensation of dura mater puncture without evidence of nerve stimulation. Clear cerebrospinal fluid flow was observed and 1.8 mL of 0.5% ropivacaine was administered slowly. After removing the spinal needle, the left hand of the anesthesiologist held in place the epidural puncture needle, and an enhanced epidural catheter (MaiChuang Medical, Jiangsu Province, China) was advanced with the right hand until the 15 cm scale. The epidural puncture needle was retracted using the left hand, ensuring that the catheter was retreated outward of the skin to the 12 cm scale, leaving the catheter positioned at a length of 5 cm in the epidural cavity. The catheter was smoothly inserted, and no blood or cerebrospinal fluid was observed upon syringe withdrawal. The patency of the catheter was good, as demonstrated by the physiological saline test. The exposed end of the catheter was fixed to the patient's back using adhesive tape. The anesthesia administered during the surgery was effective, and the procedure was conducted smoothly.

Ten minutes before the conclusion of the operation, the injection of the initial dose of analgesia through the epidural catheter failed due to significant resistance during administration. Preliminary speculation suggested that a section of the catheter might have formed a knot under pressure on the patient's back. However, no knots were observed in the catheter after the surgery. The patient’s position was adjusted to a right lateral tilt, but an attempt to remove the catheter was unsuccessful. The patient did not experience any pain or abnormal sensations during the catheter traction process. Consequently, a decision was reached to postpone the catheter removal. The exposed portion of the catheter was disinfected, dressed, and secured. Intravenous analgesia was administered as an alternative. With the consent of the patient and her family, an emergency computed tomography (CT) examination was performed, revealing a tight knot in the catheter at the right subvertebral notch of the L2 vertebra (Figure 1). Evaluation using the spinal model showed that placing the patient in a left lateral position with the left lower limb extended and the right lower limb flexed at a 90-degree angle allowed the anesthesiologist to apply pressure on the patient's right scapula, pushing it backward and downward with the left hand. Simultaneously, the anesthesiologist applied pressure to the patient's right hip joint, pushing it forward with the right hand. This maneuver effectively "spiraled" and separated the small joints of the spine (Figure 2). A careful attempt was made at the bedside to remove the catheter by using this method with the consent of the patient and her family. The catheter was gently pulled with a constant force. Despite encountering resistance, the catheter was successfully removed. The patient did not experience pain or abnormal sensations during the removal process. Examination of the catheter showed that a knot had formed approximately 3.2 cm from the catheter tip. Additionally, the inner wire coil of the catheter had significantly elongated under continual tension, and the outer part of the catheter coil, located 8 cm from the tip, had fractured, leaving an intact end (Figure 3). The patient was monitored for 1 wk following catheter removal, and no adverse complaints or complications were reported.

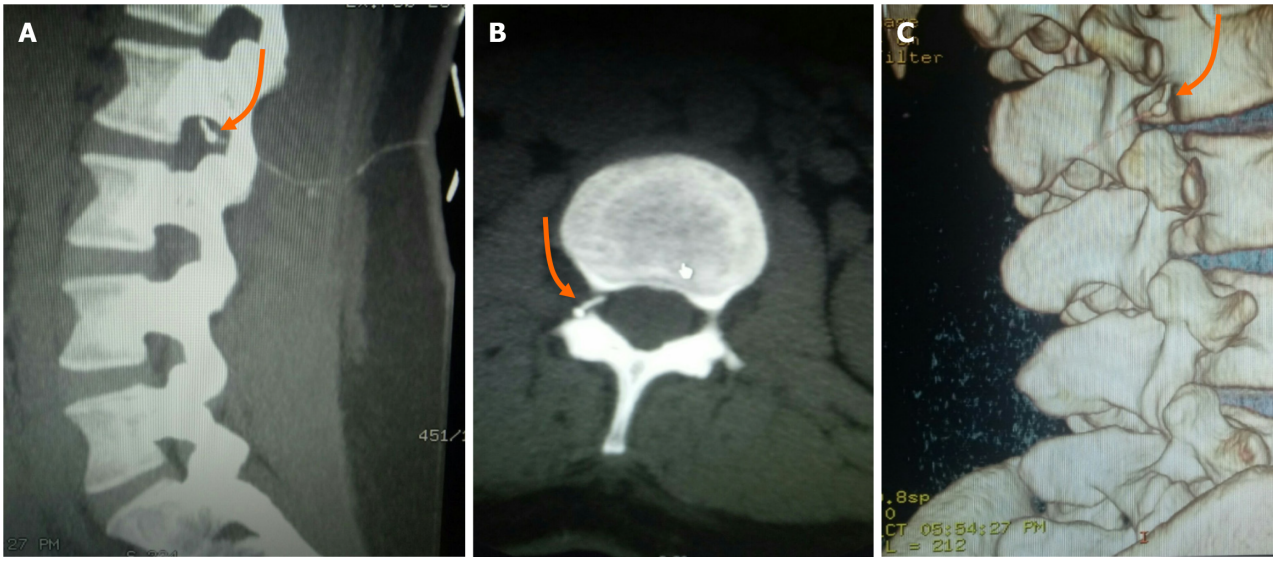

Figure 1 Computed tomography images of the patient. A-C: Computed tomography images of the lumbar region show a knot in the catheter at the right subvertebral notch of the L2 vertebra (indicated by orange arrows).

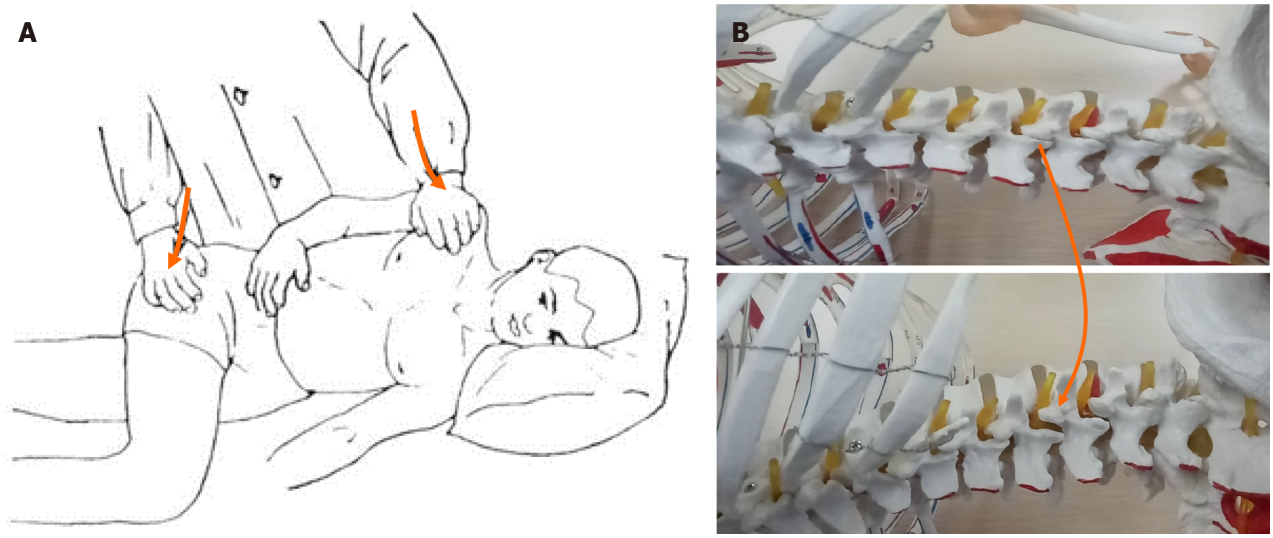

Figure 2 A unique method was adopted in order to pull out the knotted catheter in the patient's epidural space. A: The patient was placed in a left lateral position with the left lower limb extended and the right lower limb flexed at a 90-degree angle. The operator applied pressure on the patient's right scapula, pushing it backward and downward with the left hand while pushing the patient's right hip joint forward with the right hand; B: Demonstration of a spinal model showing the steps presented in A, which effectively opened the right-sided facet joint of the lumbar vertebrae.

History of past illness

The patient had a history of ectopic pregnancy three years ago, and the ectopic pregnancy lesions were removed under laparoscopy.

Personal and family history

The patient had good living habits and denied any family history of disease or other genetic diseases.

Physical examination

The vital signs of the patient were as follows: Body temperature, 36.8 °C; heart rate, 89/min; respiratory rate, 18/min; blood pressure, 138/86 mmHg; weight, 80 kg; and height, 154 cm.

Laboratory examinations

The patient's platelet count was 132 10^9, thrombin time was 16 s, prothrombin time was 10.4 s, fibrinogen was 3.85 g/L, and activated partial thromboplastin time ratio was 0.98.

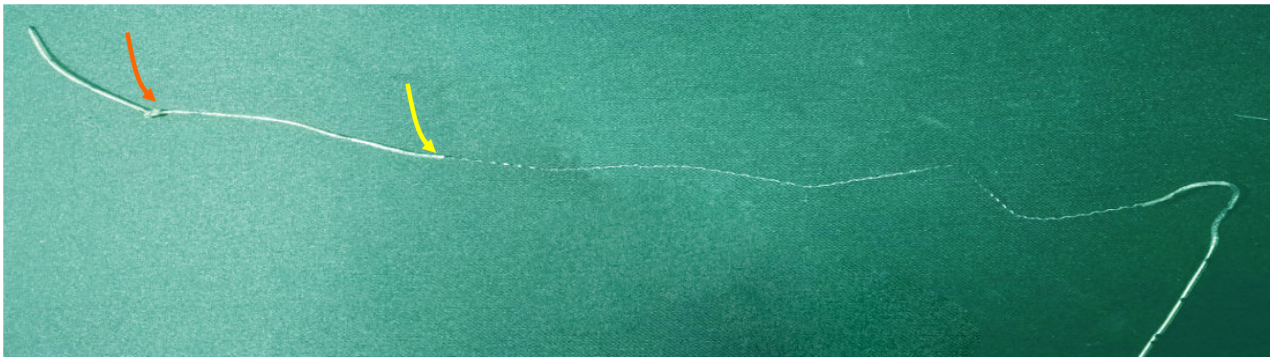

Figure 3 The shape of the knotted catheter in the epidural space after it was successfully pulled out. A knot located approximately 3.2 cm from the catheter tip (indicated by the orange arrow). The soft portion of the catheter coil fractured at a distance of 8 cm from the catheter tip (indicated by the yellow arrow).

Imaging examinations

The preoperative electrocardiogram was normal. Emergency CT examination after the operation showed that the catheter had a tight knot at the right subvertebral notch of the L2 vertebra (Figure 1A-C).

FINAL DIAGNOSIS

The reinforced catheter formed a knot in the epidural space.

TREATMENT

The doctor placed the patient's body in a specific position, with both hands at the right shoulder blade and the right hip joint of the patient, used the "spiral" force in the opposite direction to separate the spinal joint, and successfully removed the catheter.

OUTCOME AND FOLLOW-UP

We used a novel extubation method and successfully removed the catheter.

DISCUSSION

The occurrence of epidural catheter knotting is rare, with an incidence of 1 in 65140 catheters and an average of 0.0015% [2]. The length of the part of the catheter retained in the epidural space is a highly debated issue as it is associated with the incidence of catheter knotting. Some researchers believe that retaining a catheter length of 5 cm in the epidural space is optimal, balancing effective analgesia with the reduction of risks such as catheter looping, extrusion, or inadvertent arterial placement[3,4]. Researchers also propose that retaining the catheter length within 3-4 cm from the catheter tip could prevent a 180° rotation and subsequent knot formation[1]. However, some studies report knot formation even when the catheter length is maintained within 3 cm from the tip[2]. In our study, the knot was located approximately 3.2 cm from the catheter tip. Brichant *et al*[5] reported the formation of a tight single knot at a distance of 4 mm from the catheter tip. Mizota *et al*[6] reported a firm single knot formed approximately 3 mm from the catheter tip. These findings indicate that there is no gold standard for the optimal length of catheter retained within the epidural space to prevent knot formation. Catheter knots are more prevalent in the lumbar region than in the thoracic region[6], with 64.4% of catheter knots occurring in the lumbar region[7]. This difference can be attributed to the perpendicular angle of needle insertion in the lumbar region compared to the obtuse angle in the thoracic region[8]. The obtuse angle allows more effective catheter insertion and advancement within the epidural space.

Researchers are exploring alternative methods for reducing the occurrence of catheter knotting. Enhancing the puncture success rate and catheter placement is important to reduce complications. Obesity is associated with a higher failure rate of epidural puncture and catheter placement[9]. Ultrasound-guided intrathecal puncture and needle guidance techniques are used to improve the puncture success rate and catheter placement[10] and to accurately identify the position of the puncture needle tip[11]. Oscar *et al*[12] observed that visualizing the blood flow in the epidural space and tracking the path of the catheter in the epidural space could be indirectly achieved by injecting 1 mL of normal saline into the catheter and performing color Doppler ultrasound. This technique aids in determining whether the catheter is

forming loops or knots in the epidural space.

A flexed lateral position during removal should be considered if challenges are encountered during the removal of the epidural catheter[13-16]. Although in most cases of catheter knotting, a continuous, gentle pull successfully facilitates catheter removal, approximately 30% of these cases ultimately require surgical intervention due to catheter breakage[14, 17-19]. Previous studies reported successful catheter removal under general anesthesia with muscle relaxation[20,21]. However, this approach should only be considered if the patient remains awake and has not experienced neurological pains or sensory abnormalities during previous catheter removal. If any abnormal neurologic symptoms are observed during catheter removal, the procedure must be stopped because there is a potential risk of the catheter entangling with nerve roots, blood vessels, or other structures[22]. In the present case, it is postulated that during the paramedian puncture, the epidural needle did not penetrate the epidural space in the correct sequence of the supraspinous ligament, interspinous ligament, and ligamentum flavum. The epidural needle traversed through the adjacent paraspinal tissue and entered the epidural space through the vertebral lamina fissure near the right upper and lower facets of the L2-3 vertebrae, ultimately resulting in knot formation in the epidural space.

Previous results indicated that reinforced catheters have higher tensile strength than traditional polyethylene or polyurethane catheters[23]. Asai *et al* reported a case in which a reinforced catheter broke approximately 7-8 cm from the catheter tip during removal, leaving the broken distal end inside the patient's body, while the steel wire from the distal end remained attached to the removed segment of the catheter[19]. Therefore, continuous strong pulling should be minimized even when using reinforced catheters. In this study, we observed that the fracture of the catheter sheath occurred at a distance of 8 cm from the distal end, which could be attributed to the low-density distal end of wire coils in the 7-8 cm segment[19]. In our case, the complete removal of the entire catheter could have been due to the catheter knotting, which prevented the fractured distal end of the catheter from detaching from the inner wire coils. Although reinforced catheters have higher tensile strength, they are more flexible than traditional polyethylene or polyurethane catheters. This prompts the question of whether reinforced catheters may have a higher risk of tangling and knotting when they encounter resistance during insertion into the epidural space.

In summary, knotting of the epidural catheter is a rare complication of spinal anesthesia, with limited clinical reports available. The approach for catheter removal must be tailored to the individual circumstances. In our case, a new and previously unreported method of removing the interdural catheter was reported, and it was done without the assistance of an orthopaedic surgeon, and we recommend using the method presented in Figure 2 of this case report, which involves the use of opposite forces to separate the spinal facet joints in a "spiral" manner based on the imaging examination findings. The results indicate that this technique is more effective for catheter removal and can serve as a reference method in challenging catheter removal situations.

CONCLUSION

The operator can use opposite forces to "spiral" apart the spinal joints by positioning the patient's body in a specific position. The findings indicate that, when combined with imaging examination results, this method is effective for the removal of epidural catheters.

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FOOTNOTES

Author contributions: Deng NH and Chen XC contributed equally to this work; Deng NH and Chen XC wrote the manuscript; Quan SB was responsible for revision and quality supervision of the manuscript; all the authors read and approved the final manuscript.

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CASE REPORT

Moyamoya syndrome may result from psoriasis: Four case reports

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Abstract

BACKGROUND

Moyamoya syndrome (MMS) is a group of diseases that involves more than one underlying disease and is accompanied by moyamoya vascular phenomena. Psoriasis is a chronic immune skin disease closely linked to high blood pressure and heart disease. However, psoriasis-related MMS has not been reported.

CASE SUMMARY

We collected data on patients with stroke due to MMS between January 2017 and December 2019 and identified four cases of psoriasis. Case histories, imaging, and hematological data were collected. The average age of the initial stroke onset was 58.25 ± 11.52 years; three cases of hemorrhagic and one case of ischemic stroke were included. The average duration from psoriasis confirmation to the initial MMS-mediated stroke onset was 17 ± 3.56 years. All MMS-related stenoses involved the bilateral cerebral arteries: Suzuki grade III in one case, grade IV in two cases, and grade V in one case. Abnormally elevated plasma interleukin-6 levels were observed in four patients. Two patients had abnormally elevated immunoglobulin E levels, and two had thrombocytosis. All four patients received medication instead of surgery. With an average follow-up time of 2 years, two causing transient ischemic attacks occurred in two patients, and no hemorrhagic events occurred.

CONCLUSION

Psoriasis may be a potential risk factor for MMS. Patients with psoriasis should be screened for MMS when they present with neurological symptoms.

Key Words: Moyamoya syndrome; Psoriasis; Stroke; Interleukin-6; Immune; Hypertension; Case report

Core Tip: As we all known that moyamoya syndrome (MMS) is a special subtype of intracranial arterial disease. Herein, we analyzed the clinical characteristics and prognosis of MMS-related ischemic and hemorrhagic stroke in patients with psoriasis retrospectively, and also, analyzed the probable mechanisms of psoriasis-related MMS, so as to make a reference for diagnosis and early etiology treatment. Finally we suspect that psoriasis may be a potential risk factor of MMS formation. Whereby, we considered that MMS should be screened in patients with psoriasis when they presented neurological symptoms.

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INTRODUCTION

Moyamoya is classified as moyamoya disease (MMD) and moyamoya syndrome (MMS). MMD is characterized by unexplained intracranial arterial stenosis and the development of characteristic moyamoya-like vessels, primarily affecting the precerebral circulation, first reported by Suzuki and Takaku in 1969[1]. It is prone to transient ischemic attack (TIA), acute ischemic stroke and hemorrhagic stroke. Some patients have a younger age of onset and are prone to severe disability[2]. MMS is a secondary intracranial arterial disease with imaging similarities to MMD but different etiologies, such as atherosclerosis, autoimmune disease or rheumatoid arthritis[2]. However, psoriasis related MMS, especially MMS-mediated cerebral hemorrhage in adult psoriasis patients, has not been reported[3]. Psoriasis is a common, chronic, immune skin disease with a global incidence of about 2%-3% per year that usually presents as red spots and scales on the scalp and extremities. Psoriasis can induce many complications, including autoimmune diseases, cardiovascular and cerebrovascular diseases, and diabetes[4]. A previous study showed that psoriasis was an independent risk factor for stroke; The incidence of stroke in patients with mild or severe psoriasis is 1/4115 and 1/530 per year, respectively[5].

The value of reporting patients with psoriasis in combination with stroke due to MMS is to reveal possible synergistic effects between the two diseases and provide vital clues for a more comprehensive understanding of stroke pathogenesis.

CASE PRESENTATION

Chief complaints

Case 1: A 42-year-old male was admitted to the hospital with sudden weakness in the right hand and foot for 5 h.

Case 2: A 71-year-old man was admitted to the hospital with recurring left-sided limb weakness of 1 year's duration with 4 h recurrence.

Case 3: A 47-year-old man was admitted to the hospital with sudden onset of headache, vomiting, and weakness of the left hand for 2 h.

Case 4: A 65-year-old man was admitted to the hospital with sudden numbness of the left hand for 3 h.

History of present illness

Case 1: Sudden right limb weakness with persistent symptoms. No headache, nausea, vomiting, or impaired consciousness was observed.

Case 2: In the last year, episodic weakness appeared on the left side of the limbs, with only a gradual relief of symptoms within 1-2 h. This time, there was a second episode of persistent weakness in the left limbs. No limb twitching, headache, nausea, vomiting, or impaired consciousness were observed.

Case 3: The patient had sudden onset of headache, vomiting, and weakness of the left hand for 2 h, with persistent symptoms. No limb convulsions or impaired consciousness was observed.

Case 4: Although no limb weakness, convulsions, or impaired consciousness, the patient had a sudden onset of numbness in the left hand for 3 h, with persistent symptoms.

History of past illness

Case 1: Had psoriasis for 30 years.

Case 2: Had psoriasis for 52 years and hypertension for 3 years.

Case 3: Had psoriasis for 30 years and hypertension for 2 years.

Case 4: Had psoriasis for 35 years and hypertension for 3 years.

Personal and family history
None of the four patients had a personal or family history of the disease.

Physical examination
Neurological examination: (1) Case 1: Grade 4 muscle strength in the right upper and lower extremities and Grade 5 muscle strength in the left extremity were observed, and the remaining examination was normal; (2) Case 2: Grade 5 muscle strength was observed in all four limbs, and the rest of the examination was normal; (3) Case 3: Examinations revealed Grade 4 muscle strength in the left upper and lower limbs, Grade 5 in the right limbs, and positive meningeal irritation signs; the rest of the examinations were normal; and (4) Case 4: Hypesthesia in the left upper limb and Grade 5 muscle strength were observed in the left and right limbs, with remaining normal examination findings.

Skin examination: All four patients had red lesions on the lower limbs, with their backs covered with white or silvery-white scales.

Cardiopulmonary and abdominal examinations of all three patients showed no abnormalities or positive signs (Table 1).

Laboratory examinations
Interleukin (IL)-6 was elevated in all cases. Patients 1 and 2 had elevated immunoglobulin E levels, and patient 3 had an elevated CD4 count. Patient 1 had elevated total cholesterol and low-density lipoprotein (Table 2).

Imaging examinations
Case 1: Cranial computed tomography (CT) showed a cerebral hemorrhagic lesion in the left basal ganglia. CT angiography (CTA) revealed severe stenosis of the bilateral middle cerebral arteries with puff of moyamoya-vessels.

Case 2: Cranial CT showed no abnormalities. Digital subtraction angiography exhibited occlusion of the right internal carotid artery with moyamoya-vessels.

Case 3: Cerebral hemorrhagic lesions in the right basal ganglia and lateral ventricle are seen on cranial CT. CTA showed severe stenosis of the bilateral ICAs with moyamoya-vessels.

Case 4: Hemorrhagic lesions were observed in the right thalamus, and foci of old softening were observed in the right basal ganglia. CTA showed severe stenosis of the ICAs with moyamoya-vessels bilaterally (Figure 1).

FINAL DIAGNOSIS

Case 1
Intracerebral hemorrhage, psoriasis, hypertension, hypercholesterolemia.

Case 2
TIA, psoriasis, hypertension.

Case 3
Intracerebral hemorrhage, psoriasis, hypertension.

Case 4
Intracerebral hemorrhage, psoriasis, hypertension.

TREATMENT

Patients 1, 3, and 4 were treated with medications to manage blood pressure and reduce intracranial pressure following the American Society of Anesthesiologists guidelines, whereas patient 2 received clopidogrel and calcium atorvastatin. No brain surgeries were performed.

After consulting with a dermatologist, glucocorticoids and carbotriol were prescribed for patients with psoriasis.

Table 1 Demographic characteristics

Items	Gender	Age of developing psoriasis (age)	Age at MMS-related stroke (age)	Duration of hypertension (yr)	Blood pressure at admission (mmHg)	Type of stroke	NIHSS on admission 0-42	Suzuki grade I-VI	mRS on admission 0-5
Case 1	Male	30	42	-	120/70	ICH	2	III	2
Case 2	Male	52	71	3	122/68	TIA	0	V	0
Case 3	Female	30	47	2	140/88↑	ICH	2	IV	2
Case 4	Male	35	65	3	190/100↑	ICH	1	IV	1

MMS: Moyamoya syndrome; NIHSS: National Institute of Health stroke scale; mRS: Modified Rankin scale; ICH: Intracerebral hemorrhage; TIA: Transient ischemic attack.

Table 2 Data of blood tests

Items	White blood cell (4-10, × 10^9/L)	Neutrophils (1.8-3.6, × 10^9/L)	Monocytes (0.1-0.6, × 10^9/L)	Platelet (100-300, × 10^9/L)	Interleukin-4 (0-3, pg/mL)	Interleukin-6 (0-5.3, pg/mL)	Immunoglobulin E (0-40, mg/L)	Treg cells (CD4+) (2.86-7.74, %)	Cholesterol (2.8-5.2, mmol/L)	LDL cholesterol (1.6-3.4, mmol/L)
Case 1	9.38	5.57	0.63↑	203	1.09	8.27↑	90.8↑	-	5.76↑	4.15↑
Case 2	7.67	4.95	0.51	244	1.22	7.63↑	68.9↑	-	4.04	3.18
Case 3	6.92	4.32	0.5	358↑	3.43	8.49↑	17.8	11.4↑	4.88	3.36
Case 4	9.4	7.5	0.74↑	338↑	0.35	8.86↑	16.9	-	4.84	2.44

The arrows indicated that the results were over the normal cutoff value.

OUTCOME AND FOLLOW-UP

Case 1

The patient was discharged from the hospital with an National Institute of Health stroke scale (NIHSS) score of 0 and a modified Rankin score (mRS) of 0. During the 2-year follow-up, the patient experienced two TIA events and no further stroke events after the administration of aspirin and atorvastatin. The itchy skin recurred.

Case 2

The patient was discharged from the hospital with an NIHSS score of 0 and an mRS score of 0. After 2 years of follow-up, although the patient did not undergo a stroke or TIA, pruritus episodes recurred.

Case 3

The patient was discharged with an NIHSS score of 1 and mRS score of 1. At 1 years after discharge, the patient experienced a TIA and was administered clopidogrel and atorvastatin. No stroke occurred during the second year of follow-up. The itchy skin recurred.

Case 4

The patient was discharged with an NIHSS score of 1 and mRS of 1. After 2 years of follow-up, the patient experienced no further strokes. The itchy skin recurred.

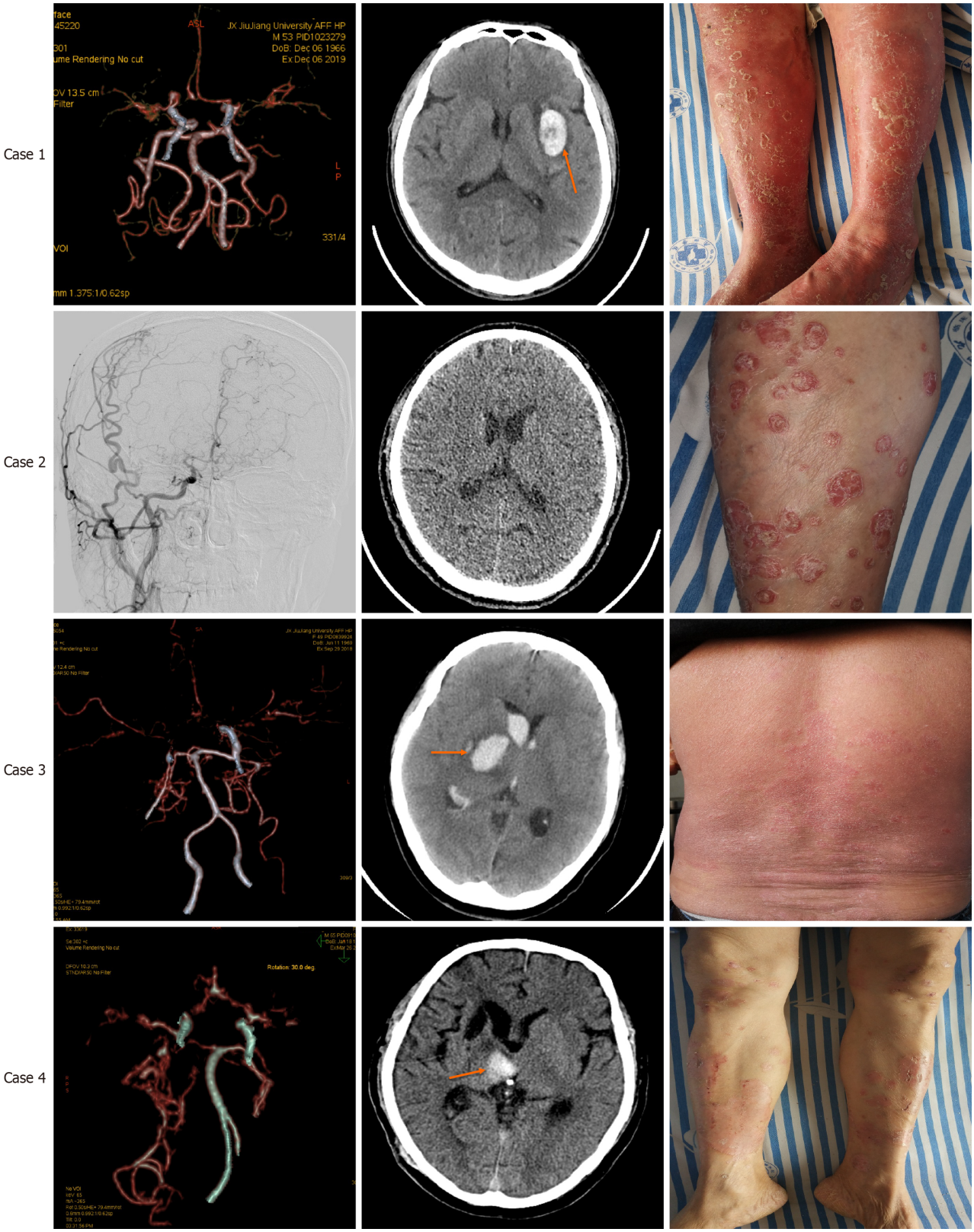

Figure 1 Cerebral arteriography or computed tomography angiography shows arterial stenosis and moyamoya-like vessels. Computed tomography shows cerebral hemorrhage, and limb imaging shows skin psoriasis. Arrows showed the intracerebral hematoma.

DISCUSSION

According to our hospital's database, the prevalence of psoriasis in patients in the moyamoya study group was 1.9% (unpublished data), which is much higher than the prevalence of psoriasis in the Chinese population of 0.47%. Therefore, we hypothesized an association between psoriasis and MMS.

Histological inflammatory infiltration and immune response exist in the pathological mechanism of psoriasis and atherosclerosis, and they have certain similarities[6]. Psoriasis causes dermal skin damage, T cell infiltration and promotes systemic immune processes. Studies have found that the degree of histological infiltration of helper T1 and T17 lymphocytes is positively correlated with the degree of psoriasis and atherosclerosis[7].

All four patients had abnormally elevated plasma IL-6 levels in this study. Immunoglobulin E was abnormally elevated in 2 patients, platelet count was increased in 2 patients, and Treg cells were abnormally elevated in 1 patient (Table 2). Therefore, we speculate that the mechanism of psoriasis-mediated MMS may be that psoriasis activates a chronic T-cell-mediated immune-inflammatory process that damages the endothelial cell layer of the cerebral vasculature, leading to arterial inflammatory intervention stenosis and inducing stroke[3]. Patient 3 had a TIA event in the first year after discharge, and his blood CD4 count was above the normal range, possibly indicating the severity of immune dysfunction. Treatment against psoriasis may require using biological agents to organize psoriasis and stroke. Unfortunately, we did not administer specific immunotherapy to these patients to see if treating psoriasis would prevent stroke recurrence.

Kazumata *et al*[8] has reported a case of MMS-induced psoriasis in an 8-year-old female patient without stroke. There was only one adult male Chinese MMS combined with psoriasis previously reported[9], who presented with typical cerebral ischemia and symptoms of dizziness, tingling, and weakness of the extremities. A meta-analysis reported a 20% increased risk of stroke and myocardial infarction in patients with psoriasis, and a study by Gelfand reported a 44% increased risk of stroke in patients with severe psoriasis[10]. However, neither study provided a detailed classification of stroke subtypes. From our four cases it seems that haemorrhagic stroke was more likely. Abnormally high expression of IgG and S100A4 in the walls of intracranial vessels in patients with MMD suggests that MMD-associated arterial intimal injury releases IgG, which recruits smooth muscle cells through the intima gap, leading to intimal thickening, and that arterial stenosis in MMS has a similar mechanism[11]. It has also been shown that vascular endothelial progenitor cells are involved in MMS-related vascular stenosis. We know that endothelial progenitor cells can induce angiogenesis, monocyte chemotactic protein-1, tumor necrosis factor and vascular endothelial growth factor participate in the activation and proliferation of vascular endothelial progenitor cells, and accelerate angiogenesis. These factors may induce the formation of abnormal vascular networks and lead to stroke[12]. Although three of the four patients had mild hypertension, which may result in stroke, all their hypertension was under control. In this case series, the predominant risk factor of arterial stenosis was psoriasis-related MMS.

To date, this is the first report of cerebral hemorrhage and TIA secondary to psoriasis associated MMS. This study suggests that T cell-mediated immune damage may be involved in the pathogenesis of psoriasis associated MMS. However, the exact molecular mechanism needs to be confirmed with larger clinical samples and basic studies.

CONCLUSION

Therefore, psoriasis may be a potential risk factor for MMS. Thus, patients with psoriasis should be screened for MMS when they present with neurological symptoms.

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CASE REPORT

Thoracic spinal cord injury and paraplegia caused by intradural cement leakage after percutaneous kyphoplasty: A case report

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Abstract

BACKGROUND

Percutaneous kyphoplasty (PKP) is a pivotal intervention for osteoporotic fractures, pathological vertebral compression fractures, and vertebral bone tumors. Despite its efficacy, the procedure presents challenges, notably complications arising from intradural cement leakage. Timely and accurate diagnosis, coupled with emergent intervention is imperative to improve patient prognosis. This case report illuminates the intricacies and potential complications associated with PKP, emphasizing the critical need for vigilant monitoring, prompt diagnosis, and immediate intervention to mitigate adverse outcomes.

CASE SUMMARY

A 58-year-old male patient, experiencing a T7 osteoporosis-related pathological compression fracture, underwent PKP at a local hospital. Two weeks post-procedure, the patient developed paraplegic and dysuric symptoms, necessitating emergency decompression surgery. Gradual improvement was achieved, marked by the restoration of muscle strength, sensation, and mobility.

CONCLUSION

PKP Intradural cement leakage following PKP is unusual and potentially fatal. Prompt imaging examinations, urgent evaluation, and the decompression surgery are essential, which help alleviate symptoms associated with spinal damage, markedly improving the overall prognosis.

Key Words: Percutaneous kyphoplasty; Intradural cement leakage; Complication; Decompression surgery; Case report

Core Tip: The report describes the first documented case of a patient experiencing spinal cord injury, paraplegia, and cerebrospinal fluid leakage after percutaneous kyphoplasty, with subsequent remission achieved through emergency decompression surgery at our hospital.

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INTRODUCTION

Percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP) have emerged as increasingly common techniques for treating osteoporotic and pathological vertebral compression fractures since the late 1980s, with PKP representing a refinement and advancement of PVP[1]. The mechanism of PKP encompasses the reinforcement of vertebral strength, enhancement of spinal stability, and alleviation of spinal pain. Comparative studies have demonstrated that PKP exhibits superior clinical efficacy, safety, pain reduction, and a lower incidence of complications when compared with PVP. Consequently, PKP is widely considered a more suitable treatment modality for most patients with osteoporotic and pathological vertebral compression fractures, as well as vertebral bone tumors[2]. Although rare, complications associated with cement leakage after PKP include symptomatic neurological compromise on nerve roots or the spinal cord, paraplegia, cerebrospinal fluid leakage, pulmonary embolism, and infection. A recent study analyzing 138 articles, encompassing 1027 levels treated with either PVP or PKP, reported no untoward cement-leak-related complications. The authors suggested that cement extravasation may be clinically insignificant, asserting that emergency decompression surgery for cement leaks is unnecessary[3]. Conversely, another recent literature review revealed only seven documented cases of neurological deficits caused by intradural cement leakage after PVP. These cases resulted in residual functional impairment necessitating emergency decompression surgery, highlighting the urgent nature of intradural cement leakage and the need for timely intervention[4]. Notably, there is currently no reported instance of serious complications associated with intradural cement leakage following PKP in the available literature. This report describes the first documented case of a patient experiencing spinal cord injury, paraplegia, and cerebrospinal fluid leakage after PKP, with subsequent remission following emergency decompression surgery at our hospital.

CASE PRESENTATION

Chief complaints

A 58-year-old male patient was admitted to our hospital complaining of lower back pain on September 15, 2023.

History of present illness

Two months before admission, the patient presented with lower back pain, leading to a diagnosis of herpes zoster at the local hospital outpatient clinic. Despite receiving oral medication and infusion therapy, the symptoms persisted. Subsequently, on August 27, the patient sought care at the Orthopedics Department of the local hospital and was admitted. He was diagnosed with T7 osteoporosis and a pathological compression fracture, prompting the performance of PKP on September 4 (Figure 1). Post-operation, the patient experienced relief from lower back pain; however, he developed bilateral hypochondrium pain and abdominal discomfort. Over the following week, the lower back pain and bilateral hypochondrium pain worsened, accompanied by progressive numbness and weakness in both lower extremities.

History of past illness

The patient had suffered from hypertension for 2 years and underwent PKP at a local hospital on September 4, 2023.

Personal and family history

The patient's medical history inquiry revealed the absence of any pertinent familial medical background or genetic predispositions to the observed condition.

Physical examination

During the physical examination, the patient's vital signs were assessed and found to be stable: body temperature was 36.2°C, blood pressure was 120/78 mmHg, heart rate was 73 bpm, and respiratory rate was 20 breaths/min. Examinations of the heart, lungs, and abdomen revealed no specific findings. Upon special examination, positive results were noted for percussion tenderness of the thoracic spinous process, positive findings for extensive tenderness beside the spinous process, and positive tenderness in the bilateral hypochondrium. Muscle strength in both lower limbs, tendon reflexes, and cutaneous sensation exhibited no significant abnormalities. The visual analog scale (VAS) for pain was recorded as 6.

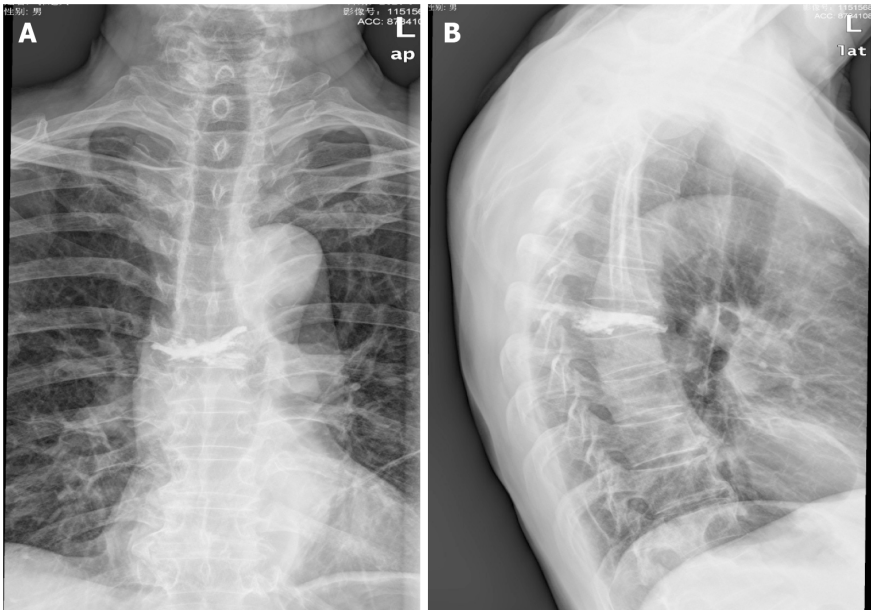

Figure 1 X-ray of the thoracic spine. A: Anteroposterior image of T7 after percutaneous kyphoplasty (PKP); B: Lateral image of T7 after PKP.

Laboratory examinations

Routine blood examination, liver function, electrolyte, infectious disease-related laboratory tests, coagulation function, rheumatoid factors, and the antistreptolysin O test all yielded normal results. Abnormal test findings are detailed in Table 1.

Imaging examinations

Three days after admission, the patient presented with lower abdominal pain, dysuria, loss of sensation below the T7 level, and immobility of both lower limbs. On September 19, 2023, T2-weighted magnetic resonance imaging (MRI) was conducted. The MRI revealed a wedge-shaped T7 vertebra, indicating spinal canal stenosis and spinal cord compression resulting from the protrusion of T7 vertebra cement into the spinal canal (Figure 2). Based on these abnormal findings, it was hypothesized that the patient's paralysis symptoms were associated with the inadvertent leakage of cement into the spinal canal during the kyphoplasty procedure.

FINAL DIAGNOSIS

The patient was diagnosed with thoracic spinal cord injury and paraplegia of both lower limbs.

TREATMENT

Urgent surgical interventions, including the incision and exploration of the spinal canal, posterolateral decompression, T7 subtotal vertebrectomy, and posterior instrumented spinal fusion (T5-T11), were performed on September 20, 2023 (Figure 3). During the operation, it was observed that cement had leaked into the dura within the spinal canal, compressing the spinal cord from the left side and causing contusions to both the spinal cord and nerve root. Post-surgery, the patient was promptly transferred to the intensive care unit (ICU) for vigilant postoperative monitoring. While in the ICU, the patient received standard treatment comprising routine mannitol and dexamethasone to mitigate spinal cord edema. Additionally, a preventative anti-infection regimen involving ceftriaxone was administered to reduce the risk of central nervous system infection.

OUTCOME AND FOLLOW-UP

The day after admission to the ICU, the patient was successfully weaned off the ventilator, and exhibited stability in both respiratory and circulatory systems. Subsequently, he was transferred to a regular ward. Over time, the patient experienced gradual improvement in muscle strength, sensation, and overall mobility, leading to a safe discharge one-week post-surgery. At the one-month follow-up, a diagnosis of pancreatic cancer was made at the local hospital. It was hypothesized that the T7 pathological compression fracture was associated with the presence of pancreatic cancer. Unfortunately, the patient opted to discontinue treatment, marking a regrettable conclusion to his medical care.

Table 1 Abnormal test results

Tests	Results	Normal range
Triglyceride (mmol/L)	3.94	< 1.7
Uric acid (μmol/L)	649	208-428
Creatinine (μmol/L)	229	57-97
C-reactive protein (mg/L)	14.3	≤ 5
Erythrocyte sedimentation rate (mm/h)	49	< 15
Urine protein	1+	Negative

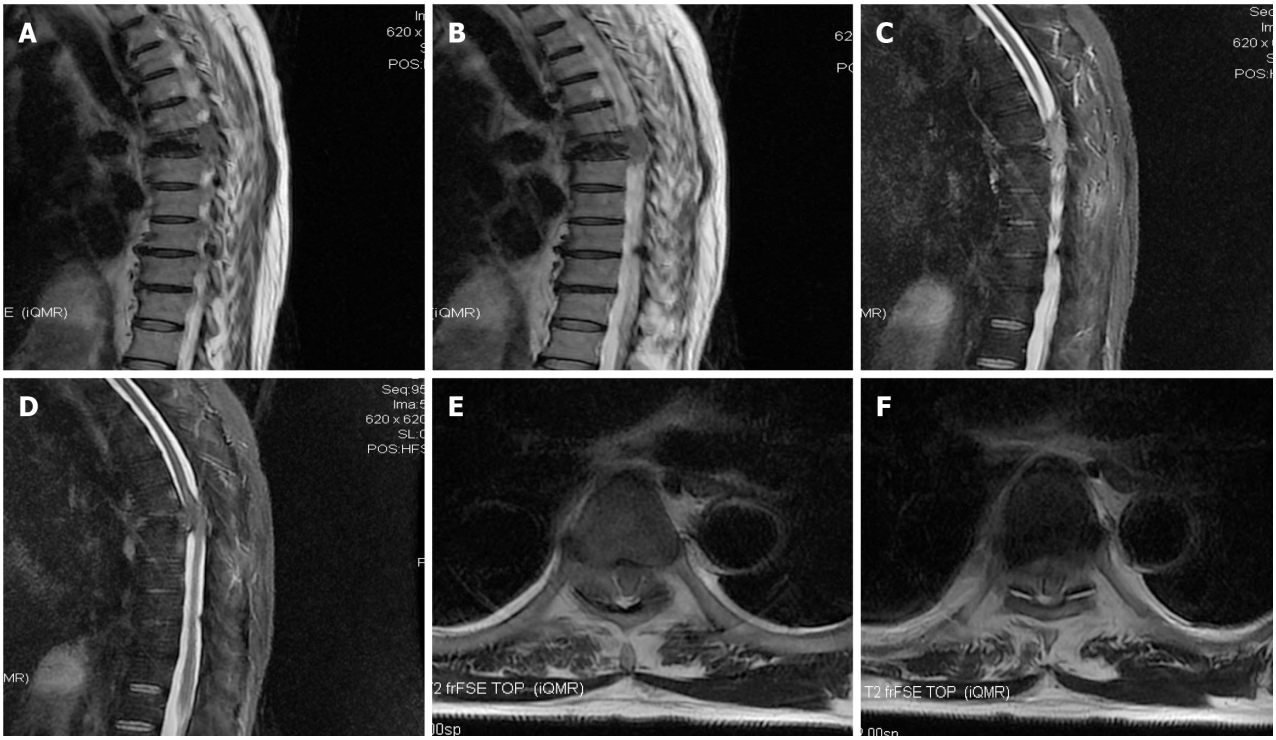

Figure 2 Preoperative T2-weighted magnetic resonance imaging of the thoracic spine. A-D: Sagittal view; E and F: Axial view.

DISCUSSION

Currently, PKP is the preferred and optimal treatment for osteoporotic and pathological vertebral compression fractures, representing an innovative departure from traditional PVP. PKP offers distinct advantages by addressing kyphosis deformity, streamlining procedures to reduce operation time, utilizing an expandable balloon to restore vertebral height, and reinforcing the vertebra while minimizing cement leakage[5,6]. Notably, the reported rate of cement leakage exceeds 80% in PVP but remains below 50% in PKP[3,7]. Cement leakage into the perivertebral or intervertebral disc space generally manifests without significant clinical symptoms. However, when it occurs in the spinal canal or epidural space, it may lead to neurological symptoms or infections, while entry into the paraspinal venous system can result in embolism [8]. Research by Hulme *et al*[9] highlighted that cement leakage in PVP primarily occurs in the spinal canal and epidural region, whereas in PKP, it predominantly occurs in the perivertebral and intervertebral disc space. Several established risk factors for cement leakage include vertebral cortex fragmentation, defects in posterior vertebral walls, pathological compression fractures, high resistance in vertebrae (fracture compression greater than 2/3 or old fracture), a large volume of injected cement, low cement viscosity, low bone mineral density, intravertebral cleft, and Schmorl nodes[10-12]. While cement infiltration into the dura is a rare and serious complication, it has been reported in PVP cases. Herein, we present the first documented case of spinal cord injury, paraplegia, and cerebrospinal fluid leakage due to cement leakage into the intradural space after PKP.

As shown in previously published studies in the same field, the primary cause of dural rupture in this context is attributed to iatrogenic techniques. Specifically, the complication arises from repeated punctures and inaccurate needle angles during the procedure, leading to rupture of the pedicle or vertebral wall cortex and subsequent dural penetration. This sequence of events can result in cement extravasation into the intradural space following withdrawal of the puncture needle[13-16]. In the case of PKP, the recovery effect of the vertebral anterior margin, operative time, and improvement of

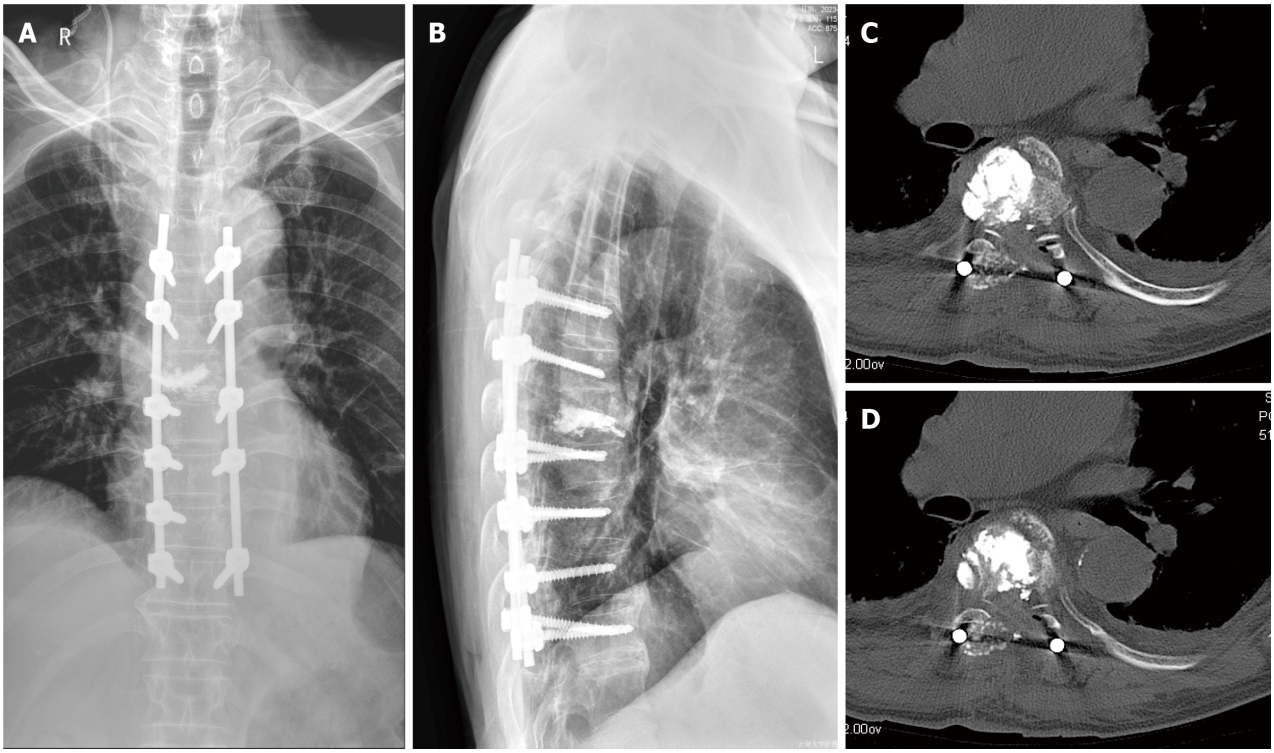

Figure 3 Postoperative image examinations: T7 subtotal vertebrectomy, and posterior instrumentation. A and B: Anteroposterior and lateral X-ray; C and D: Axial computed tomography scan.

postoperative low back pain VAS did not show a significant difference between unilateral and bilateral punctures. However, unilateral puncture demonstrated the advantage of a shorter operative time and reduced cement injection[17]. It is crucial to note that in the unilateral approach, an excessively large puncture angle may lead to damage to the medial wall of the pedicle. Therefore, during the procedure, the needle tip should not traverse the medial border of the pedicle on the anteroposterior view until it reaches the posterior cortex of the vertebral body on the lateral view[13-16].

To effectively prevent cement leakage, several key strategies based on summarized experiences have been identified. Firstly, comprehensive preoperative imaging, including computed tomography (CT) and MRI examinations, is imperative to fully understand the conditions of the injured vertebrae. Careful consideration and meticulous operation are particularly crucial for vertebral bodies with cortical damage. Intraoperatively, maintaining clear visualization of the cement is essential, as blurry images and blind punctures not only heighten the risk of cement leakage but also contribute to the inability to detect intraoperative leakage[18]. Secondly, the selection of cement with an appropriate viscosity is crucial. This, coupled with a strategy to reduce repeated punctures and avoid damaging the medial wall of the pedicle, allows for better control over the speed of cement injection[19]. Studies by Lu *et al*[20] have suggested that infusing a smaller dose (1.8-3 mL) of cement during PKP can achieve equivalent clinical effects to conventional doses (3.5-6 mL) while significantly reducing the incidence of cement leakage. Thirdly, precise control of the strength and depth of the screw tap and guide needle is essential to prevent rupture of the vertebral anterior cortex and subsequent cement extravasation. Implementation of these strategies collectively enhances the safety and efficacy of the PKP procedure[18-20].

Postoperative and meticulous CT scans play a pivotal role in accurately assessing cement leakage. For patients displaying intradural cement leakage and varying degrees of neurological deficits, prompt decompression surgery is imperative[13-16,21-24]. Literature reviews in this specific field indicate symptom improvement in the majority of patients, except one elderly patient who opted against open surgery[24]. Neurological deficits may arise from thermal injury resulting from the exothermic reaction at the posterior cortex of cement leakage in the spinal canal[25]. Early surgical intervention facilitates the removal of cement, reduces chronic inflammation and fibrosis on the cement surface, and prevents further damage to nerve tissue. In our case, the patient developed neurological symptoms, including urination disturbance and paraplegia, two weeks post-PKP. After confirming the precise location of cement leakage by MRI, immediate decompression surgery was performed. After the operation, the patient's muscle power gradually recovered. Our analysis suggests that the root cause of cement leakage in this patient may be attributed to the puncture technique employed by the surgeon.

CONCLUSION

In presenting this rare and distinctive case of intradural cement leakage following PKP, we emphasize the critical role of refining surgical techniques, conducting thorough preoperative evaluations, ensuring clear intraoperative visualization of

the cement, and carefully selecting cement with appropriate viscosity and quantity to mitigate the risk of such complications. In the event of neurological deficits post-PKP, swift action is essential. Performing a prompt CT scan or MRI exploration is imperative to precisely identify the site of cement leakage, facilitating urgent surgical decompression. Our findings underscore the significance of a comprehensive approach to enhance procedural safety and address complications swiftly for improved neurological outcomes.

FOOTNOTES

Author contributions: Xiong ZH and Li JF contributed equally to this work; Xiong ZH and Li JF performed the research and analysis; Mao Z analyzed the data and wrote the manuscript.

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CASE REPORT

Panhypopituitarism caused by a suprasellar germinoma: A case report

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Abstract

BACKGROUND

Suprasellar germinomas are rare intracranial tumors frequently associated with permanent endocrine disorders. We present the clinical picture, treatment, and complications of suprasellar germinoma at pediatric age which, besides being life-threatening, has lifelong endocrinological consequences.

CASE SUMMARY

A 12-year-old female patient was presented having had intensive headaches for three weeks and visual disturbances for six months. An ophthalmological examination revealed bilateral papilledema and a marked loss of vision. Emergency brain magnetic resonance imaging (MRI) showed a suprasellar tumor, involving the infundibulum and the optic chiasm, extending to the third ventricle. Laboratory tests confirmed decreased levels of thyroxine, cortisol, gonadotropins, and insulin-like growth factor 1. Maximal tumor reduction was performed, and immunohistopathology established the diagnosis of suprasellar germinoma. MRI of the spine and cerebrospinal fluid cytology confirmed the localized disease. Adjuvant chemotherapy and radiotherapy were performed according to the SIOP CNS GCT II protocol. A post-treatment MRI showed no residual tumor, but pituitary function had not recovered. Three and a half years after the end of the treatment, the patient is in a complete remission, requiring hormonal replacement therapy, continuous education, and psychological support.

CONCLUSION
This complex case highlights the importance of timely diagnosis, a multidisciplinary approach, and close follow-up in children with suprasellar germinomas.

Key Words: Germinoma; Germ cell tumor; Suprasellar tumor; Hypopituitarism; Management; Pediatrics; Case report

Core Tip: Suprasellar germinomas are rare tumors that may be associated with hypopituitarism at diagnosis and after therapy. We report the presentation, diagnosis, treatment, and complications of a suprasellar germinoma in a 12-year-old patient. The tumor caused visual impairment, headaches, and hypopituitarism. The patient was treated surgically, followed by adjuvant chemotherapy and radiotherapy. Post-treatment panhypopituitarism required hormonal replacement therapy. The case underscores the complexity of managing these rare tumors and the importance of a multidisciplinary approach. The findings contribute to the understanding of the long-term consequences and holistic lifelong care of pediatric patients with suprasellar germinomas.

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INTRODUCTION

Germinomas are germ cell neoplasms that primarily affect the gonads but can appear extragonadally, along midline structures of the body[1]. Intracranial germinomas are rare brain tumors predominantly affecting pediatric and young adult patients. They often occur in the pineal or the sellar/suprasellar regions, and less frequently in the basal ganglia/thalamus[2]. Patients may present with a wide spectrum of non-specific endocrinological, visual, and cognitive disturbances, contributing to delayed diagnosis[2,3]. Slow tumor progression may additionally hamper the diagnosis[4]. Accurate diagnosis is based on the characteristic immunohistopathology and molecular biology[5,6]. No optimal treatment strategy has been established[7]. Germinomas generally respond well to radiotherapy, chemotherapy, or a combination of both, leading to 5-year overall survival rates up to 96%[8,9]. Recently, increasing attention has been paid to the late consequences of the treatment[2].

Germinomas of the suprasellar region cause the clinical picture of diabetes insipidus, visual disturbances, and hypopituitarism, due to the lack of stimulating hormones from the pituitary gland[10,11]. The aim of this case report is to present a patient with a rare brain tumor – a suprasellar germinoma, associated with a rare endocrine condition – hypopituitarism, that persists even after the underlying cause has been cured.

CASE PRESENTATION

Chief complaints

A twelve-year-old female patient presented to the Emergency Department with gradual vision loss for 6 months and frontoparietal headache in the morning for 3 wk.

History of present illness

The patient reported gradual vision loss over the previous 6 months and a 3-wk long frontoparietal headache in the morning. She had no nausea, vomiting, double vision, or other symptoms.

History of past illness

The patient was being followed-up regularly by an ophthalmologist due to strabismus surgery performed at the ages of 8 and 11.

Personal and family history

Parents denied any family history of malignant tumors.

Physical examination

The patient was in a good general condition. Her vital signs included blood pressure 105/69 mmHg, pulse rate 82 beats/min, oxygen saturation 100%, and axillar temperature of 36.7 °C. The girl had age-appropriate growth [height 157 cm (75th

percentile), body weight (BW) 49 kg (75th percentile), and body mass index (BMI) 19.8 (75th percentile)]. Sexual maturation was normal with Tanner stage 2 breast development and Tanner stage 1 pubic hair development. Neurological examination was normal. An ophthalmological examination revealed bilateral papilledema and loss of vision of 50% compared to the previous examination carried out 6 months earlier.

Laboratory examinations

Abnormal laboratory findings included lower levels of thyroxine (7.46 pmol/L, reference range 10-26 pmol/L), cortisol (53.52 nmol/L, range 171-536 nmol/L for a blood sample taken at 8 in the morning), follicle stimulating hormone (FSH) (< 0.1 IU/L, range 3-10 IU/L), luteinizing hormone (LH) (< 0.1 IU/L, range 2-8 IU/L), estradiol (< 18 pg/mL, range 30-400 pg/mL), progesterone (< 0.05 ng/mL, range 0.1-0.3 ng/mL for prepubescent girls), testosterone (< 0.087 nmol/L, range 0.29-1.67 nmol/L), and insulin-like growth factor 1 (IGF-1) (6.7 nmol/L, range 12.5-70.9 nmol/L). Thyroid stimulating hormone (TSH) (1.53 mIU/L, range 0.58-4.1 mIU/L) and adrenocorticotropic hormone (ACTH) (2.20 pmol/L, range 2-11 pmol/L) were within normal limits. Prolactin level (1063 mIU/L, range 40-530 mIU/L) was elevated. The diagnosis of hypopituitarism was established on the basis of diminished levels of anterior pituitary gland hormones (gonadotropins FSH and LH) and target hormones, thyroxine and cortisol. Beta-human chorionic gonadotropin (β-hCG) and alpha fetoprotein (AFP) tumor markers were negative. Lactate dehydrogenase (318 U/L, range 152-284 U/L) and uric acid concentrations (436 μmol/L, range 125-293 μmol/L) were slightly elevated.

Imaging examinations

Emergency magnetic resonance imaging (MRI) of the brain showed a suprasellar mass measuring 22 mm × 18 mm. The tumor was compressing the anterior commissure and the tuber cinereum, extending to the bottom of the third ventricle. The lesion was isointense to the brain on non-contrast T1 weighted image (WI) and showed homogenous contrast enhancement. The axial T2WI MRI scan showed the lesion isointense to the brain. The infundibulum and optic chiasm were incorporated into the mass, and a cyst 13 mm × 10 mm was found in the pineal region. No calcifications, signs of ischemia, or hemorrhage were observed (Figure 1).

FINAL DIAGNOSIS

The final diagnosis of suprasellar germinoma was established by imaging studies and immunohistopathology.

TREATMENT

Replacement therapy with hydrocortisone and levothyroxine was started, but no additional hormone levels in basal conditions and dynamic stimulation tests were performed as the patient's clinical condition dictated emergency intervention.

The patient was transferred to another hospital for neurosurgery. Maximal tumor reduction was performed, and brain MRI at 48 h after surgery showed minimal residual tumor. The postoperative course was uneventful. MRI of the spine and cytology of the cerebrospinal fluid (CSF) confirmed non-metastatic disease. A diagnosis of suprasellar germinoma was established by pathohistological examination. Immunohistochemistry revealed positivity for CD117, OCT-3/4, focal cytokeratin, and placental alkaline phosphatase, and negative staining for CD30, β-hCG and AFP, contributing to the accurate identification of the tumor type.

Postoperative treatment was continued according to the SIOP CNS GCT II protocol for children, adolescents, and young adults with intracranial germ cell tumors. Pretreatment investigations included repeated endocrine status including TSH (0.66 mIU/L, range 0.58-4.1 mIU/L) and ACTH (< 0.22 pmol/L, range 1.6-13.9 pmol/L) and tumor markers, routine blood tests, renal function, and hearing, ophthalmological and neurocognitive assessments.

A central venous catheter was implanted. Adjuvant chemotherapy consisted of two courses of carboplatin/etoposide, alternating with two courses of ifosfamide/etoposide. The courses were given at 21-d intervals; only the second course was delayed due to hematological toxicity. MRI of the brain after four courses of chemotherapy revealed no residual tumor (Figure 2). In the later course the patient was treated with radiotherapy. She received whole ventricular irradiation and tumor bed irradiation in a total dose of 24 Gy (15 fractions, dose per fraction 1.6 Gy).

Due to persistent hypopituitarism, hormonal replacement therapy with recombinant human growth hormone (GH) (somatropin, 1 × 2.25 mg subcutaneously daily), hydrocortisone (10 + 5 + 5 mg per os daily), levothyroxine (1 × 125 mcg per os daily, and estrogens (17 β-oestradiol, 1 × 1 mg per os daily) was conducted. A water deprivation test provided a diagnosis of central diabetes insipidus, requiring therapy with desmopressin (2 × 60 mcg sublingually daily). Progestogens (medroxyprogesterone acetate, 1 × 5 mg per os daily) were added after two years.

The patient was followed-up regularly by an oncologist and endocrinologist. Eight months of treatment with GH led to a height increase of 7 centimeters (from 162 to 169 centimeters). After the end of antitumor treatment, significant weight gain was observed, from BW of 49 kg and BMI of 19.2 to BW 95 kg (94% increase) and BMI of 32.3 (68% increase) over a three-year period. The girl had her first menstrual period at the age of 15. She had marked psychological changes in the form of low self-esteem, depression, anxiety, and maladjustment to her peer group, which required psychological and psychiatric support.

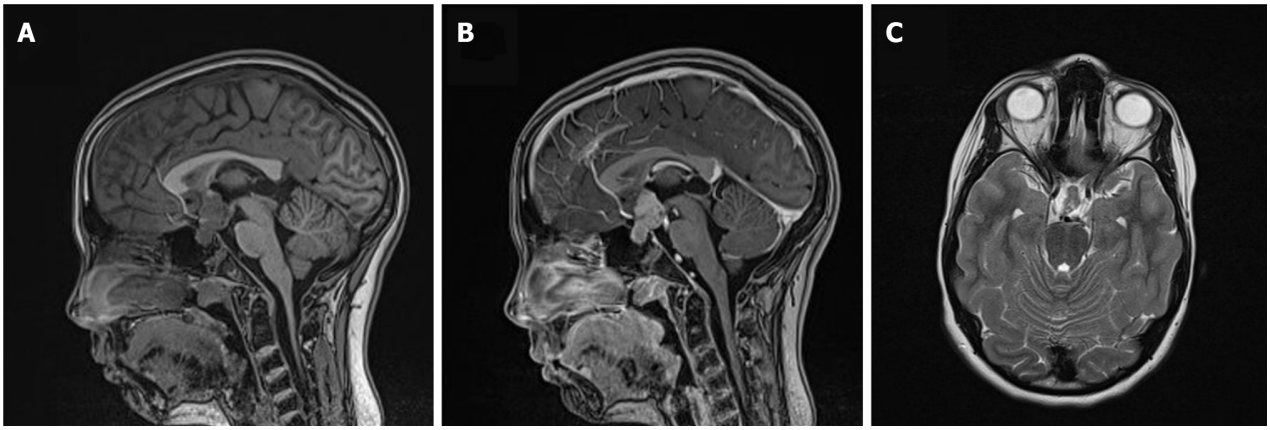

Figure 1 Suprasellar germinoma in a twelve-year-old girl. The sagittal brain magnetic resonance imaging (MRI) scan demonstrates a suprasellar lesion with lobular contours, adjacent to the tuber cinereum and anterior commissure, involving the infundibulum of the pituitary gland and the optic chiasm. A and B: The lesion is isointense to the brain on non-contrast T1 weighted image (WI) (A) and shows homogenous contrast enhancement (B); C: The axial T2WI MRI scan shows the lesion isointense to the brain.

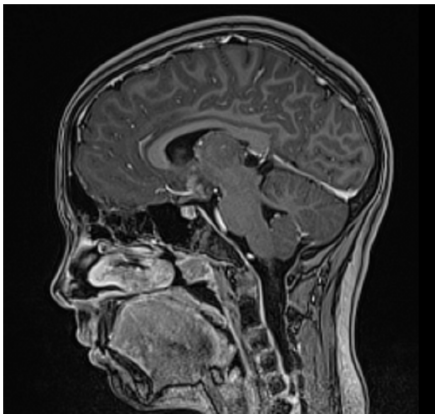

Figure 2 Brain magnetic resonance imaging after the end of chemotherapy. Magnetic resonance imaging shows no residual tumor.

OUTCOME AND FOLLOW-UP

Three and a half years after the end of treatment, the patient is in remission, with regular oncological follow-up (MRI) and hormonal replacement therapy.

DISCUSSION

Hypopituitarism is defined as partial or complete deficiency of a single or multiple pituitary hormones[12]. The clinical presentation varies depending on the underlying disorder, and the number and severity of specific pituitary hormone deficiencies. The presence of signs and symptoms suggestive of hypopituitarism warrants prompt further investigation, including a thorough clinical history and physical examination, baseline biochemical testing, measurement of hormone levels in basal conditions and after appropriate stimulation, and imaging of the brain with pituitary focus[12,13].

Hypopituitarism is divided into primary (caused by disorders of the pituitary gland), and secondary (caused by disorders of the hypothalamus). It can be congenital (associated with structural pituitary and hypothalamic abnormalities) and acquired. Acquired hypopituitarism can result from any damage to the pituitary gland, including tumor, trauma, infection, autoimmune disease, chemotherapy, and irradiation[13,14]. The beginning is insidious, GH is usually the first to be lacking, followed by gonadotropins, and finally TSH and ACTH. Vasopressin deficiency is rare in primary pituitary disorders, but the frequency is higher in lesions of the pituitary stalk and hypothalamus. Lack of all hormones (panhypopituitarism) leads to hypofunction of all target glands. In children, the lack of GH leads to slow height growth, and the lack of gonadotropins leads to a delay in pubertal development. TSH deficiency causes hypothyroidism, with the typical clinical picture of a puffy face, a hoarse voice, bradycardia, and cold intolerance. ACTH deficiency leads to hypoadrenalism, with fatigue, hypotension, reduced tolerance to stress, and infections[13,15].

Treatment is based on the removal of the primary pathology, along with hormone replacement of hypofunctioning target glands. In the case of pituitary apoplexy and hypothalamic compression with progressive deterioration of con-

sciousness, emergency surgery is indicated[16].

The predominant cause of primary hypopituitarism is pituitary tumors, including tumors of germ cell origin[14]. Germinomas are rare intracranial tumors, with an estimated frequency between 0.4%-3.4% in Western countries[10]. Most of these tumors develop along the midline, mainly from the pineal gland, and are usually manifested by diabetes insipidus, visual impairment, and failure of the hypothalamic-pituitary axis[2]. Histopathological and immunohistochemical diagnostics are necessary for optimal treatment[5]. Preoperative staging includes craniospinal MRI, CSF cytology, and measurement of biological tumor markers in the serum and CSF. The surgical approach is determined by the MRI findings, and the extent of resection by staging and intraoperative histopathological evaluation of frozen sections [2]. Treatment should be individualized, and usually consist of a combination of surgery, platinum-based chemotherapy, and focal radiotherapy (whole ventricular and tumor bed radiotherapy[2,17]. Germinomas are very responsive to chemotherapy and radiotherapy, with excellent therapeutic outcomes[8]. The greatest challenge is to minimize the adverse effects of irradiation treatment, and to improve the quality of life of patients who develop neurological, neurocognitive, and endocrine impairments[19].

Our patient had a typical presentation with vision loss and headaches related to the underlying disorder. Her hypopituitarism, with reduced levels of thyroxine, cortisol, IGF-1, and gonadotropins, was clinically silent. Emergency MRI of the brain demonstrated the suprasellar tumor, which was diagnosed as a germinoma with immunohistopathology after surgery. Adjuvant chemotherapy and radiotherapy were performed, and complete remission was achieved. Due to post-treatment panhypopituitarism, hormonal replacement therapy with somatropin, hydrocortisone, levothyroxine, estrogens, progestogens and desmopressin was prescribed.

There are several other reports of suprasellar germinomas with hypopituitarism at a younger age. Jevalikar *et al*[20] reported a 10-year-old boy with central diabetes insipidus and multiple autoimmune disorders, who developed progressive panhypopituitarism. Serial brain MRI showed changes suggestive of germinoma, and the patient was successfully treated with radiotherapy.

Celik *et al*[21] reported on lasting remission from multimodal treatment in an 18-year male presenting with blurred vision, headache and delayed sexual development. Pal *et al*[22] reported a 12-year-old girl with a sellar/suprasellar germinoma, masquerading as secondary granulomatous hypophysitis, presenting with panhypopituitarism and central diabetes insipidus. da Nóbrega *et al*[23] described a 14-year-old boy with a suprasellar germinoma, initially presenting with diabetes insipidus, in whom panhypopituitarism developed after chemotherapy and radiotherapy. Partenope *et al* [24] examined endocrine manifestations in 55 children with intracranial germ cell tumors at diagnosis and during follow-up. Endocrine disorders were present in 50.9% of patients at diagnosis. The most common was diabetes insipidus (85.7%), followed by central adrenal insufficiency (57.1%), central hypothyroidism (50%), GH deficiency (28.5%), hypogonadotrophic hypogonadism (10.7%), and precocious puberty (10.7%). If not diagnosed previously, endocrinopathies arose 15.15 months (1.3-404.2) after the end of treatment in an additional 16.4% patients[24].

All reported cases emphasize the significance of careful clinical and radiological follow-up in patients with endocrine and neurological manifestations. Integrated multidisciplinary involvement, including pediatric oncology, endocrinology, neurosurgery, pathology, radiation oncology and psychology, can optimize the complex care of children with suprasellar tumors and hypopituitarism.

CONCLUSION

Suprasellar germinomas are rare malignant brain tumors that may be associated with hypopituitarism at diagnosis and after treatment. Although the prognosis is good, they still present a diagnostic and therapeutic challenge. Our case highlights the importance of timely diagnosis, multimodality treatment with a multidisciplinary approach, and careful lifelong care of affected patients.

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CASE REPORT

Can we triumph over locally advanced cervical cancer with colossal para-aortic lymph nodes? A case report

Abdulla Alzibdeh, Issa Mohamad, Lina Wahbeh, Ramiz Abuhijlih, Fawzi Abuhijla

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Abstract

BACKGROUND

Para-aortic lymph nodes (PALNs) are common sites for the regional spread of cervical squamous cell carcinoma (SCC).

CASE SUMMARY

We report the case of a 36-year-old woman who presented with cervical SCC with multiple bulky PALNs, largest measured 4.5 cm × 5 cm × 10 cm. The patient was treated with radical intent with definitive chemoradiation using sequential dose-escalated adaptive radiotherapy, followed by maintenance chemotherapy. The patient achieved a complete response; she has been doing well since the completion of treatment with no evidence of the disease for 2 years.

CONCLUSION

Regardless of the size of PALN metastases of cervical carcinoma origin, it is still treatable (with radical intent) *via* concurrent chemoradiation. Adaptive radiotherapy allows dose escalation with minimal toxicity.

Key Words: Cervical cancer; Bulky; Lymph node; Radiotherapy; Para-aortic; Case report

Core Tip: In rare case of locally advanced cervical cancer with massive para-aortic lymph node involvement, we demonstrated successful treatment with concurrent chemoradiotherapy, achieving a complete response without surgery. Our study underscores the challenge of managing such cases because of the limited evidence on the optimal radiation doses for bulky lymph nodes. Despite this, our case highlights the potential efficacy of high-dose radiation, and the importance of multidisciplinary collaboration in treatment planning. Further research is warranted to refine treatment strategies and improve outcomes in similar cases.

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INTRODUCTION

Cervical cancer is a gynecological cancer, with an incidence of 604127 recorded cases globally in 2020[1]. In Jordan, however, cervical cancer is considered a rare cancer, with 39 recorded cases according to the annual cancer registry by the Ministry of Health, and 115 new cases in 2020, according to the International Agency for Research on Cancer[1]. Locally advanced cancer, defined as International Federation of Gynecology and Obstetrics (FIGO) stage IB2 or higher, is treated with definitive chemoradiation and has a 5-year relative survival rate of 58%[2]. Many prognostic factors have been associated with poor survival in patients with locally advanced cervical cancer treated with chemoradiation. Such factors include enlarged regional lymph nodes on imaging, especially para-aortic lymph node (PALN) involvement (stage IIIC2)[3-5]. PALN metastasis was found to be an independent prognostic factor for survival[5].

In this study, we report a case of locally advanced cervical cancer with bulky PALN involvement. To our knowledge, the size of the lymph nodes in the reported case is the largest in the literature. There is no consensus regarding the radiation dose required to control the disease.

CASE PRESENTATION

Chief complaints

The patient was complaining of intermenstrual and postcoital bleeding for 2 months duration.

History of present illness

Her initial symptoms started 2 months prior to diagnosis (May 2021); as she complained of intermenstrual bleeding and postcoital bleeding that became more frequent with time.

History of past illness

Her medical history included endometriosis at the cesarean section scar, which was managed by resection and mesh reconstruction in 2008. She was not taking any medications and reported no family history of cancer. She was a working woman and did not smoke. The patient had been using combined oral contraceptives.

Personal and family history

She was not on any medications and reported no family history of cancer.

Physical examination

Upon examination, her height was 59.84 in (152.00 cm), and her weight was 143.30 kg (65.14 Lb.). Her BMI was 28 kg/m^2. Abdominal examination revealed a Pfannenstiel scar without tenderness or masses on palpation. Her vaginal examination was limited because the patient was nervous during examination and showed a narrowed vagina with an irregular cervical os surface. Bleeding was evident after examination. The inguinal lymph nodes were not palpable, and rectal and speculum examinations were not performed for patient comfort.

Laboratory examinations

Her initial labs showed unremarkable kidney and liver function tests and a HGB level of 13.9 g/dL.

Imaging examinations

Initial pelvic MRI showed thickening of the external os, consistent with cervical cancer, with no definite parametrial invasion. Contrast CT of the chest, abdomen, and pelvis showed multiple enlarged para-aortic and pelvic lymph nodes, some of which showed foci of calcification, measuring up to 4.8 cm in the short axis (Figure 1).

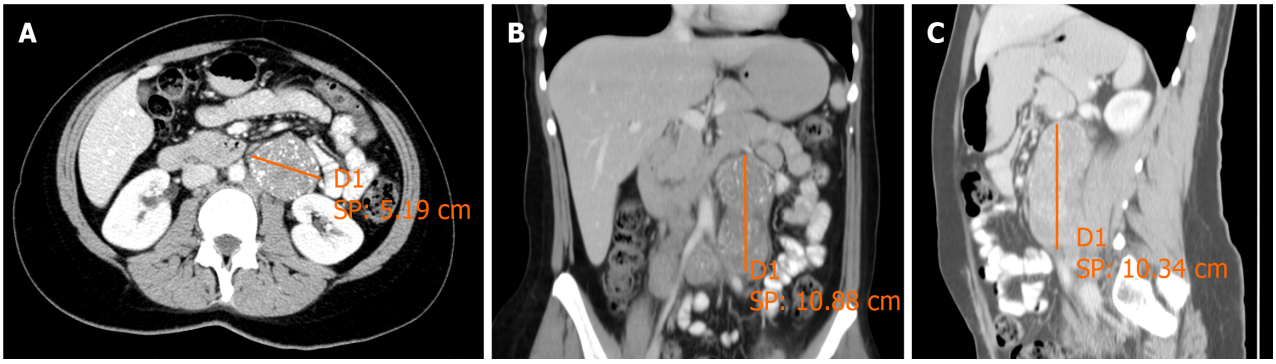

Figure 1 CT scan showing bulky para-aortic nodes. A: Axial view; B: Coronal view; C: Sagittal view.

Her case was discussed in a weekly multidisciplinary clinic for gynecological cancers at our institute, and FDG-18 whole-body PET/CT was recommended. FDG-18 whole body PET/CT scan showed multiple hypermetabolic enlarged abdomino-pelvic lymphadenopathy, involving: retrocrural, aorto-caval, retrocaval, bilateral para-aortic, bilateral common, external, and internal iliac lymph nodes, some of them with calcifications, the most prominent one is measuring about: 5 cm × 4.6 cm in max axial dimension with SUV max of 15. Otherwise, staging was negative for distant metastases.

MULTIDISCIPLINARY EXPERT CONSULTATION

After completing the workup, the case was discussed again in the multidisciplinary clinic for gynecological cancers, and the final staging was determined to be IIIC2 according to the 9th FIGO staging system. The recommended treatment plan was concurrent chemoradiotherapy with cisplatin-based chemotherapy and radiotherapy with external beam radiation therapy and brachytherapy, followed by subsequent assessment with imaging for possible surgical resection of any residual disease, if necessary.

FINAL DIAGNOSIS

Cervical poorly differentiated squamous cell carcinoma (stage IIIC2), according to 9th FIGO staging system.

TREATMENT

Radiation treatment was planned over three sequential phases *via* volumetric arc radiotherapy (VMAT): 45 Gy/25 Fx to the primary tumor, upper vagina, parametrium, entire uterus, and elective and positive lymph nodes, as shown in Figure 2. The second and third phases were boost doses targeting the primary tumor and positive bulky lymph nodes up to 65 Gy, instead of brachytherapy. A brachytherapy boost was deferred as the patient had internal iliac deep vein thrombosis (DVT) with submissive pulmonary embolism (PE) and was deemed at moderate risk for general anesthesia after cardiology and respiratory assessment. In addition, the patient prognosis correlated with the nodal disease status rather than the primary disease since she had minimal thickening at the cervical os *via* MRI following the first phase. Anticoagulation therapy was initiated.

The patient started radiation treatment on September 15, 2021; she required one re-planning CT simulation during treatment as adaptive radiotherapy to account for nodal volume reduction. She also underwent a subsequent CT simulation to plan the boost phase. She completed her treatment on November 24, 2021, with a total duration of 71 d.

She concurrently started chemotherapy with 64 mg of cisplatin and 25 mg of mannitol. The patient received six cycles, and the last cycle was completed on October 24, 2021. Apart from her DVT and PE during treatment, the patient tolerated her treatment well and was seen weekly in a radiotherapy clinic with an acute Radiation Therapy Oncology Group gastrointestinal and genitourinary toxicity profile of grade 1.

After completing chemoradiotherapy, the patient was discussed again by the medical team within the multidisciplinary clinic, and the plan was to administer maintenance chemotherapy with carboplatin/paclitaxel-based therapy. She received five cycles, which were completed in February 2022.

OUTCOME AND FOLLOW-UP

The patient underwent a CT scan with contrast for the chest, abdomen, and pelvis on February 16, 2022, which showed excellent response with no residual uterine cervix tumor and no distant metastases. Stable calcified left para-aortic

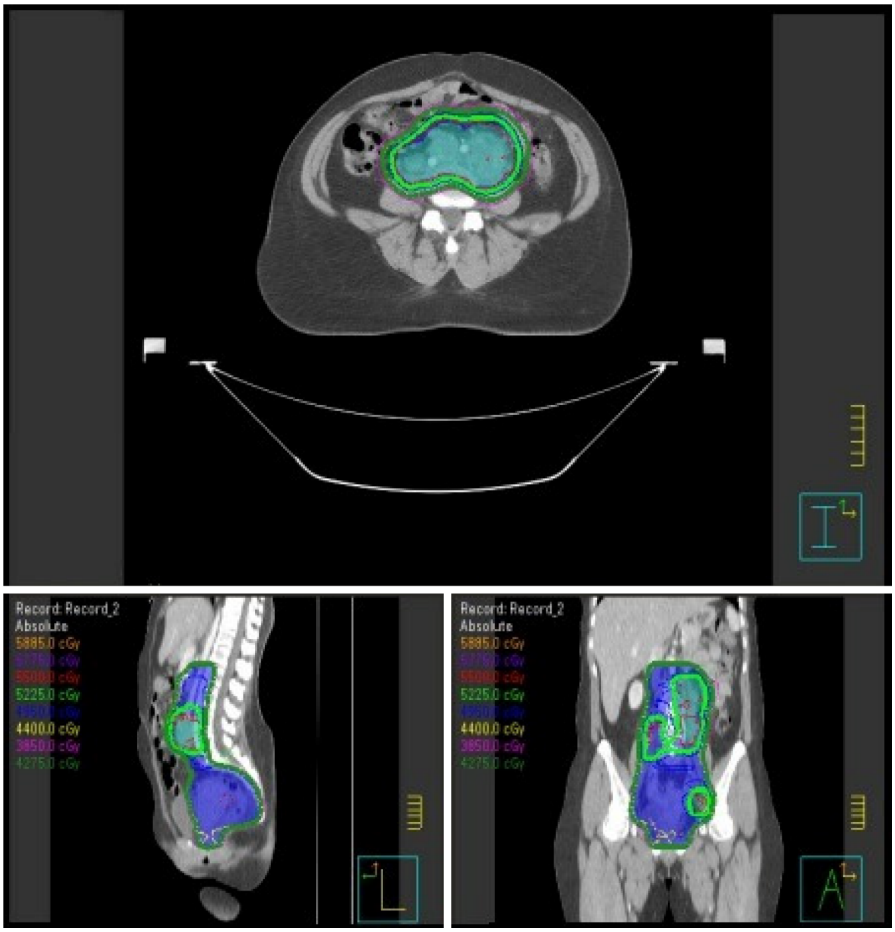

Figure 2 Radiotherapy dosimetric plan, including primary disease and locoregional lymph nodes with simultaneous integrated boost to bulky para-aortic nodes.

PALNs were also observed. Enlarged pelvic lymph nodes were not observed.

Follow-up imaging with MRI and CT on May 21, 2022, showed no local recurrence of cervical cancer. Pelvic lymph nodes were unremarkable. Stable calcified left para-aortic PALNs were also observed.

A Pap smear was performed on August 16, 2022, revealing radiation changes, negative for intraepithelial lesion or malignancy, and the subsequent smear on August 15, 2023, was within normal limits.

A CT scan was performed on October 13, 2022, which showed stable left para-aortic inferior calcified lymph nodes, the largest measuring 2 cm. Otherwise, no definite para-aortic, mesenteric, pelvic, or inguinal lymphadenopathy was observed. MRI was performed on January 15, 2023, and showed no suspicious recurrent or metastatic disease in the pelvis.

Her last follow-up images by chest, abdomen and pelvic CT scan and MRI in January 2024 showed a complete response, with no local recurrence or distant metastasis, as shown in Figure 3. She was assessed in gynecology and radiation oncology clinics in January 2024, she is doing well, and has no gastrointestinal or genitourinary related symptoms, pap smear was performed and came back negative for malignancy.

DISCUSSION

Cervical cancer comes fourth in global female cancers, and also the fourth most common cause of female mortality[1], however it is a rare cancer in Jordan, most likely due to the conservative culture of sexual practice before marriage, although under reporting is also a contributing factor, considering the imperfect cancer registry systems in developing countries like Jordan.

Locally advanced cancer is treated with definitive chemoradiation, and many prognostic factors have been found to be associated with poor survival in locally advanced cervical cancer treated with chemoradiation. These factors include large size of the primary tumor (> 6 cm), non-squamous cell carcinoma histology, advanced stage (IIIA-IVA), a lower pretreatment hemoglobin level (120 and 126 g/L have been identified as cut-off level/value), enlarged regional lymph nodes on imaging, especially PALN (stage IIIC2), HIV positivity, poor functional status, and treatment duration longer than 56 d[3-8]. Pelvic and PALN metastases were significantly associated with worse progression-free survival (PFS), whereas only PALN metastasis was an independent prognostic indicator of survival[5]. In one study, PALN involvement was the most important prognostic factor in radical radiotherapy for cervical cancer[4].

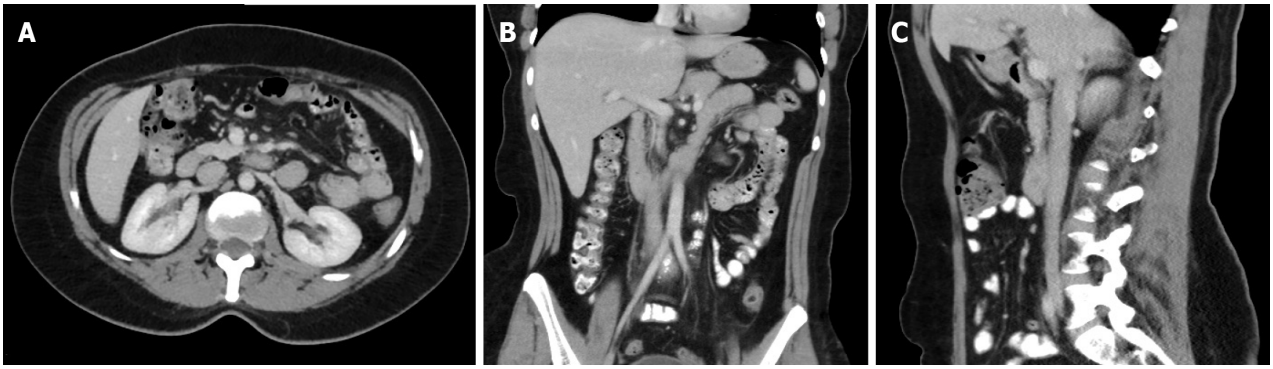

Figure 3 CT scan showing stable calcified para-aortic node. A: No other enlarged nodes on axial view; B: Coronal view; C: Sagittal view.

Oncological outcomes are worse with lymph node metastases and depend on the number, size, and affected region of nodal metastases[9,10]. The term 'bulky' nodes does not have an affixed definition, but a range of ≥ 1.5 or ≥ 2.0 cm of the short axis on imaging has been frequently reported in the literature[11-15]. One study showed that patients with large metastatic nodes (≥ 15 mm) are at an increased risk of early distant disease failure and death from distant metastasis[14]. Large positive pelvic or PALNs (> 10 mm) have been found to be associated with in-field failure after concurrent chemoradiotherapy[9]. A size ≥ 10 mm of the involved pelvis and PALNs was a significant prognostic factor for poor overall survival and disease-free survival rates[9].

Resection of bulky lymph nodes prior to radiotherapy may affect patient survival. A study published in 1995 found that survival was comparable for patients with completely resected bulky pelvic and common iliac nodes in comparison with patients with micrometastases, suggesting that resection prior to concurrent chemoradiotherapy may benefit patients, especially when higher doses may be required to eradicate bulky nodes[15]. There is a paucity of data regarding the dose of radiation that is sufficient to effectively treat bulky lymph nodes, particularly PALNs that reside at levels that require a significantly larger field of radiation.

A study published in 2014 studied 61 patients with locally advanced cervical cancer with nodal involvement (pelvis only in 67% and pelvis + para-aortic in 33%). The median nodal size was 1.8 cm, ranging from 0.7 cm to 4.5 cm. The patient was treated with concurrent chemoradiotherapy and brachytherapy. External beam radiotherapy was performed with extended-field intensity-modulated radiation therapy at a dose of 45 Gy in 25 fractions with simultaneous boost to the involved nodes to a median of 55 Gy in 25 fractions. Local failure rates were low (at a mean follow-up time of 29 months, eight patients experienced recurrence), suggesting that a dose of 55 Gy in 25 fractions was effective in treating the involved nodes[16].

Adjuvant systemic treatment after concurrent chemoradiotherapy is an area of research aimed at improving the outcomes of locally advanced cervical cancer. However, the OUTBACK trial showed that chemotherapy after concurrent chemoradiotherapy for locally advanced cervical cancer did not improve overall survival or PFS[17].

CONCLUSION

Despite their large size, bulky PALNs can still be treated with chemoradiation for locally advanced cervical carcinoma with curative intent. More prospective studies and trials are needed to fill in the gaps to determine the best radiation doses and regimens and the most suitable adjuvant treatments in terms of oncologic outcomes and toxicity profiles.

FOOTNOTES

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