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Contents

Thrice Monthly Volume 12 Number 12 April 26, 2024

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Clinical Trials Study

META-ANALYSIS

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 12 April 26, 2024

Contents

CASE REPORT

LETTER TO THE EDITOR

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 12 April 26, 2024

Contents

ABOUT COVER

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EDITORIAL

Protein C deficiency with venous and arterial thromboembolic events

Nan Zhang, Dong-Kun Sun, Xu Tian, Xin-Yu Zheng, Tong Liu

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Abstract

Protein C (PC) is a key component of the vitamin K-dependent coagulation pathway. It exerts anticoagulant effects by inactivating factors V and VIII. Acquired or inherited PC deficiency results in a prothrombotic state, with presentations varying from asymptomatic to venous thromboembolism. However, there has been an increasing number of reports linking PC deficiency to arterial thromboembolic events, such as myocardial infarction and ischemic stroke. This editorial focuses on the association between PC deficiency and thromboembolism, which may provide some insights for treatment strategy and scientific research.

Key Words: Protein C deficiency; Venous thromboembolism; Myocardial infarction; Editorial; Arterial thromboembolism

Core Tip: Protein C (PC) deficiency impairs the balance between the procoagulant and anticoagulant system, which results in venous thromboembolism. However, there has been an increasing number of reports linking the condition to arterial thromboembolic events. A thorough understanding of PC deficiency is essential for the development of new management strategies against PC deficiency-related thromboembolism events.

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INTRODUCTION

In this editorial, we comment on the case report by Seo *et al*[1] published in the recent issue of the *World Journal of Clinical Cases*. The authors presented a case of unprovoked pulmonary thromboembolism and deep vein thrombosis followed 9 month later by acute myocardial infarction without any underlying major risk factors for atherosclerosis cardiovascular disease, which possesses important clinical implication[1]. Therefore, in this editorial, we discuss the biology and pathophysiology of protein C (PC) and PC deficiency-related venous and arterial thromboembolism (ATE), as well as treatment strategy.

PC AND PC DEFICIENCY

PC is a vitamin K-dependent proenzyme that is synthesized in hepatocytes and circulates in the blood as an inactive zymogen[2]. Thrombin with thrombomodulin cleaves PC, converting it into its activated form, activated PC (APC). Along with its co-factor protein S, APC inhibits thrombin generation by inactivating activated factors V (Va) and VIII (VIIIa)[3]. Both factors Va and VIIIa are required for factor X activation, which then converts prothrombin to thrombin. Factors Va and VIIIa act as substrates for APC, which irreversibly inactivates them through proteolytic activity on cleavage sites, thereby inhibiting their pro-coagulant effect (Figure 1)[4]. In addition to its anticoagulant function, APC also exhibits potent cyto-protective and anti-inflammatory effects and has indirect fibrinolytic properties[5].

A PC deficiency impairs the balance between the procoagulant and anticoagulant system and engenders a prothrombotic state. The etiology of PC deficiency may be genetic (heterozygous or homozygous) or acquired, the latter often due to vitamin K antagonist therapy or liver disease. Hereditary PC deficiency is caused by mutation in the protein C (PROC) gene located on chromosome 2q14.3[5]. It has been reported that more than 500 mutations identified throughout the PROC gene length may lead to inherited PC deficiency. The molecular basis of inherited PC deficiency is complicated, as results from a recent study demonstrated that nucleotide variations in the signal peptide and propeptide of PC lead to PC deficiency by differentially affecting the biological process of PC, including posttranscriptional pre-mRNA splicing, translation, and post-translational modifications[6]. Heterozygous PC deficiency is estimated to occur in 0.02%-0.05% of the general population, whereas homozygous PC deficiency is much rarer and can lead to disseminated intravascular coagulation, thrombosis and purpura fulminans that often appears within hours or days after birth[7]. Most cases of inherited PC deficiency in clinical practice are heterozygous deficiencies, with presentations varying from asymptomatic to thromboembolism events.

PC DEFICIENCY AND VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) represents the cardinal clinical manifestation of heterozygous PC deficiency. It has been reported that patients with PC deficiency have a 10- to 15-fold higher risk of VTE than wild-type individuals, and nearly 5% of patients with VTE may have heterozygous PC deficiency[8,9]. The risk of VTE among patients with PC deficiency varies, which may be related to both the degree of deficiency and the presence of other acquired or inherited risk factors for thrombosis, such as fracture, immobilization, and surgery. Additionally, a 38% recurrence rate of VTE among patients with PC deficiency and prior VTE has been reported[10]. Therefore, evaluation of PC deficiency should be considered in patients with recurrent VTE.

PC DEFICIENCY AND ATE

Compared to the established association between PC deficiency and VTE, the relationship with ATE remain controversial. A previously large family cohort study has observed a 6.9-fold (95%CI: 2.1-22.2) higher risk of ATE among patients with PC before 55 years of age[11]. PC deficiency was also observed in 12% of reported cases of myocardial infarction with normal coronary arteries[12]. Besides, as seen in the case reported by Seo *et al*[1], most of the evidence linking PC deficiency to ATE events stems from case reports[7,13]. However, some studies failed to identify the association between PC deficiency and ATE[4]. Therefore, to address the knowledge gap, further large-scale studies are required to investigate the effects of PC deficiency on ATE and explore the underlying mechanisms.

MANAGEMENT OF PC DEFICIENCY

The management of PC deficiency are mostly based on previously reported cases and experiences. For severe PC deficiency cases, lifelong PC replacement therapy may be required[5]. In addition, according to a recent guideline, subcutaneous PC concentrate with or without vitamin K antagonists may be the most appropriate long-term management for severe congenital PC deficiency patients, whereas there are little data available on pharmacokinetics and the most appropriate dosing regimen[14]. For most cases, oral anticoagulants remain the primary treatment option. According to the CHEST Guideline and Expert Panel Report, vitamin K antagonists have been the cornerstone of treatment and

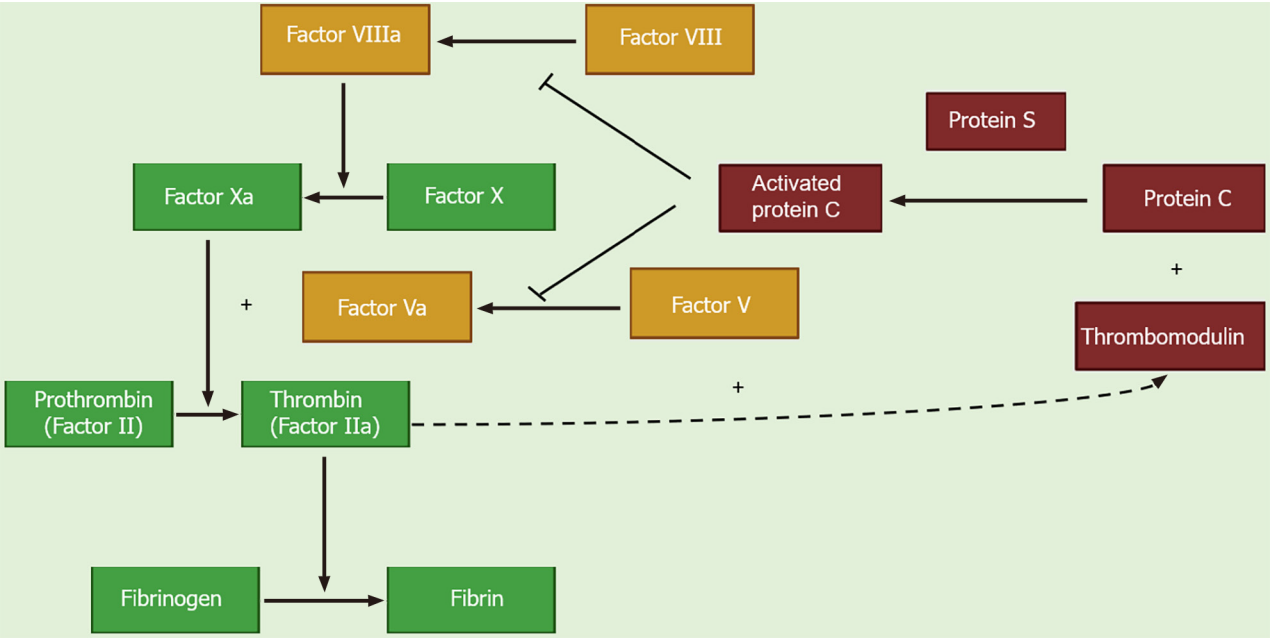

Figure 1 Biological role of protein C.

secondary prophylaxis in patients with hereditary thrombophilia[15]. Some reported cases suggested a possible role of direct oral anticoagulants in thrombophilic patients, which needs further validation[7]. In addition, there is also a lack of treatment strategies for PC deficiency-related ATE. Hence, more data is required to establish efficacious strategies for the treatment and secondary prophylaxis in patients with PC deficiency manifesting as thromboembolic events.

CONCLUSION

PC deficiency is a risk factor for thrombophilia with higher risks of VTE. Emerging data have linked PC deficiency with increased risk of ATE, which requires further validation in large-scale studies. In addition, future studies are needed to establish efficacious treatment strategy for PC deficiency-related thromboembolic events.

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EDITORIAL

Indication and surgical approach for reconstruction with endoprosthesis in bone-associated soft tissue sarcomas: Appropriate case management is vital

Recep Öztürk

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Abstract

It is important for surgeons performing sarcoma surgery to know that bone resection and tumor prosthesis applications in soft tissue sarcomas (STS) have unique features in terms of indication, surgical approach and follow-up, in terms of the management of these cases. Some STS are associated with bone and major neurovascular structures. Bone-associated STS are generally relatively large and relatively deep-seated. Additionally, the tendency for metastasis is high. In some cases, the decision about which structures to resect is difficult. These cases are often accompanied by poor oncological and surgical outcomes. Management of cases should be done by a multidisciplinary team in advanced centers specialized in this field. The surgical team must have sufficient knowledge and experience in the field of limb-sparing surgery. Preoperative evaluation and especially good planning of bone and soft tissue reconstruction are vital.

Key Words: Soft tissue sarcoma; Bone invasion; Bone resection; Endoprosthesis replacement; Prosthesis; Limb salvage; Indication; Approach

Core Tip: In soft tissue sarcomas with bone invasion, resection of the tumor with wide margins including the relevant bone segment and endoprosthesis applications continue to be the recommended treatment method with satisfactory results. Preoperative evaluation and planning before surgery is crucial. In cases where there is a dilemma in surgical procedures, the decision of whether to perform bone resection affects the fate of the case. Bone and soft tissue reconstruction, especially after resection, should be planned meticulously to ensure adequate soft tissue coverage.

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INTRODUCTION

In the management of soft tissue sarcomas (STS), wide excision is essential to achieve tumor-free surgical margins to preserve the limb. Radical resection of huge extracompartmental soft tissue sarcoma often requires simultaneous bone resection and reconstruction[1]. In these cases, endoprosthetic reconstruction may provide satisfactory results as a limb salvage strategy.

It is well known that the treatment and follow-up of bone, and STS should be managed with a multidisciplinary approach in advanced centers specialized in this field. This strong recommendation is especially valid in a special field such as bone resection, and tumor prosthesis applications in STS. Not adhering to diagnostic and treatment algorithms in the treatment management of sarcomas, or making interventions without having the knowledge and experience to interpret the patient's history, clinical examination, and radiological data, may lead to irreversible limb loss or fatal complications[2-4].

UNIQUE FEATURES OF BONE-RELATED SOFT TISSUE SARCOMAS

It is known that approximately 5% of all STS have bone invasion[5]. Bone resection, and tumor prosthesis applications in bone-related STS have their own unique nature/characteristics, different from classical prosthesis applications due to bone sarcomas. It has its own indications, differences in surgical practices and its own complications. Before making an indication for surgery in a case of soft tissue sarcoma that is relatively large in size and close to bone and major neurovascular structures, it is very important to review some important points.

Compared to prosthetic applications related to bone sarcomas, applications related to STS have their own difficulties [6]. One of these is the increased patient age[2,7]. Another is the frequent need for neoadjuvant or adjuvant radiotherapy. Especially the presence of bone invasion increases the patient's likelihood of receiving radiotherapy. Some other challenges are the presence of decreased chemosensitivity of the lesions and the potentially larger defects resulting from muscle compartment resections. Especially patients with bone invasion are likely to be metastatic, and therefore chemotherapy is usually administered to these patients. Despite additional chemotherapy, these cases still have worse survival than cases without bone invasion[5]. Another difficulty is the existence of sarcoma cases that have undergone unplanned R1 resection. These accidental surgeries are generally performed without preoperative imaging, staging and biopsy, and are generally performed in centers that do not specialize in musculoskeletal system tumors. Although extensive resection is performed along with bone resection and adjuvant treatments are given, these interventions can make management difficult and worsen the results[8,9]. In conclusion, current data show that the probability of a case of soft tissue sarcoma with bone invasion resulting in amputation is higher than the possibility of continuing with preservation of the limb[5].

PREOPERATIVE APPROACH

In the preoperative evaluation of STS, relatively less attention is paid to the presence or absence of bone invasion[10]. In fact, magnetic resonance imaging (MRI) is the gold standard in the preoperative evaluation of these sarcomas[2-4]. It provides vital information about the location of the tumor, its size, extensions, and its relationship with important structures such as bones, vessels and nerves. Plain radiographs and computed tomography are valuable in evaluating the presence of bone erosion[2,3]. The tumor may abutting to the bone, and this can involve less than one-third of the bone, or two-thirds of the bone. Sometimes, it not only abutt, but also erodes the adjacent bone, in which case medullary signal changes may also be observed. In tumors that abutting is less than one-third of the bone, subperiosteal resection is sufficient and there is no need for bone resection and reconstruction. Conversely, abutting to the bone is usually present in tumors that involve at least two-thirds or more of the bone. And in the presence of evidence of bone invasion, resection of the involved segment is essential for adequate surgical margins[1]. The decision on whether to perform resection for tumors that abutt to approximately two-thirds of the bone should be made carefully. In case of dilemma, an another method that can help in making a decision is whether the sarcoma is mobile or not on the adjacent bone[3,5]. This evaluation should be made preoperatively and intraoperatively. In intraoperative evaluation, it should be evaluated whether the tumor is mobile or not, especially after opening the fascia around the tumor. If the tumor is mobile, subperiosteal resection is usually sufficient. Because the periosteum, which is a strong barrier, protected the bone from tumor. Cases with "planned positive" surgical margins performed in cases close to structures with natural barrier properties such as bones, vessels or nerves, have similar recurrence rates to series with negative surgical margins, especially when they supported by adjuvant treatments[3,5,10]. In cases like this, each cases necessary to be evaluated by a multidisciplinary team in a specialized center in the field of tumors. This team should include at least a medical oncologist, radiation

oncologist, orthopedist, radiologist and pathologist. The patient should be evaluated in terms of neoadjuvant treatments, surgery and adjuvant treatments, taking into account the tumor subtype, location, size, age, and general condition of the patient. It is vital that the surgery is performed by a surgical team with knowledge, and experience in this field[2,4].

Another difficulty in the treatment management of STS is experienced in some cases in interpreting bone changes in preoperative examinations. It should be carefully examined whether there is a signal change in the bone marrow space adjacent to soft tissue sarcoma and whether the signal change is bone edema, invasion or metastasis. Ferguson *et al*[5] reported that in cases where there was a signal change in the bone marrow space, they performed resection, taking into account the risk of tumor presence. In the study of Lin *et al*[11], there was suspicion of bone invasion in 9 patients in preoperative images. They performed bone resection in all cases, and histological evaluation revealed no bone invasion in 8 cases.

In some cases, especially juxta-articular STS, the tumor is near critical structures such as vessels, nerves and bone, and removal of the tumor alone is very difficult or not possible with wide margins. In such cases, resection of the tumor-related bone segment may be planned. Additionally, if there is evidence of invasion of the vessels and nerves, their resection is required[1]. One of the nightmare complications after endoprosthesis reconstruction is infection[2,12,13]. Bone-associated STS are usually larger than 10 cm and sometimes larger than 15 cm. Just as a bone defect may occur after resection, a serious soft tissue coverage defect may also occur. Providing adequate soft tissue coverage after reconstruction of the bone defect with a prosthesis is a very critical factor in reducing infections. Therefore, before surgery, planning regarding soft tissue coverage should be planned meticulously and the operation should be completed after the necessary preparations[2,7,13].

The presence of a mass abutting to the bone, involving approximately two-thirds of the bone on MRI, poses a dilemma for treatment. Especially when the mass is located in an area close to the joint, such as the distal femur, it becomes more difficult to decide because the shape of the bone is relatively more irregular and the beginnings and endings of the muscles are more common here. The thin cortex of the metaphysis may make it difficult to determine whether a cortical erosion is present. Other areas noted to be difficult to interpret include tendinous insertions in bone and the linea aspera of the femur[14].

BIOLOGICAL BEHAVIOR OF SUBGROUPS

When evaluated in terms of subgroups of STS, subperiosteal resection can usually be sufficient in well-differentiated liposarcoma, while high-grade tumors such as synovial sarcoma, malignant fibrous histiocytoma, and malignant peripheral nerve sheath tumor generally tend to erode the bone and may require resection of the affected segment[1,2,4]. It is clear that these tumors require more careful evaluation and a more cautious surgical approach in terms of bone erosion.

INDICATIONS FOR BONE RESECTION

To summarize the indications for bone resection and potential endoprosthesis in sarcomas; the presence of bone invasion clearly detected in preoperative radiological examinations is an indication for resection. Even if there is no bone invasion in radiological examinations, in the presence of a mass that covers almost the entire bone or surrounds it 360 degrees, bone resection should be performed since wide surgical margins will not be possible without resection of the relevant bone segment. When it is determined that there is no bone invasion and no signal change in the bone marrow space in preoperative radiological examinations, tumor mobility should be examined manually preoperatively and intraoperatively. Bone resection is indicated for tumors that are not mobile on the bone. In mobile tumors, resection with periosteum seems sufficient[1,5,6,11,13].

CLINICAL CASE SERIES

When studies analyzing bone-related STS are examined; Rowell *et al*[6] compared 29 cases of lower extremity STS with bone invasion on preoperative radiological examination with cases without bone involvement. They found that survival was lower in cases with bone invasion. Yan *et al*[1] reported 30 cases of juxta-articular bone invasion located in the distal thigh. The complication rate was 17% and they reported that these results were acceptable. However, Nakamura *et al*[13], in their multicenter study, examined 27 high-grade cases located in the lower extremities with bone invasion. They observed a total of 22 surgical complications (infection, relapse, aseptic loosening) and noted the high complication rates. LeVay *et al*[15] reported that in STS, the direct spread pattern of the tumor invading the neurovascular structures and bone reduces the survival rate. Ferguson *et al*[5] reported that survival was significantly worse in the presence of histologically confirmed bone invasion. However, they found that the presence of bone invasion did not increase local recurrence but significantly increased the amputation rate. In another study, Panicek *et al*[16] reported that the presence of bone invasion on preoperative MRI did not increase the risk of recurrence or metastasis, but negatively affected survival.

FOLLOW UP

Follow-up functional scores of endoprostheses applied for STS can be consistent with the scores of endoprostheses after bone resection, although they are generally performed after soft tissue resections larger than 10 cm[1,2]. However, the majority of reports show that these cases are accompanied by high surgical complication rates and poor oncological outcomes. One of the most important reasons for poor functional outcomes is massive muscle resection with tumor. During follow-up, 5-year limb preservation rates are approximately 75%. The most common major complications are infection and recurrence[13].

STS with bone invasion is usually deep-seated, usually metastatic at diagnosis, and relatively larger. These features negatively affect the prognosis[5]. In addition, features such as their relatively large size and deep location have resulted in the metastasis-free survival of cases with bone invasion being worse than those without bone invasion. There are reports stating that the presence of bone invasion in STS alone is a risk factor in terms of metastasis development and surveillance, regardless of the treatments applied[1,2,10,13].

OTHER APPROACHES

However, it should be clearly noted that despite numerous clinical studies investigating the role of preoperative radiotherapy and computed tomography in STS, there is still no consensus[1-4]. This further increases the importance of the surgical management. However, the results of limb-sparing surgery supported by radiotherapy are similar to amputation in terms of recurrence[5]. In the treatment management of soft tissue sarcoma, each case should be evaluated individually, taking into account all conditions, and the option of amputation should also be considered in selected cases. If poor limb function is anticipated after tumor resection and possible reconstruction, or if it is not possible to preserve or reconstruct motor nerves or main arteries and veins, or if reconstruction of the bone and/or soft tissue defect does not seem possible, the case should be evaluated for amputation[17].

LIMITATIONS AND FUTURE STUDIES

Although there are some studies on the indications for bone resection and the results of endoprosthesis applications in STS, the available information is still limited. There are no standardized guidelines. One of the main reasons for this is the rarity of STS and the very rare indication for bone resection and endoprosthesis application in these tumors. The literature is mostly in the form of case series containing data from a single center, with no comparison. Another reason is that it is not possible to do some studies due to their nature. If bone resection is not performed in cases where the bone relationship cannot be understood in preoperative evaluation and relapse occurs, there is a possibility that the relapse may be caused by microscopic residual disease in the cortical bone. It is impossible to understand whether this recurrence is due to tumor cells remaining on the bone. And this does not justify routine bone resection in these cases[11]. More studies are needed on the interpretation of radiological changes detected in the bone adjacent to soft tissue and the treatment decision. The frequency of indications for bone resection may also be a subject of further research. Is the most common indication the presence of a tumor that has a close relationship with the bone and requires bone resection, even though there is no bone invasion in radiological evaluation? Or is it bone invasion? Additionally, in different studies, it is stated that surrounding the bone at least 180 degrees or two-thirds of it is an indication[1,2,5]. However, in clinical practice, there are cases where the bone is surrounded at the specified rates, but on intraoperative examination, it is completely mobile and subperiosteal resection can be performed, and there are also cases where the bone is surrounded at less than 180 degrees, but the bone needs to be resected[6,10-17]. This seems to be another issue that needs to be focused on in the field of indications. The majority of available literature data report that recurrence does not increase in cases where bone invasion is proven by preoperative MRI or histologically. However, data show that limb and patient survival decreases in these cases. This stands out as another point that requires further examination. As a result, it is a fact that there is a need for multicenter comparative studies with a sufficient number of cases that examine in depth the different aspects of bone-associated STS in the future.

CONCLUSION

Wide resections of high-grade STS with involved bone and reconstruction with endoprostheses are often associated with high surgical complication rates and poor oncological outcomes. Despite everything, in cases with bone invasion, resection of the tumor with wide margins, including the relevant bone segment, and endoprosthesis applications continue to be the recommended treatment method with satisfactory results. Preoperative evaluation and planning before surgery is crucial. "Planned positive" surgical resection, when supported by adjuvant treatments, has similar recurrence rates to amputation. In cases where there is a dilemma in surgical procedures, the decision of whether to perform bone resection affects the fate of the case. Especially bone and soft tissue reconstruction, after resection, should be planned meticulously to ensure adequate soft tissue coverage. Careful periodic postoperative follow-up is required for surgical complications and oncological events.

FOOTNOTES

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EDITORIAL

Comprehensive and personalized approach is a critical area for developing remote cardiac rehabilitation programs

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Abstract

In the evolving landscape of cardiac rehabilitation (CR), adopting digital technologies, including synchronous/real-time digital interventions and smart applications, has emerged as a transformative approach. These technologies offer real-time health data access, continuous vital sign monitoring, and personalized educational enhanced patient self-management and engagement. Despite their potential benefits, challenges and limitations exist, necessitating careful consideration. Synchronous/real-time digital CR involves remote, two-way audiovisual communication, addressing issues of accessibility and promoting home-based interventions. Smart applications extend beyond traditional healthcare, providing real-time health data and fostering patient empowerment. Wearable devices and mobile apps enable continuous monitoring, tracking of rehabilitation outcomes, and facilitate lifestyle modifications crucial for cardiac health maintenance. As digital CR progresses, ensuring patient access, equitable implementation, and addressing the digital divide becomes paramount. Artificial intelligence holds promise in the early detection of cardiac events and tailoring patient-specific CR programs. However, challenges such as digital literacy, data privacy, and security must be addressed to ensure inclusive implementation. Moreover, the shift toward digital CR raises concerns about cost, safety, and potential depersonalization of therapeutic relationships. A transformative shift towards technolo-

gically enabled CR necessitates further research, focusing not only on technological advancements but also on customization to meet diverse patient needs. Overcoming challenges related to cost, safety, data security, and potential depersonalization is crucial for the widespread adoption of digital CR. Future studies should explore integrating moral values into digital therapeutic relationships and ensure that digital CR is accessible, equitable, and seamlessly integrated into routine cardiac care. Theoretical frameworks that accommodate the dynamic quality of real-time monitoring and feedback feature of digital CR interventions should be considered to guide intervention development.

Key Words: Cardiac rehabilitation; Digital approaches; Remote care; Equity in technology access; Synchronous/real-time interventions; Digital innovation in healthcare

Core Tip: Digital technologies have revolutionized cardiac rehabilitation (CR), offering flexible and novel approaches to care. The integration of digital health technologies and artificial intelligence in remote CR is transforming traditional paradigms, providing real-time access to health data, and enhancing patient self-management. Mobile and digital CR models, including synchronous/real-time digital interventions, are addressing accessibility barriers, and promoting equity in healthcare delivery. Despite the potential benefits, challenges such as the digital divide, cost, safety, and data security must be addressed. Future research should prioritize accessibility, equity, and the seamless integration of digital CR into routine cardiac care.

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INTRODUCTION

Cardiac rehabilitation (CR) is a comprehensive program that includes risk factor management, exercise training, and optimization of psychosocial health[1,2]. It is recommended by guidelines for individuals with cardiovascular disease (CVD)[3]. Numerous studies have demonstrated that participation in CR programs following a cardiac event, such as myocardial infarction or percutaneous coronary intervention, is associated with improved health outcomes and reduced mortality rates[4,5]. Despite its well-established benefits, CR remains underutilized, and there exist significant differences in referral, admission, and completion rates[6]. With the increasing body of literature on the topic, there is a growing interest in exploring novel delivery models for CR, particularly digital and remote approaches (Figure 1). These innovative models have the potential to enhance participation in CR programs, ultimately leading to better health outcomes for individuals with CVD[7]. Remote delivery of CR has received endorsement from international sources, including the European Association of Preventive Cardiology (EAPC)[8]. The EAPC has emphasized the importance of maintaining the delivery of core components of CR through tele-rehabilitation interventions during the COVID-19 pandemic. However, concerns have been raised regarding equity in the use of technology to ensure access to equitable access to outpatient care.

Research findings indicate that alternative delivery models for CR are not only safe but also yield similar effect as standard center-based CR programs[9-11]. However, significant questions remain unanswered regarding which specific remote CR models offer the most substantial benefits for individuals. In this editorial, we aim to provide an overview of various remote CR models and identify key research questions that demand attention. We propose strategies for addressing these questions, which can serve as a valuable solution for scientists, researchers, and clinicians in the field. Two central research focuses emerge as crucial: First, the development of personalized remote CR programs; and second, the implementation of comprehensive methodologies to ensure the delivery of core CR components. Establishing these essential priorities is vital to ensure the provision of high-quality remote CR programs and can serve as a basis for future investigations.

Adopting a comprehensive and personalized approach is crucial for enhancing remote CR programs. This includes addressing issues related to equity in technology access, ensuring that all individuals who could benefit from CR have equal opportunities to participate[12]. Additionally, these programs should prioritize individualized care, tailoring interventions to each patient's specific needs and preferences in both short and longer term[13]. Embracing innovative methods and technology, such as virtual, remote, or mobile CR, can enable the delivery of comprehensive and personalized care to a broader population[14], ultimately improving access and health outcomes for individuals with cardiovascular conditions[15].

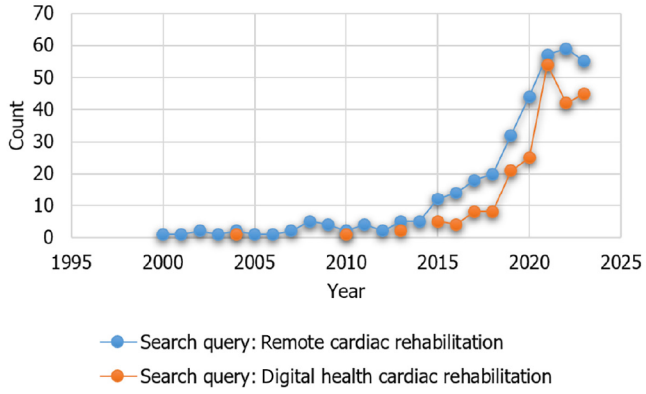

Figure 1 Trend of remote cardiac rehabilitation research. The number of published papers incorporating a remote or digital component in cardiac rehabilitation is shown. The search was conducted (September 30, 2023) through the PubMed database using specific keywords ("remote cardiac rehabilitation" and "digital health cardiac rehabilitation").

SYNCHRONOUS/REAL-TIME DIGITAL CR

Synchronous/real-time digital CR represents a contemporary alternative mode of CR delivery defined by real-time, two-way, remote audiovisual communication between patients and CR staff[16]. This approach primarily relies on real-time communication *via* videoconferencing platforms and remote monitoring of vital signs, such as electrocardiography, blood pressure, and heart rate, to facilitate safe and comprehensive home-based digital CR interventions[17]. Data from recent literature support the feasibility of synchronous/real-time digital CR interventions in enhancing the overall cardiac profile *via* improvements in cardiorespiratory fitness, physical activity levels and quality of life[18]. Despite the initial investment required for digital infrastructure, the cost-effectiveness of digital CR is highly advocated[19]. Furthermore, several barriers to CR enrolment and attendance such as transportation costs, lack of free time and remote residence locations, can be effectively addressed through the implementation of synchronous/real-time digital CR interventions [20]. Additionally, incorporating digitally delivered CR interventions could serve as the sole alternative solution for the continuation of CR during pandemic circumstances in the foreseeing future[21]. Though, numerous logistical, ethical, and clinical issues arise with digital CR, primarily concerning the risk of online patients' personal data leakage, insufficient internet access and digital literacy. It is essential to prioritize underrepresented racial and ethnic groups, women and older patients for integration into digital synchronous CR[22]. Bearing in mind that the acceptance of digitally delivered CR services and interventions is generally high[23], there is a strong need to further investigate and incorporate synchronous digital CR into the routine of cardiac patients' secondary prevention routine.

SMART APPLICATIONS FOR CR

In the evolving landscape of remote CR, the transition toward mobile health technology interventions represents a transformative approach to providing more personalized and accessible cardiac care. These technologies extend beyond the traditional healthcare setting, providing real-time access to health data and fostering patient empowerment in their care management. Wearable devices and mobile applications enable continuous monitoring of vital signs and physical activities, contributing directly to the enhancement of patient self-management[24,25]. This approach is particularly crucial in remote settings[25], where traditional healthcare resources are less accessible, emphasizing the need for patient-centered care that adapts to their lifestyle and environment. Mobile platforms not only facilitate the tracking of rehabilitation outcomes but also play a critical role in lifestyle modifications essential for cardiac health maintenance[26,27]. Additionally, the provision of customized educational content and reminders through these platforms ensures sustained patient engagement and informed participation in their rehabilitation journey[28]. The transition to mobile CR represents a significant move towards redefining patient care in CR, focusing on technology's role in enabling a more dynamic, responsive, and patient-tailored approach.

The integration of digital technologies in CR has sparked discussion about selecting appropriate measures for outcome evaluation, as traditional methods fall short in capturing the dynamic and real-time nature of digitalized interventions. Unlike the static measures from center-based CR trials, digital platforms offer granularity, real-time, and precision through automated, real-time tracking and analysis using sensors and monitors for heart rate, blood pressure and movement[18]. This is crucial as increased digital technology-based theories guiding interventional studies highlighted the dynamic qualities and emphasized the need to unpack the use of technology at home to explain the causal-effect relationship[29].

The formality of the digital CR intervention is diverse and changing rapidly, such as virtual reality, gamification, robot assisted, Chatbot (AI-powered). When researchers use digital technology to deliver CR, the focus is often on evaluating a specific technology such as a wearable device, certain virtual reality scenario, or mobile app, within short duration. The safety and ethical issues should be considered before recommending them as a new standard of care, such as discomfort

(*e.g.*, dizziness) from virtual reality and depersonalization when over-relying on technology. Evaluating user experiences in home settings through qualitative research is crucial to ensure intervention fidelity and guide future developments.

Future opportunities for digital innovation in CR

Artificial intelligence applies to the use of Information and Communication Technologies (commonly referred to as ICTs) for data-driven policy decision. AI has been broadly studied in various fields such as medicine[30] and economics[31] and is currently embedded in the CR implementation procedures. By engaging AI technology *via* wearable sensors (worn as wristbands or embedded in smartwatches), early detection of cardiac events is promoted, thereby enhancing the safety of home-based CR interventions, and improving clinician decision-making[32]. Additionally, AI tools offer real-time feedback and support to patients, which could contribute to the improvement of CR adherence, increase of patients' engagement and the proliferation of their overall cardiac profile[18,28]. The potential of the AI tools to analyze thoroughly the large amounts of data collected by ICT devices enables the provision of patient-tailored CR programs and serves as a cornerstone for improving health outcomes and quality of life. However, the incorporation of digital technology into the CR procedures raises several challenges to be addressed. Innovative technologies such AI might require digital literacy[29]. Consequently, those patients with limited digital literacy may be denied access to AI–based CR; thus, leading to health inequality. Furthermore, considering the importance of data privacy and security, measures should be taken to prevent the unethical use of patients' data and ensure transparency, fairness, and accountability in algorithmically automated decisions. AI can act as an alternative key component potential enough to improve the efficiency and effectiveness of home-based CR interventions[32]. However, further research is needed to maximize their comprehensive and optimal implementation.

Challenges and limitations

Digital technologies in CR offer a transformative shift from traditional supervised programs to proactive, remotely supported self-care approaches, enhancing accessibility and sustainability. However, this rapid technological advancement risks deepening the digital divide, particularly impacting those with lower socio-economic and educational backgrounds, women, people with disabilities, and those with sensory or motor impairments[33]. Future research should focus not just on technological advancements but also on customizing these interventions to meet the diverse needs and preferences of these subgroups (Table 1). It is crucial to view technology to overcome barriers to CR participation, rather than as the central focus.

Moreover, the implementation of digital technologies in CR brings forth concerns about cost and safety[34]. The expenses associated with acquiring and maintaining advanced digital health tools can be substantial, potentially limiting their widespread adoption, especially in resource-constrained settings[35]. Additionally, ensuring safety while using these technologies remotely poses a significant challenge. This includes managing the risk of incorrect usage of equipment, ensuring accurate data transmission, and providing immediate assistance in case of adverse events during unsupervised exercise sessions[18].

Equally important is the concern over data security in digital CR[36]. As patient health information and sensitive data are transmitted and stored digitally, there is a heightened risk of data breaches and unauthorized access[37]. Ensuring the confidentiality, integrity, and availability of patient data is paramount, requiring robust cybersecurity measures and adherence to data protection regulations. This aspect is crucial to maintaining patient trust and the credibility of digital CR programs.

Furthermore, the scope of technology in CR could be broadened to include interventions aimed at preventing CVDs. This may involve managing risk factors in high-risk groups or individuals with metabolic syndrome[38]. Additionally, there is potential for extending CR to patients with co-morbid conditions, such as cancer, who may require cardio-oncology interventions. While CR is traditionally recognized for secondary prevention[39], expanding its application to primary or palliative care settings requires more evidence.

The technologically enabled CR can facilitate culturally sensitive communication and reduce stigma in mental health assessments and psychological interventions. However, this raises concerns about depersonalization, where authentic care and interpersonal connection in therapeutic relationships might be overshadowed by interactions with technology [40,41]. Future studies should explore ways to integrate moral values such as compassion and caring into digital therapeutic relationships, preserving the human element in healthcare[42].

CONCLUSION

CR has evolved significantly with the advent of digital technologies, offering novel and flexible approaches to delivering care. The integration of digital health technologies and AI in remote CR has transformed the traditional paradigms of cardiac care. These technologies provide real-time health data access, enable continuous monitoring of vital signs and physical activities, and offer personalized educational content, thereby enhancing patient self-management and engagement. The shift towards mobile and digital CR models, including synchronous/real-time digital interventions, addresses barriers such as physical access to care and promotes equity in healthcare delivery. However, adopting these technologies also presents challenges, including the need for digital literacy among patients and concerns regarding data privacy and security. Future research should ensure that digital CR is accessible, equitable, and effectively integrated into routine cardiac care (Table 1). This entails developing personalized remote CR programs and implementing comprehensive methodologies to deliver core CR components.

Table 1 Recommendations for future development of digital technology in cardiac rehabilitation

No.	Items	Description
1	Enhance AI and ICT Integration	Continue to embed AI in CR procedures, using wearable sensors for early cardiac event detection, thereby improving home-based CR safety and clinician decision-making
2	Provide real-time feedback	Utilize AI tools to offer real-time feedback and support to patients, aiming to improve CR adherence and patient engagement
3	Develop patient-tailored programs	Use AI to thoroughly analyze data from ICT devices for creating personalized CR programs, enhancing health outcomes and quality of life
4	Address digital literacy gaps	Recognize the challenge of digital literacy and work to make AI-based CR accessible to all patients, reducing health inequalities
5	Ensure data privacy and security	Focus on ethical considerations, including data privacy, security, and the transparency of AI decision-making processes
6	Evaluate cost and safety concerns	Study the financial and safety implications of implementing digital technologies in CR, especially in unsupervised settings
7	Customize interventions for diverse needs	Tailor digital CR interventions to meet the varied needs and preferences of different patient subgroups, such as those with lower socio-economic status or disabilities
8	Maintain the human interaction in digital CR	Address concerns of depersonalization by integrating moral values into digital therapeutic relationships, ensuring compassionate, patient-centered care

AI: Artificial intelligence; CR: Cardiac rehabilitation; ICT: Information and communication technology.

FOOTNOTES

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EDITORIAL

Pain management in chronic pancreatitis

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Abstract

Pain in chronic pancreatitis (CP) is difficult to manage. Many patients suffer from inadequate pain relief, completely incapacitating them in their daily activities. Historically, despite their well-known adverse effects, opioids have been the pillar of treatment regimens in painful CP. The management is now gradually evolving with a better understanding of the underlying pathophysiology of CP-related pain. Clinicians should follow a holistic approach to the management of CP-associated pain, which must involve lifestyle changes that are coupled with analgesic medications and other pain-relieving interventions. Furthermore, there is no easy cure for vanquishing CP-associated pain. Each patient must be evaluated on a case-by-case basis by a multidisciplinary team to decide which treatment option is best suited for that individual.

Key Words: Pancreatitis; Abdominal pain; Palliative care; Analgesics; Life style; Psychology

Core Tip: Management of pain associated with chronic pancreatitis (CP) is difficult because of the intricate pathophysiology of this pain and the lack of universal guidelines. Recent evidence suggests an altered central response to the chronic inflammatory changes in the pancreas, which may rewrite the approach to control pain in CP. Currently, several treatment modalities are available to clinicians. However, optimal patient care must be taken into account comprehensively with inputs from multiple disciplines.

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INTRODUCTION

Severe abdominal pain is the most debilitating symptom that is associated with chronic pancreatitis (CP)[1]. The patients typically describe a dull-aching pain around the epigastrium, which frequently radiates to the back and flanks. As the disease progresses, the pain becomes severe and excruciating[2]. This intractable pain, if not managed adequately, may drastically reduce the quality of life of patients by interfering with their physical, psychological, and social domains. Since there is no definitive cure for CP, its pain management is primarily aimed at providing patients with symptomatic relief and palliative care. Hence, adequate pain relief is fundamental to the pain management of CP. Despite our improved knowledge of chronic pain management, clinicians still face challenges in treating painful CP because of the complex nature of the disease process and the paucity of universal treatment guidelines. In the current editorial, we have delved into the pathophysiology of CP-associated pain and reviewed the recommended treatment modalities.

Pathophysiology of pain

Pain in CP is multifactorial and poorly understood. The pathophysiology of pain was believed earlier to be primarily due to the nociceptive inputs that arise from the inflammatory changes in the pancreas. However, recent evidence suggests that the pain is more neuropathic[3,4]. In the background of continuous bombardment of nociceptive inputs from the inflamed pancreas, there is neural modulation or sensitization of the peripheral and central nervous system. Neural sensitization is clinically exhibited by hyperalgesia and allodynia observed commonly in CP[5,6]. Additionally, electroencephalographic and imaging studies have shown neural remodeling and functional changes in the central nervous system [7,8]. Histopathologically, it is exhibited by neural hypertrophy, edema, and increased density of intrapancreatic nerves. These changes result in the development of neuroplasticity and a maladaptive response to pain[9]. There are two distinct types of clinical manifestations of pain in CP. The "A-type pain" or intermittent pain is characterized by discrete episodes of pain with pain-free periods in between. The "B-type pain" is described as persistent background pain with episodes of acute exacerbation[10]. Studies have shown that the intermittent type of pain has a more predicted response to treatment than the latter one ("B-type pain")[11]. The mechanism of pain is summarized in Figure 1.

Pain management approaches in CP

Management of pain in CP requires a structured approach that focuses on the stage, type, and primary pathophysiology of the disease process. A consensus guideline has recently suggested a stepwise approach to managing pain in CP[12]. Even so, one approach may not fit all patients considering that every patient is different. Thus, an individualized treatment plan is the best means to provide optimum benefit to the patient.

Pain management in CP can be divided into the following sections: Pain assessment, lifestyle modification, dietary changes, pharmacotherapy, interventional pain management, endoscopic treatment, and surgical interventions.

Pain assessment in CP

The first step of pain management is the accurate assessment of the severity of pain. Multiple pain assessment tools are available, but very few have been validated to be employed in the pain management of CP. Simple pain rating scales such as the numeric rating scale and visual analog scale only measure the intensity of pain and neglect other aspects of pain [13]. CP-associated pain is complex, with a significant psychosocial undertone; hence, it must be assessed through multidimensional pain scales. The Izbicki pain scale is specifically developed to address this aspect of pancreatic pain, but it is not appropriately validated to be applied in the pain management of CP[14].

The brief pain inventory pain assessment scale is a self-administered questionnaire-based tool validated to be used in CP-related pain management[15]. It quantifies the severity of pain and its impact on daily function including general activity, mood, behavior, and sleep[16]. The McGill pain questionnaire is another self-reporting measure of pain that can be useful in the pain management of CP. It provides a holistic view of pain severity by measuring the sensory, cognitive, and emotional aspects of pain[17]. Quantitative sensory testing helps assess and characterize pain mechanisms in patients with CP[18]. It can be employed in treatment-resistant cases of CP to assess pain sensitivity and to check the response of medications to pain[19].

Lifestyle modification and dietary changes

Patients with CP are strongly advised to abstain from alcohol and smoking. Studies have demonstrated that refraining from alcohol intake significantly reduces the frequency of recurrences in pancreatitis and painful episodes[20]. Smoking is frequently associated with alcoholism, and it can be an independent risk factor for pain exacerbation in CP[21].

A low-fat elemental diet has been extensively studied in CP for pain control, considering that it reduces pancreatic secretion and reduces pain by decreasing ductal pressure[22,23]. It is suggested to be more effective in the early stage of the disease when the exocrine function of the pancreas is preserved[23]. The early institution of the nasojejunal tube is also recommended. Besides improving the nutritional status of the patient, nasojejunal feeding also reduces pain[24]. The benefit is achieved probably by a reduction in pancreatic secretion or may be due to bypassing of the stomach. The latter explanation is more plausible since delayed gastric emptying is common in CP cases[25].

Pancreatic enzymes have been shown to ameliorate pain in CP by negative feedback inhibition of pancreatic secretion [26]. It works by degrading the cholecystokinin-releasing factor that releases cholecystokinin responsible for the stimulation of pancreatic secretion[27]. The preparation of pancreatic enzyme must be in the uncoated form (nonacid protected form) to be effective, since the acid resistance form (coated form) may not get released in the duodenum. Nevertheless, a systemic review and meta-analysis was not able to come up with significant evidence of pain relief in CP by using pancreatic enzymes[28].

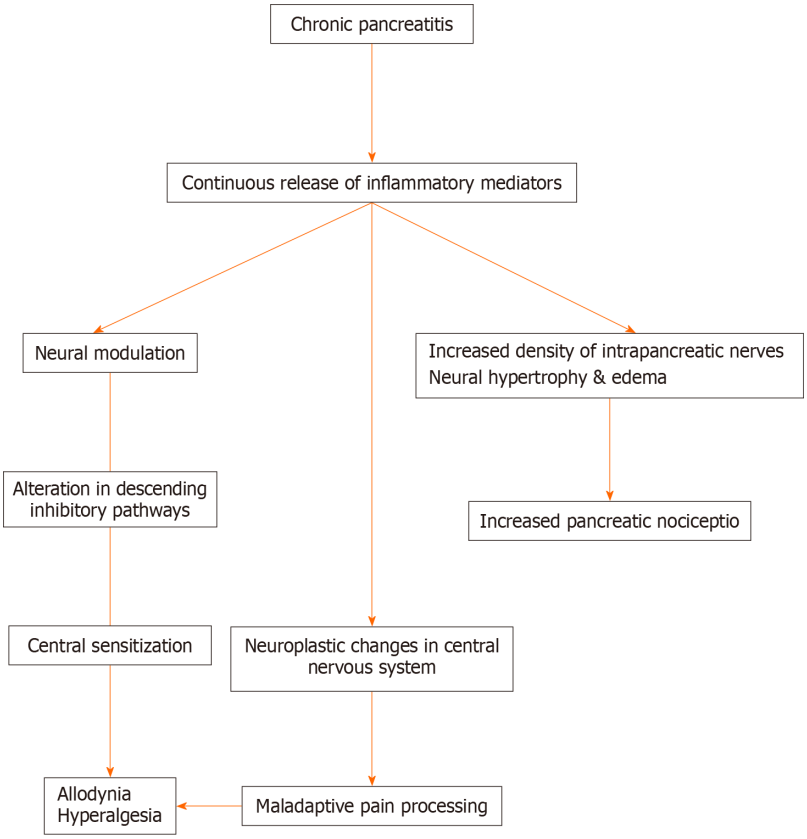

Figure 1 Mechanism of pain in chronic pancreatitis.

Antioxidants are advocated with the rationale that there is micronutrient deficiency in CP that results in oxidative stress and free radical injury[29]. A combination of antioxidants (β-carotene, vitamin C, vitamin E, selenium, and methionine) with other pain-relieving medication (Pregabalin) has been shown to avert painful episodes and recurrences [30,31].

Analgesic medication

The World Health Organization (WHO) analgesic ladder has been an enduring guide for the management of cancer pain for more than two decades, and it is still applicable in planning treatment for pain in CP[32]. The WHO ladder recommends stepwise escalation of analgesics with increasing potency until pain relief is achieved. Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line of analgesics advocated for mild to moderate pain. Although paracetamol is safe in CP, it cannot be a standalone medication to provide satisfactory pain relief[26]. It is usually effective when combined with other medications. NSAIDs are better avoided, considering that patients suffering from CP are prone to develop duodenal and gastric ulcers[33,34].

Opioids are invariably added to the pain management regimen as pain severity increases in CP. Despite this, opioids are the most prescribed medications to manage pain, and their role is controversial in nonmalignant chronic pain scenarios such as those of CP-related pain[35]. The controversy is further aggravated by the widespread prevalence of opioid abuse. The recommendation is that opioids should never be the first-line therapy[36]. Before initiating opioid therapy, clinicians must be aware of the long-term side effects including misuse, addiction, opioid-induced hyperalgesia, and bowel dysfunction[37]. The patient who is on opioid therapy, especially strong opioids such as morphine, must be monitored closely to look for the development of such adverse effects. Tramadol, a weak opioid, is suggested to be more effective than morphine in controlling pain in CP with an equianalgesic dose[38]. It does not have any serious adverse effects or dependency potential in therapeutic doses, unlike strong opioids. Tramadol has weak activity on the μ-opioid receptor with an additional inhibitory effect on noradrenaline and serotonin reuptake[39]. It modulates the descending inhibitory pain pathway and can play a significant role in managing central sensitization associated with CP[40]. A maximum adult dose of 400 mg/day can be advocated safely in patients with CP. Transdermal preparation of opioids is also used, but it is usually reserved for patients who cannot tolerate oral preparations[41].

Considering that the neural mechanism of pain in CP is now well established, the drugs interfering with neural transmission are expected to be efficacious. Anticonvulsants (pregabalin and gabapentin), tricyclic antidepressants (amitriptyline), and selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitor (duloxetine) are the centrally acting drugs commonly used to treat neuropathic pain and can be beneficial in CP[42]. Pregabalin has been extensively researched in patients with CP. It reduces synaptic release of neurotransmitters (glutamate, noradrenaline, and substance-P) by binding to alpha2-delta subunits of voltage-gated Ca^{2+} channel and thereby reducing neuronal excitability. Pregabalin must be started at a low dose to prevent its neurological adverse effects and slowly escalate until

clinical benefit is appreciated[43]. The maximum recommended dose of pregabalin is 600 mg. Likewise, gabapentin, amitriptyline, and duloxetine can be tried as monotherapy or preferably in combination with other analgesics.

Other novel medications such as ketamine, an N-methyl-D-aspartate antagonist, can be effective by enhancing descending inhibition of pain in CP[43]. The S-enantiomer of ketamine is particularly more effective with fewer psychosomatic side effects and is currently being used in an ongoing trial that involves CP patients[44]. Somatostatin-analog inhibits pancreatic secretions and can lessen pain by reducing ductal pressure. However, current data are limited to suggest its use. Certain experimental drugs such as clonidine and benzodiazepines may be tried in the patient's refractory to conventional medications[12].

Interventional pain management approaches

Recent evidence suggested that patients of CP may benefit from sympathetic blocks such as celiac plexus and splanchnic nerve blocks[45,46]. These minimally invasive interventions can reduce analgesic requirements and may be considered as parts of a multimodal analgesic strategy. In one study, pulsed radiofrequency ablation of celiac plexus provided excellent pain relief in two cases of CP[47]. Spinal cord stimulation has shown significant pain relief in multiple studies[48,49]. It may be used in cases of CP refractory to analgesic medications.

Psychological intervention and standardized nursing interventions

The emotional and psychological impact of pain in CP is often a neglected aspect. Recent data support the use of behavioral interventions as part of a multidisciplinary approach in the management of pain in CP. Cognitive–behavioral therapy is one such intervention that has proved to be useful in reducing pain intensity and enhancing quality of life by helping patients cope with pain better[50]. Protocolized nursing interventions with focused stress reduction can effectively mitigate pain, anxiety, and depression in pancreatitis[51].

Endoscopic therapy and surgical management

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the most common modalities utilized in the treatment of painful CP. Endoscopic therapy is particularly useful in patients with obstructive pathology in the main pancreatic duct. The rationale behind it is that it releases the outflow obstruction and decompresses the pancreas, thereby reducing the pain[52]. Often extracorporeal shockwave lithotripsy is carried out to reduce pain in CP, especially in cases of large pancreatic stones localized in the head of the pancreas[53].

Surgical management was once the last resort employed when all other modalities failed to provide pain relief in CP. Nevertheless, evidence for the benefits of early surgical interventions is now emerging[54,55]. The surgical approach for pain management in CP depends on the morphological changes in the pancreas, duration of the disease, and response to other treatment modalities. Three modalities of surgery are commonly employed: Decompression surgery, resection, and a combined procedure depending on the pathology in the pancreas. The optimal timing of surgery is controversial. However, surgery should not be delayed beyond 2–3 years of onset of CP and should be done before the patient develops central sensitization[56].

CONCLUSION

The current evidence suggests that CP-associated pain is less of a nociceptive and more of a neuropathic type with significant psychosocial connotation. Neural sensitization along with neuroplastic changes in the nervous system causes the pain refractory to conventional treatment. Therefore, treatment modality should be aimed at preventing the development of neural sensitization by judicious use of medications and other interventional modalities. Pain assessment in CP should be conducted by using validated multidimensional pain scales to have a better understanding of the pain and its impact on daily living. To minimize painful episodes, lifestyle modification by complete abstinence from alcohol and smoking is strongly recommended. A low-fat elemental diet and nutritional delivery by nasojejunal tube may have an impact on pain recurrence by reducing pancreatic secretion. Pancreatic enzymes and antioxidants in combination with other medications are useful pain-relieving measures, although evidence regarding their effectiveness is equivocal. The WHO pain ladder should be employed as a guide for the timing and escalation of analgesics. NSAIDs should be avoided, and paracetamol should be used in combination with other drugs. Tramadol has proven beneficial in painful CP with a good safety profile. Stronger opioids like morphine must be used cautiously because of their serious long-term impact on pain pathophysiology. Central medications like pregabalin appear to be the mainstay of treatment as monotherapy or in combination with other modalities. Endoscopic treatment (ERCP) should be the first line of management in cases of ductal obstruction due to stricture or stone. Surgery can be a game changer in pain management selected cases, but the optimal timing of surgery is crucial for its success. The various intervention methods in CP are summarized in Figure 2.

In conclusion, our current understanding of the etiopathogenesis of pain in CP opens multiple pain-relieving options for clinicians. However, to provide the best possible treatment modalities for the successful management of pain in CP, a multidisciplinary approach that involves gastroenterologists, surgeons, and pain physicians must be developed.

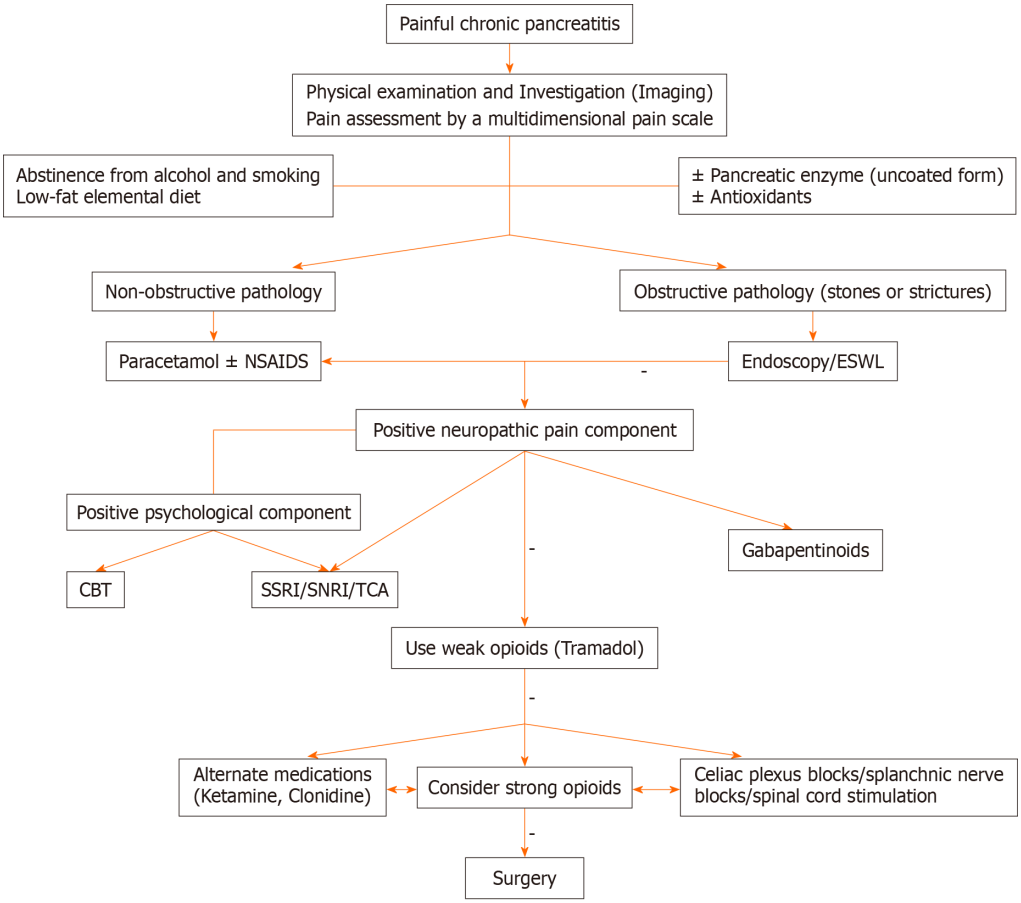

Figure 2 Intervention methods in chronic pancreatitis. NSAIDS: Non-steroidal anti-inflammatory drugs; ESWL: Extracorporeal shock wave lithotripsy; CBT: Cognitive behavioral therapy; SSRI: Selective serotonin reuptake inhibitors; SNRI: Selective norepinephrine reuptake inhibitors; TCA: Tricyclic antidepressants; -: No response/Inadequate response.

FOOTNOTES

Author contributions: Nag DS and Swain BP designed the overall concept and outline of the manuscript; Swain BP, Anand R, Barman TK and Vatsala contributed to the discussion and design of the manuscript; all authors contributed to the writing, and editing the manuscript and review of literature.

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EDITORIAL

Predicting intensive care unit-acquired weakness: A multilayer perceptron neural network approach

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Abstract

In this editorial, we comment on the article by Wang and Long, published in a recent issue of the *World Journal of Clinical Cases*. The article addresses the challenge of predicting intensive care unit-acquired weakness (ICUAW), a neuromuscular disorder affecting critically ill patients, by employing a novel processing strategy based on repeated machine learning. The editorial presents a dataset comprising clinical, demographic, and laboratory variables from intensive care unit (ICU) patients and employs a multilayer perceptron neural network model to predict ICUAW. The authors also performed a feature importance analysis to identify the most relevant risk factors for ICUAW. This editorial contributes to the growing body of literature on predictive modeling in critical care, offering insights into the potential of machine learning approaches to improve patient outcomes and guide clinical decision-making in the ICU setting.

Key Words: Intensive care units; Intensive care unit-acquired weakness; Risk factors; Machine learning; Computer neural network

Core Tip: Predicting intensive care unit-acquired weakness (ICUAW) is crucial for improving patient outcomes. This editorial presents the potential of machine learning, specifically the multilayer perceptron neural network model, in predicting ICUAW. Insights into ICUAW risk factors and guides clinical decision-making in critical care are offered. The importance of developing accurate and reliable predictive models to improve patient outcomes in the intensive care unit setting is also emphasized.

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INTRODUCTION

Intensive care unit-acquired weakness (ICUAW) is a neuromuscular disorder that affects patients who have been admitted to an intensive care unit (ICU) for an extended period[1]. It is characterized by a generalized weakness that can affect both the respiratory and limb muscles, leading to difficulties in breathing, moving, and performing activities of daily living[1,2]. ICUAW can result from a combination of factors, including immobility, prolonged use of mechanical ventilation, and systemic inflammation[1].

ICUAW is a significant concern in critical care medicine for several reasons including prognostic indicators, impact on functional outcomes, resource utilization, and clinical decision-making[1-3].

The development of ICUAW is associated with increased morbidity and mortality rates among ICU patients. Patients with ICUAW are at higher risk of complications such as pneumonia, sepsis, and prolonged hospital stays. Predicting the development of ICUAW can help clinicians identify high-risk patients early and implement preventive measures to mitigate its impact[1,2]. ICUAW can have long-term consequences on a patient's functional status and quality of life. It can lead to muscle wasting, weakness, and difficulty in performing basic activities, which can impair the patient's ability to return to their pre-ICU level of functioning. Predicting ICUAW can help clinicians develop targeted rehabilitation programs to improve patient outcomes[1,3]. ICUAW can increase the need for prolonged mechanical ventilation, rehabilitation services, and long-term care, leading to increased healthcare costs and resource utilization. Predicting ICUAW can help healthcare providers allocate resources more efficiently and improve the cost-effectiveness of care delivery[1-3]. Predicting ICUAW can inform clinical decision-making regarding the use of sedation, mechanical ventilation, and physical therapy interventions. Early identification of patients at risk of developing ICUAW can guide the implementation of preventive strategies and optimize patient care[2,3].

Overall, predicting the performance of ICUAW is important for improving patient outcomes, optimizing resource utilization, and guiding clinical decision-making in the critical care setting. It allows healthcare providers to identify high-risk patients early and implement targeted interventions to mitigate the impact of ICUAW on patient morbidity and mortality. However, predicting ICUAW is challenging due to its multifactorial nature and the lack of a gold standard diagnostic test[1-3].

However, several methods have been used to assess the risk of ICUAW and predict its development including clinical assessment, electrophysiological testing, biomarkers, muscle ultrasound, and machine learning models[1,4-6]. Clinicians often use a combination of clinical signs and symptoms to assess the risk of ICUAW. These may include muscle weakness, difficulty weaning from mechanical ventilation, and prolonged ICU stay. However, clinical assessment alone may not be sensitive or specific enough to accurately predict ICUAW[1-4]. Electrophysiological tests, such as electromyography and nerve conduction studies, can assess the function of the peripheral nerves and muscles. These tests can detect abnormalities in nerve conduction and muscle activation, which may indicate the presence of ICUAW. However, these tests are invasive, time-consuming, and may not be feasible in critically ill patients[1-3,5-7]. Biomarkers, such as creatine kinase and myosin light chain, have been investigated as potential indicators of muscle injury and ICUAW. Elevated levels of these biomarkers may suggest muscle damage, but their specificity for ICUAW is limited, and they may also be elevated in other conditions[1-3,6,8]. Muscle ultrasound can assess muscle thickness and echogenicity, which may be altered in patients with ICUAW. However, the interpretation of ultrasound findings can be subjective, and the technique may be operator-dependent[1-3,9]. Table 1 illustrates the strengths and weaknesses of these methods for predicting ICUAW.

Recent studies have explored the use of machine learning models, such as artificial neural networks, to predict ICUAW. These models can analyze large datasets and identify patterns that may be predictive of ICUAW. However, the performance of these models may vary depending on the quality and size of the dataset used for training[1-3,8,9].

THE MULTILAYER PERCEPTRON NEURAL NETWORK MODEL

The multilayer perceptron (MLP) neural network model is a type of artificial neural network that has been widely used in various fields, including healthcare, for predictive modeling tasks[10]. It is a feedforward neural network with multiple layers of nodes (neurons) that are interconnected by weighted edges. Each node in the input layer represents a feature of

Table 1 Strengths and weaknesses of existing approaches to predicting intensive care unit-acquired weakness

Approach	Strengths	Weaknesses
Clinical assessment	Clinicians can use clinical signs and symptoms to assess the risk of ICUAW, which is a non-invasive and readily available method	Clinical signs and symptoms may not be sensitive or specific enough to accurately predict ICUAW
Electrophysiological Testing	Electrophysiological tests, such as electromyography and nerve conduction studies, can provide objective measures of muscle function and help diagnose ICUAW	Electrophysiological tests are invasive, time-consuming, and may not be feasible in critically ill patients
Biomarkers	Biomarkers, such as creatine kinase and myosin light chain, can indicate muscle damage and may be useful for diagnosing ICUAW	Biomarkers are not specific to ICUAW and may be elevated in other conditions
Muscle ultrasound	Muscle ultrasound can provide information about muscle thickness and echogenicity, which can be altered in patients with ICUAW	The interpretation of ultrasound findings can be subjective, and the technique may be operator-dependent

ICUAW: Intensive care unit-acquired weakness.

the input data, and each node in the output layer represents a prediction or classification label. The nodes in the hidden layers perform nonlinear transformations of the input data, allowing the model to capture complex patterns and relationships in the data[11].

The MLP model has several advantages that make it a potential solution to improve prediction accuracy for ICUAW. The MLP model can capture nonlinear relationships between input features and the target variable[11], which is essential for predicting complex medical conditions like ICUAW that may involve multiple interacting factors. The MLP model can automatically learn relevant features from the input data, reducing the need for manual feature engineering and potentially capturing subtle patterns that may be missed by traditional statistical models[12]. The MLP model can be easily scaled to handle large datasets with many features, making it suitable for analyzing electronic health record data and other healthcare datasets[13]. The MLP model can generalize well to new data, making it suitable for predicting ICUAW in different patient populations or healthcare settings[10]. Although MLP models are often considered "black box" models, techniques such as feature importance analysis and model visualization can help interpret the model's predictions[14] and understand the factors that contribute to ICUAW risk. There are several open-source libraries and tools available for building and training MLP models, making them accessible to researchers and clinicians without extensive machine-learning expertise[15].

Overall, the MLP neural network model is a promising approach for predicting ICUAW, and its flexibility, scalability, and ability to capture complex patterns in the data make it a potential solution to improve prediction accuracy for this condition. However, further research is needed to validate the model's performance in larger patient populations and to identify the most effective predictive variables.

ICU PREDICTION MODELS THAT HAVE USED NEURAL NETWORK AND MACHINE LEARNING MODELS

Several studies have investigated the use of prediction models, including those based on neural networks and machine learning models to assess the risk of ICU and improve patient outcomes.

Neural network-based models

The study by Benyó *et al*[16] focuses on computational glycemic mechanism (GM) used to manage stress-caused hyperglycemia in ICUs. The Stochastic-TARgeted GM procedure, employed in ICUs across several countries, is a simulation-driven GM procedure that utilizes a personalized, algorithmic insulin sensitivity to explain the individual's current condition. The research presents two methodologies rooted in neural networks for forecasting the individual's insulin sensitivity factor: A deep neural network for classification and a technique based on Mixture Density networks. These methods are trained using treatment data from three distinct patient cohorts. The precision of the neural network forecasts is contrasted with the existing computational model predictions employed in clinical practice, and it is found to be either matching or surpassing the benchmark. The authors propose that these approaches could present a hopeful substitute in computational treatment planning for individual health status prognosis, but they emphasize the need for further research, including in-silico simulations and clinical validation trials, to validate these findings[16].

The study by Pappada *et al*[17] emphasizes the critical importance of achieving glycemic control in patients in ICUs, as it has been associated with reduced mortality, shorter ICU stays, and lower risks of complications such as infection. However, maintaining glycemic control in this setting is challenging due to the diverse range of illnesses and patient conditions. The study collected continuous glucose monitoring (CGM) data and other relevant measures from the electronic medical records of 127 patients for the first 72 h of ICU care. These patients had either type 1 or type 2 diabetes or had a glucose value > 150 mg/dL upon admission to the ICU. The researchers developed a neural network-based model to predict a complete trajectory of glucose values up to 135 min in advance. The model's accuracy was validated using data from 15 patients not included in the training set, simulating real-world healthcare settings. The predictive models showed improved accuracy and performance compared to previous models developed by the research team. The model error, expressed as the mean absolute difference percent, was 10.6% for interstitial glucose values and 15.9% for

serum blood glucose values collected 135 min in the future. A Clarke Error Grid Analysis of model predictions concerning the reference CGM, and blood glucose measurements revealed that over 99% of model predictions could be considered clinically acceptable and would not lead to inaccurate insulin therapy or treatment recommendations. This high level of clinical acceptability suggests that these models could be valuable tools within a clinical decision support system to assist healthcare providers in optimizing glycemic management in critical care patients[17].

The study by Wang and Long[9] recently published in the *World Journal of Clinical Cases*, focuses on identifying significant risk factors for ICUAW and offering recommendations for its prevention and treatment. The study utilized a MLP neural network model to analyze data from the initial 14 d of ICU stay, including age, comorbidities, sedative and vasopressor dosages, duration of mechanical ventilation, length of ICU stays, and rehabilitation therapy. The relationships between these variables and ICUAW were examined. The study found that age, duration of mechanical ventilation, lorazepam and adrenaline dosages, and length of ICU stay were significantly higher in the ICUAW group. Additionally, several comorbidities and conditions were significantly more prevalent in the ICUAW group. The most influential factors contributing to ICUAW were identified as the length of ICU stay and the duration of mechanical ventilation. The neural network model developed in the study predicted ICUAW with high accuracy, sensitivity, and specificity. These findings highlight the importance of minimizing both ICU stay and mechanical ventilation duration as primary preventive strategies for ICUAW.

Machine learning models

The study by Chang *et al*[18] focuses on predicting the need for ICU admission in patients with myasthenia gravis (MG), an autoimmune neuromuscular disorder characterized by muscle weakness. Although specialized neuro-intensive care can lead to good long-term outcomes, predicting the need for ICU care is critical for optimizing patient management. The study used three machine learning-based decision tree algorithms to predict ICU admission in 228 MG patients admitted between 2015 and 2018. The C5.0 decision tree outperformed the other models and identified several significant risk factors for ICU admission, including the Myasthenia Gravis Foundation of America clinical classification at admission, thymoma history, azathioprine treatment history, disease duration, sex, and onset age. The developed decision tree can serve as a supportive tool for clinicians to identify MG patients who require intensive care, thereby improving the quality of care and potentially reducing morbidity and mortality.

The study by Tran *et al*[8] concentrates on crafting a clinical tool grounded in machine learning to anticipate muscle ailment subcategories utilizing multi-cohort microarray expression information. The information was curated from 42 separate cohorts with expression outlines in publicly available gene sources, encompassing a diverse spectrum of subject ages and muscle tissue samples from non-central regions. The research classified cohorts into five categories of muscle disorders: Limited mobility, inflammatory muscle diseases, ICU-acquired weakness, congenital conditions, and chronic systemic illnesses. The dataset includes evidence on 34.099 genes, and procedures to augment the information was employed to rectify imbalances in subtype representation within muscle disorders. Support direction mechanism algorithms were trained on two-thirds of the 1260 samples using the most significant gene signatures identified through statistical tests. Validation of the model was conducted on the residual testers utilizing the area under the receiver operator curve (AUC). The study found that chronic systemic disease was the best-predicted class with an AUC of 0.872, while ICUAW and immobility were the least discriminated classes with AUCs of 0.777 and 0.789, respectively. Condition-particular gene set enhancement findings revealed that the genetic profile exhibited improvement in biological pathways such as proliferation of neural progenitor cells for ICU-acquired weakness and aerobic metabolism for congenital conditions. The research concludes that the devised molecular categorization instrument featuring the chosen genetic indicators for categorizing muscle disorders fills a notable void in the literature on muscular ailments and introduces a potentially valuable diagnostic aid for discerning muscle disorder variety in clinical practice.

In summary, these investigations underscore the promise of prediction models in evaluating risk and enhancing patient outcomes. Nonetheless, additional research is required to validate these models across larger patient cohorts and to pinpoint the most efficacious predictive variables.

DATASET USED TO TRAIN AND TEST THE MLP MODEL

The dataset used to train and test the MLP model for predicting ICUAW would typically consist of a variety of clinical and demographic variables collected from patients admitted to the ICU. The variables that could be included in the model are presented in Table 2.

The dataset would typically be divided into two subsets: A training set and a test set. The training set would be used to train the MLP model, while the test set would be used to evaluate the model's performance. The dataset may also be divided into a validation set, which is used to tune the model's hyperparameters and prevent overfitting. It is important to note that the dataset should be large enough to adequately represent the patient population and include enough patients who develop ICUAW to allow for meaningful analysis. Additionally, missing data and outliers should be carefully handled to ensure the reliability of the model's predictions.

Table 2 Variety of clinical and demographic variables collected from patients admitted to the intensive care unit

Patient profile and assessment	Variable
Demographic information	Age
	Sex
	Race
	Other demographic characteristics of the patient
Clinical characteristics	Comorbidities
	Severity of illness scores (*e.g.*, APACHE II, SOFA)
	Reason for ICU admission
Laboratory values	Creatinine
	Liver function tests
	Complete blood count
	Inflammatory markers
Vital signs	Heart rate
	Blood pressure
	Respiratory rate
	Temperature
Medication and treatment	Sedatives
	Analgesics
	Neuromuscular blocking agents
	Other medications
Mechanical ventilation	Duration of mechanical ventilation
	Mode of ventilation
	Ventilator settings
Muscle strength and function	Assessment of muscle strength (*e.g.*, Medical Research Council scale, handgrip dynamometer)
Neurological status	Glasgow coma scale score
	Neurological examination findings
	Presence of delirium
Functional status	Pre-ICU functional status (*e.g.*, ability to perform activities of daily living)
Outcomes	Development of ICUAW
	Duration of ICU stay
	Duration of mechanical ventilation
	Mortality

ICU: Intensive care unit; ICUAW: Intensive care unit-acquired weakness.

SPECIFIC FEATURES AND PARAMETERS OF THE MLP MODEL FOR PREDICTING ICUAW

The specific features and parameters of the MLP model for predicting ICUAW can vary depending on the dataset and the specific implementation of the model. However, some common features and parameters must be included, such as the number of layers, activation functions, optimization algorithm, regularization, batch size, learning rate, and dropout rate.

The MLP model typically consists of an input layer, one or more hidden layers, and an output layer. The number of hidden layers and the number of nodes (neurons) in each layer are hyperparameters that need to be determined based on the complexity of the dataset and the desired level of prediction accuracy[11-13,19].

Activation functions are used to introduce nonlinearity into the model, allowing it to capture complex patterns in the data. Common activation functions used in MLP models include the sigmoid function, the hyperbolic tangent function, and the rectified linear unit function[11-14].

The optimization algorithm is used to update the weights of the model during training to minimize the loss function. Common optimization algorithms used in MLP models include stochastic gradient descent (SGD), Adam, and RMSprop [11-14].

Regularization techniques, such as L1 and L2 regularization, are used to prevent overfitting by penalizing large weights in the model. Dropout is another regularization technique that randomly drops a fraction of the nodes in each layer during training to prevent co-adaptation of neurons[11-13].

The batch size is the number of samples used to compute the gradient of the loss function during each iteration of training. A smaller batch size may lead to faster convergence but may result in noisy updates, while a larger batch size may lead to more stable updates but may require more memory[11-14].

The learning rate is a hyperparameter that determines the size of the step taken by the optimization algorithm during each iteration of training. A higher learning rate may lead to faster convergence but may result in overshooting the minimum of the loss function, while a lower learning rate may lead to slower convergence but may result in more stable updates[11-14].

The dropout rate is the fraction of nodes that are randomly dropped during training. A higher dropout rate may lead to more regularization but may result in slower convergence, while a lower dropout rate may lead to faster convergence but may result in overfitting[12-15].

These are just some of the features and parameters that can be used in an MLP model for predicting ICUAW. The specific choices of features and parameters should be based on the characteristics of the dataset and the desired level of prediction accuracy.

PROCESS OF TRAINING AND VALIDATING THE MLP MODEL FOR PREDICTING ICUAW

The process of training and validating the MLP model for predicting ICUAW involves several steps, including data preprocessing, model training, hyperparameter tuning, cross-validation, model evaluation, and interpretation (Figure 1). The step-by-step process is described below.

The first step is to preprocess the dataset by handling missing values, normalizing numerical features, and encoding categorical variables. This ensures that the data is in a suitable format for training the model. Next, the MLP model is trained using the training set. During training, the model's weights are updated iteratively using an optimization algorithm (*e.g.*, SGD) to minimize the loss function. The loss function measures the difference between the model's predictions and the actual outcomes[20]. Hyperparameters are parameters that are not learned during training but are set before training begins. Examples of hyperparameters include the number of hidden layers, the number of nodes in each layer, the learning rate, and the dropout rate. Hyperparameter tuning involves selecting the optimal values for these hyperparameters to improve the model's performance. This can be done using techniques such as grid search, random search, or Bayesian optimization[21]. Cross-validation is a technique used to assess the generalization performance of the model. It involves splitting the dataset into multiple subsets (folds), training the model on some of the folds, and evaluating its performance on the remaining folds. This process is repeated multiple times, with different subsets used for training and evaluation each time. The average performance across all folds is used as an estimate of the model's generalization performance[10]. Once the model has been trained and validated, its performance is evaluated using the test set, which was not used during training or validation. The evaluation metrics used to assess the model's performance may include accuracy, precision, recall, F1 score, and area under the receiver operating characteristic curve[22]. These metrics provide insights into the model's ability to correctly classify patients with and without ICUAW. After evaluating the model, it is important to interpret its predictions and understand the factors that contribute to ICUAW risk. Techniques such as feature importance analysis and model visualization can help identify the most important predictive variables and understand the model's decision-making process[10,21,22]. The process is iterative and may involve multiple rounds of data preprocessing, model training, hyperparameter tuning, cross-validation, model evaluation, and interpretation.

By following these steps, researchers and clinicians can develop and validate an MLP model for predicting ICUAW that is accurate, reliable, and interpretable.

CONCLUSION

This editorial on predicting ICUAW using an MLP neural network model presents a comprehensive approach to addressing the challenges associated with predicting ICUAW. By leveraging the capabilities of the MLP model, researchers and clinicians can develop a predictive model that is accurate, reliable, and interpretable. The editorial highlights the importance of predicting ICUAW for improving patient outcomes, optimizing resource utilization, and guiding clinical decision-making in the critical care setting. The editorial presents the strengths and weaknesses of existing approaches to predicting ICUAW, including clinical assessment, electrophysiological testing, biomarkers, and muscle ultrasound. It emphasizes the limitations of these approaches and how the MLP model addresses these limitations by providing a nonlinear modeling approach, feature learning capabilities, scalability, generalization, and interpretability.

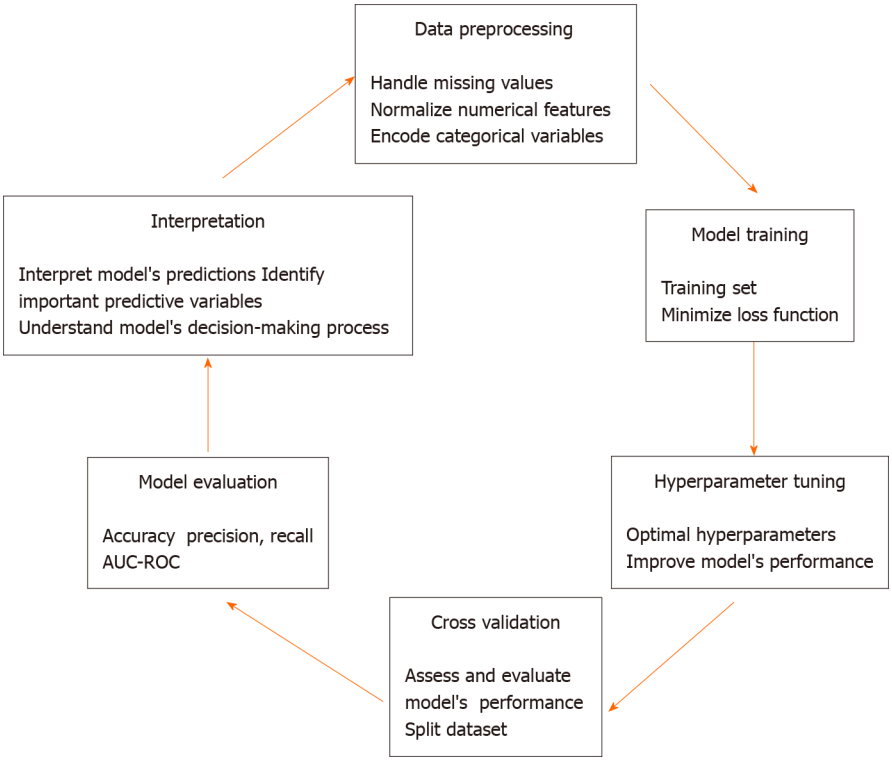

Figure 1 Training and validating the multilayer perception model for predicting intensive care unit-acquired weakness. AUC-ROC: Area under the receiver operating characteristic curve.

FOOTNOTES

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MINIREVIEWS

Autoantibodies related to ataxia and other central nervous system manifestations of gluten enteropathy

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Abstract

Gluten ataxia and other central nervous system disorders could be linked to gluten enteropathy and related autoantibodies. In this narrative review, we focus on the various neuro-logical manifestations in patients with gluten sensitivity/celiac disease, immunological and autoimmune mechanisms of ataxia in connection to gluten sensitivity and the autoantibodies that could be used as a biomarker for diagnosing and following. We focused on the anti-gliadin antibodies, antibodies to different isoforms of tissue transglutaminase (TG) (anti-TG2, 3, and 6 antibodies), anti-glycine receptor antibodies, anti-glutamine acid

decarboxylase antibodies, anti-deamidated gliadin peptides antibodies, *etc.* Most studies found a higher prevalence of these antibodies in patients with gluten sensitivity and neurological dysfunction, presented as different neurological disorders. We also discuss the role of a gluten-free diet on the clinical improvement of patients and also on imaging of these disorders.

Key Words: Gluten ataxia; Celiac disease; Gluten enteropathy; Autoantibodies; Anti-gliadin antibodies; Anti-bodies to tissue transglutaminase; Anti-tissue transglutaminase antibodies; Anti-transglutaminase 6 antibodies; Anti-glycine receptor antibodies; Anti-glutamine acid decarboxylase antibodies

Core Tip: Crucial insights into the complex nexus between gluten enteropathy and neurological disorders underscore the significance of specific autoantibodies. Anti-gliadin, anti-transglutaminase 2, anti-glycine receptor, anti-glutamine acid decarboxylase, and anti-deamidated gliadin peptides antibodies emerge as pivotal biomarkers, linking conditions from the gluten spectrum to diverse neurological manifestations. The prevalence of these antibodies in patients with gluten enteropathy and associated neurological dysfunction offers a diagnostic compass. Furthermore, the transformative impact of a gluten-free diet on clinical outcomes highlights its therapeutic relevance.

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INTRODUCTION

Ataxia (from the Greek "lack of order") is a spectrum of neurological symptoms characterized by a dysfunction of motor control affecting coordination and balance, occasionally also accompanied by cognitive impairment. Depending on the affected area of the nervous system, ataxia could be divided into cerebellar, sensory or vestibular and, depending on the causative factor, into sporadic, hereditary and acquired[1].

Celiac disease (CD) is a chronic, multisystemic, autoimmune condition caused by gluten consumption in genetically susceptible individuals. Almost 20 years ago, Fasano and Catassi[2] reported that for every one patient with gluten enteropathy with gastrointestinal symptoms, there are seven patients with extraintestinal manifestations. Moreover, it is assumed that the small bowel is no longer "the sole protagonist in gluten sensitivity"[3].

Conditions like dermatitis herpetiformis, gluten ataxia, *etc.*, changed our perspective on CD. Although neurological disorders have been observed in patients with biopsy-proven CD[4]. Hadjivassiliou *et al*[5] demonstrated that gluten sensitivity, and gluten enteropathy particularly, can manifest as neurological dysfunction alone. The most prevalent neurological symptom of gluten enteropathy is ataxia (gluten ataxia)[6]. However, only a subset of individuals who present with neurological impairment due to gluten sensitivity will also have an enteropathy[7].

Additionally, idiopathic cerebellar ataxia (CA) (with a prevalence of 2%-15%)[8], peripheral neuropathy (1.5%-8%), some forms of epilepsy, migraine, attention/memory impairment, Guillain-Barre-like syndrome, chorea, myelopathy, mononeuritis multiplex, *etc.*, could be neurological manifestations of CD[9,10].

The other individuals do not have histological signs of small intestinal damage but serological markers (serum autoantibodies) consistent with gluten enteropathy, a scenario similar to dermatitis herpetiformis. Genetic susceptibility may be tested in challenging cases because human leucocyte antigen (HLA) DQ2 is prevalent in up to 90% of CD patients [8].

IMMUNOLOGICAL AND AUTOIMMUNE MECHANISMS OF ATAXIA

The multisystem involvement in CD is probably due to the expression of transglutaminase (TG) isoforms, the main antigen for the disease, in many tissues and organs. The widespread localization of TG2 and TG3-6 includes skin, nervous system, pancreas, muscle, liver, joints, thyroid, *etc.*, allowing for multiple damage in case of anti-TG production[11]. However, the pathogenesis of neurological involvement in gluten enteropathy is unclear and still discussed. Previous hypotheses focused on intestinal malabsorption and related vitamin deficiencies (*i.e.*, folic acid, cyanocobalamin, vitamin E, thiamine, *etc.*).

Pathologic studies on the central nervous system (CNS) of patients with neurological CD, on the other hand, have recently revealed that immune-mediated processes can play a role by inducing neuronal damage and dysfunction[12]. In this vein, it has been revealed that circulating anti-neuronal antibodies (NA) of the IgG class target the central and enteric nervous systems (ENS) (CNS and ENS, respectively) in a considerable number of neurological CD patients[13].

An important aspect of the different causes of ataxia is the possibility of autoimmune-mediated damage of the cerebellum or its related structures by impaired cellular or cell-mediated immunity or humoral immunity with production of antibodies targeting the neuronal structures[14]. Autoimmune neuronal damage could occur in the setting of classical autoimmune diseases presenting with ataxia when the cerebellum is one of the multiple autoimmune targets, such as in multiple sclerosis (MS), Behçet syndrome, connective tissue disorders such as systemic lupus erythematosus, hypothyroidism, *etc.* The term immune-mediated CA (IMCA) is therefore used to describe primary or mainly pure CA when the cerebellum is the main autoimmune target. IMCA is divided into two main subtypes-triggered by another disease or condition (neoplasm, infection, gluten enteropathy) and not triggered by another disease or condition [anti-glutamine acid decarboxylase (GAD) ataxia]. When immune-mediated mechanisms are highly suspected but no serological markers are found, the disease is described as primary autoimmune CA[14-16].

Possible pathophysiological autoimmune-mediated mechanisms related to neuronal damage include both cell- and humoral-driven processes. Mechanisms such as deficits in immune tolerance or molecular mimicry have been linked to dysfunction of T- and B-cells and subsequent autoantibody production, cell cytotoxicity, exacerbation of local neural inflammation and cell death[1].

Studies in MS have shown that cell cytotoxicity has been linked to infiltration of CNS with Th1/Th17, CD8+ cells and macrophages and dysfunction of regulatory T cells resulting in increased production and secretion of cytokines leading to demyelination and cell death[17]. Cell-mediated cytotoxicity has also been suggested in some types of IMCA due to the increased CD8+ cells in the cerebrospinal fluid (CSF) and macrophage infiltrates in the neuronal structures[18].

An essential aspect of the pathophysiology of IMCA is the autoimmune response triggered by the formation of autoantibodies. The latter could be due to exposure to environmental factors or diseases and are directed against self-antigens, causing the formation of immune complexes, complement activation with subsequent cell migration, tissue damage and organ failure. Autoantibodies in IMCA have been described against nuclear, intracellular and extracellular antigens and have also been found in the CSF, suggesting an increased permeability and disruption of the blood-brain barrier[19].

Depending on the different subtypes of the IMCA, the neuropathological findings could include loss of Purkinje neurons with Bergmann gliosis, gliosis of the cerebellar granular neurons, inferior olivary nucleus neurons and deep cerebellar nuclei, variable inflammatory changes and perivascular lymphoid infiltrates[20].

Some of the neurological manifestations in gluten enteropathy and the connection between gut and brain are shown in Figure 1.

AUTOANTIBODIES IN GLUTEN ATAXIA AND OTHER CNS DISORDERS

Anti-gliadin antibodies

Hadjivassiliou *et al*[21] investigated the prevalence of gluten-related autoantibodies in a group of patients with gluten ataxia, hypothesizing that conditions related to gluten sensitivity and especially gluten enteropathy may explain a large number of patients with sporadic idiopathic and familial ataxia (including spinocerebellar ataxia, Friedrich's ataxia, sporadic olivopontocerebellar atrophy-a cerebellar variant of multiple system atrophy). The prevalence of anti-gliadin antibodies (AGA) varied between 12%-41% depending on the type of ataxia. Furthermore, gluten enteropathy was diagnosed in 24% of tested patients. The authors suggested that gluten ataxia could be the sole most common trigger for sporadic idiopathic ataxia[3,21].

Bushara[8] also reviewed the presence of AGA in patients with gluten ataxia and other neurological manifestations in CD patients. They gathered information on the prevalence of AGA varying from 1.9% to 16.7% depending on the ataxia type. In the case of ataxia of unknown cause, the prevalence of AGA could be up to 41% in different studies. However, the antibodies were significantly higher in people with ataxia than in the general population[8].

It is worth mentioning that AGA could present in up to 50% of patients with non-celiac gluten sensitivity. In line with this, some of the symptoms from the gluten enteropathy repertoire could also be attributed to neurological manifestations (*i.e.*, brain fog, limb numbness, headache, depression). However, it is not known whether AGA or other celiac-related antibodies cause these symptoms[22,23].

Antibodies against tissue TG

Further investigations of the team were focused on the different isoforms of TG. The authors suggested that TG6 and anti-TG6 antibodies may activate the immune system in patients with CD and neurological manifestations, such as idiopathic sporadic ataxia and peripheral neuropathy[24].

The authors reported that the prevalence of anti-TG6 antibodies was 32% in idiopathic sporadic ataxia, 73% in gluten ataxia, 32% in CD patients, and 5% in neurological controls, 4% in healthy controls. Interestingly, 42% of patients with gluten ataxia had enteropathy, and 51% of patients with ataxia had antibodies against TG6. Some patients were administered a gluten-free diet, and anti-TG6 antibodies were significantly lowered or undetectable after 1 year of treatment[24].

Still, whether the anti-NA to CNS/ENS may target or cross-react with TG6 or other isoforms is unclear[10]. Other investigators connected anti-TG antibodies to neurological and enteral damage, not just an epiphenomenon[12,25].

Sarrigiannis *et al*[26] hypothesized that brain hyperexcitability is a characteristic of patients with CD and neurological symptoms (*i.e.*, cortical myoclonus, ataxia, and other dysfunctions). Furthermore, it was evidenced that these patients tend to develop refractory CD and are at risk of T cell lymphoma.

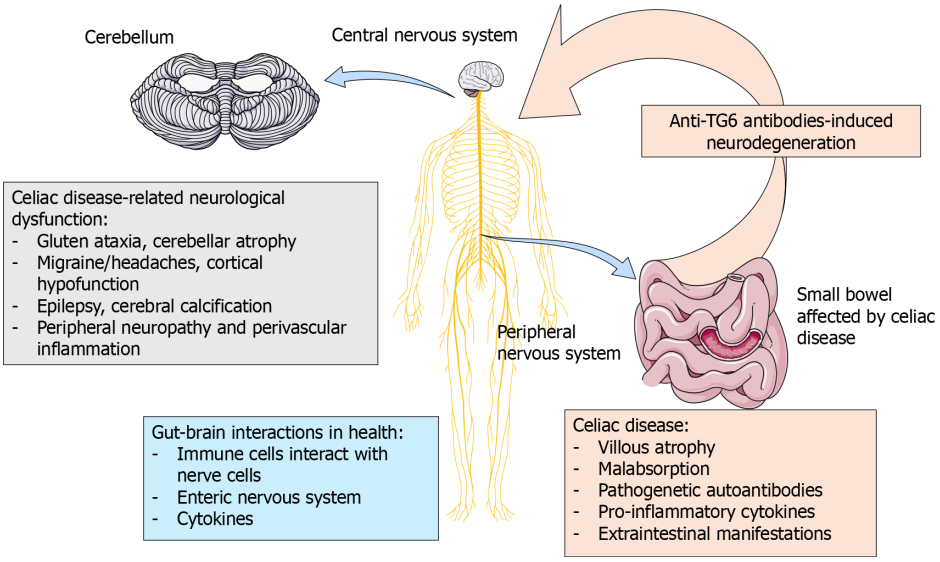

Figure 1 Gut-brain interactions in health, pathophysiological mechanisms and clnical manifestations from nervous system related to gluten enteropathy. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License.

Recently, Ferlazzo *et al*[27] published similar results on the significance of anti-TG6 antibodies in epilepsy, cerebral calcifications and gluten-related disorders. They confirmed that anti-TG6 antibodies are biomarkers for gluten-related ataxia and neuropathy but not epilepsy[27].

The prevalence of anti-TG6 antibodies was estimated as follows: 11% in patients with CD, posterior cerebral calcifications and epilepsy; 22%-in patients with epilepsy and posterior cerebral calcifications but without CD; 0% in patients with focal epilepsy of unknown origin; 13.6%-in healthy subjects[27].

Stenberg *et al*[28] investigated celiac-related antibodies in children and adults with cerebral palsy, estimating a prevalence at about 36% for IgG AGA and 61% for IgA AGA, hypothesizing that poor growth in children with cerebral palsy could be associated with CD. About 7% were positive for anti-tTG2 IgA and 17.5%-for anti-deamidated gliadin peptides (DGP) antibodies[28,29].

When assessing the prevalence of anti-TG6 antibodies in patients with cerebral palsy, they found that 13% of patients with cerebral palsy and 6% of healthy controls were positive. Furthermore, the tetraplegic cerebral palsy subgroup had a significantly higher level (35%) than other groups. Additionally, the authors concluded that an early brain insult and inflammation could be prone to autoimmunity development, especially associated with anti-TG antibodies[30].

Stamnaes *et al*[31] speculate on the possible mechanisms of development and correlation between anti-TG6 antibodies and anti-TG2 IgA antibodies, which could explain the gluten enteropathy in patients with skin and CNS involvement.

We also know that TG6 expression is linked to neurogenesis in CNS in mice, with maturation and functional activity of the cerebellum and cerebral cortex[32].

It is now accepted that these antibodies are cross-reactive to different isoforms of TG, including TG2, TG3 and TG6. Furthermore, it was demonstrated that anti-TG antibodies from patients could induce ataxia-like defects in mice *via* intraventricular injection, revealing their pathogenetic potential[33]. The authors also reported the prevalence of anti-neural IgA/IgG antibodies in CD patients without neurological manifestations at 75%.

Also, Wang *et al*[34] and Li *et al*[35] conducted genetic investigations identifying mutations in the TG gene associated with autosomal dominant spinocerebellar ataxia development, suggesting the broad role of TG6 in cerebellar functioning [34,35].

However, the specificity of anti-TG6 IgA antibodies to gluten ataxia could be questioned since such antibodies were also found in patients with amyotrophic lateral sclerosis (15.3% *vs* 4.3% in healthy controls). Additionally, when tested for celiac-related HLA antigen alleles, 59.1% of seropositive patients were positive for celiac-related alleles. The authors concluded that amyotrophic lateral sclerosis could be associated with autoimmunity, gluten enteropathy, or sensitivity [36].

The most recent paper on anti-TG6 antibodies as a biomarker for gluten ataxia is by Sato and Nanri[37] (2017). Their review followed the presence of anti-TG6 antibodies in sporadic ataxia and also shared an experience with patients with a profound sensory disturbance that contributes to ataxia in contrast to the usually reported mild sensory disturbances[37].

Anti-NA

Caio *et al*[10] investigated anti-NA in patients with CD based on the data for neurological manifestations at about 10% in these patients. They found anti-NA IgG to the CNS (at titer 1:50 to 1:400) in 21% of patients. Moreover, the prevalence of these antibodies was higher in patients with neurological dysfunction (49% *vs* 8%, $P < 0.0001$). Twenty-four percent of patients demonstrated ani-NA to the ENS, where 11/12 with antibody tire > 1:200 and severe constipation. Anti-NA to CNS and ENS were found in 7% and 5% of the healthy control group, respectively[10].

The authors conclude that anti-NA in patients with CD could be used as a marker for neurological dysfunction. Besides, this study also provides supportive data on the immune-mediated pathogenesis of CNS and ENS impairment and gut dysfunction related to gluten enteropathy, thus recommending celiac-related antibodies screening for patients with gluten ataxia peripheral neuropathy drug-resistant epilepsy. Caio *et al*[10] also discussed the role of anti-NA in damaging the morpho-functional integrity of the ENS, causing bowel dysmotility and altering secretion, which is linked to constipation. Moreover, sera of patients with CD containing anti-NA caused apoptosis and neuronal loss in neuronal cultures[12].

Similar to these results are those of Volta *et al*[13], who demonstrated that anti-NA are in low titers in patients with non-neurological CD, strengthening the association between the presence of anti-NA to CNS and neurological involvement in CD. Hadjivassiliou *et al*[6] also hypothesized possible mechanisms in the pathogenesis of neuronal damage in CD patients (*i.e.*, humoral and cellular immune infiltrate in CNS, mainly cerebellum).

Antibodies against glycine receptor and GAD

Other antibodies related to neurological dysfunction in CD are those against glycine receptors. Kass-Iliyya *et al*[38] in their recent research (2021), discussed gluten enteropathy as a presentation of CNS hyperexcitability and cortical myoclonus, usually seen in refractory CD. This CNS hyperexcitability could be attributed to glycine receptor antibodies (GlyR-Abs) or, more frequently, GAD antibodies[38].

The authors previously documented a connection between gluten enteropathy and anti-GAD-associated ataxia, improved with a gluten-free diet. They were interspersed with finding a similar association with anti-GlyR-Abs. Usually, anti-GAD antibodies are associated with Stiff person syndrome, a rare autoimmune condition characterized by neuropsychiatric symptoms and axial muscle stiffness and spasms[39-41].

Furthermore, a gluten-free diet can lower the levels of anti-GAD antibodies and clinical improvement. This raised the hypothesis that gluten sensitivity is broad spectrum of conditions where anti-GAD-related neurological manifestations could occur[26,42].

Kass-Iliyya *et al*[38] also confirms that in the case of gluten sensitivity without enteropathy but with neurological involvement, antibodies against gliadin and TG6 could be the only positive biomarkers. In line with this, Manto *et al*[42] demonstrated with *in vivo* studies that anti-GAD antibodies inhibit GABA release leading to CA. Besides, antibodies to glycine receptors alter glycinergic neurotransmission *in vitro*[43]. Furthermore, it was shown that anti-GlyR-Abs related to neurological disease are a spectrum[44], and approximately one-fourth of all patients with these antibodies have other autoimmune disorders[40]. However, whether the gluten-free diet would benefit these patients is still unknown. Other authors suggested that the presence of these antibodies is an epiphenomenon rather than a pathogenetic mechanism. The other option is these antibodies are pathogenic- and the trigger is gluten sensitivity. Ashizawa et and Xia[45] suggested that a gluten-free diet in patients with CD protects against developing other autoimmune diseases in adulthood.

THE ROLE OF RADIOLOGY AND IMAGING IN ATAXIA

Ataxia is a clinical sign, not a specific disease, with diverse etiologies. Usually, imaging has a role in identifying cerebellar damage. Finding the exact site of the changes aids diagnosis-unilateral damage causes ipsilateral symptoms, while diffuse damage results in symmetrical ataxia. Limb ataxia is caused by lesions in the cerebellar hemispheres and impaired gait results from damage to the middle part of the cerebellum[45].

Ataxia can be congenital or acquired. Congenital ataxia is characterized by a smooth, chronic progression, while acquired ataxia has a more acute manifestation. Acquired ataxia can be caused by various inflammatory diseases such as cerebellitis or cerebellar abscess. Other causes of ataxia are systemic inflammatory diseases, vascular diseases such as ischemic or hemorrhagic infarction, or intoxication. Ataxia can also be caused by vitamin deficiency, various endocrinological diseases, paraneoplastic syndrome, neurodegenerative diseases and cerebellar tumors[45].

Diagnostic imaging plays a significant key role in the diagnosis of ataxia. Computed tomography (CT) and especially magnetic resonance imaging (MRI) are the methods of choice for detecting ischemic and hemorrhagic infarcts. The diffusion-weighted technique detects ischemic infarction up to 5 min after its onset, making the method indispensable in this regard. CT also immediately detects the hemorrhagic infarction. CT and MRI are the gold standard in diagnosing various cerebellar tumors and other tumors in the posterior cranial fossa with different origins[46].

In addition to acquired ataxia, imaging methods also play a role in diagnosing the congenital form of the disease[47]. The most common finding is atrophy of the cerebellum, which can be global or more pronounced in the vermis region. MRI, particularly T2 and fluid attenuated inversion recovery (FLAIR) sequences, is the preferred method for diagnosing cerebellar involvement. Characteristic findings are hyperintense lesions in the T2 sequence, most often in the deep cerebral white matter. Non-specific signs associated with ataxia are also the cortical atrophy of the cerebral hemispheres, expansion of the lateral ventricles, and the increased intensity of the frontal and parietal brain white matter. These changes are found in FLAIR sequences. Sometimes, atrophy of the cerebellum is combined with atrophy of the brainstem, with characteristic smoothing of the pons[47].

Spinocerebellar ataxia is a heterogeneous group of congenital ataxias, with over 28 subtypes described. A characteristic finding of this type of ataxia is the degeneration of the cerebellum and its tracts, as well as the brainstem, basal nuclei, cortex and peripheral nerves. Unfortunately, these findings are non-specific and do not always correspond to the severity of the disease. A modern diagnostic method is magnetic resonance morphography, which currently gives promising results[48,49].

Diffusion tensor imaging is an important sequence in detecting ataxia. A reduction in fractional anisotropy is most commonly found in the corticospinal and the pontine tract. In some cases, an increased mean diffusivity is also detected [50]. Magnetic resonance spectroscopy is another modern sequence used in ataxia. The most indicative markers are total N-acetyl aspartate (NAA), myoinositol (mI), glutamate/glutamine (Glx), and total creatine in the cerebellar hemispheres and NAA, mI and Glx in the pons. The most important change is the disturbance of the ratios between NAA and mI[51].

Gluten ataxia is relatively common in CD and can be found in patients without gastrointestinal symptoms. It occurs in both children and adults; the disease is characterized by a cerebellar type of ataxia and sometimes by a sensory type. In gluten ataxia, imaging methods (CT and MRI) reveal cerebellar atrophy, which occurs gradually but can sometimes occur suddenly. Differential diagnosis includes spinocerebellar ataxia and multisystem atrophy cerebellar type (MSA-C). In both diseases, atrophy is present, but typical for MSA-C is the disproportionate atrophy of the cerebellum and the brainstem, as well as the presence of T2 hyperintense lesions (typically in the pontocerebellar tracts, pons and the middle cerebellar peduncles)[52,53].

LIMITATIONS OF THE SEROLOGICAL TESTS FOR GLUTEN ENTEROPATHY

Nevertheless, we have to acknowledge the limitations of the serological tests and relying to them for making the diagnosis of gluten enteropathy, and gluten ataxia as well. Several studies confirmed that serologic tests, particularly the IgA EMA and the IgA tTGA, have become a relatively sensitive and specific way to initially detect CD. Many studies demonstrate a specificity of IgA tTGA greater than 95% and a sensitivity in the range of 90% to 96% and EMA has a slightly lower and variable sensitivity but an excellent specificity (99.6%). However, many individuals without CD may express AGA IgG antibody (sensitivity of AGA IgA among adults ranges between 0.65 and 1.0 and the specificity between 0.71 and 0.97). In line with this, AGA IgG is similar in sensitivity to the AGA IgA, but the specificity is much lower, approximately 0.5. Because of the variable and generally inferior accuracy of the AGA, the use of AGA IgA and AGA IgG tests is no longer recommended for identifying individuals with CD[54-57]. Nevertheless, false positive antigliadin antibody tests have been recorded in individuals with a variety of other gastrointestinal disorders, including esophagitis, gastritis, gastroenteritis, inflammatory bowel disease, cystic fibrosis and cow's milk protein intolerance. Moreover, we have also bear in mind that serologic tests may have false positive results (usually low antibody titers) in patients with other immune or inflammatory conditions such as many neurological disorders. For this reason and others, AGA Institute recommended testing for CD in persons with peripheral neuropathy, CA, and recurrent migraine, but confirmation of the diagnosis of CD requires an intestinal biopsy in all cases[56].

CONCLUSION

Based on the data accumulated so far, we can conclude that many autoantibodies related to gluten enteropathy and other conditions could be assessed in patients with ataxia or other undiagnosed neurological disorders, revealing the involvement of immunological mechanisms associated with CD. Some of these antibodies are AGA, antibodies to different isoforms of tissue TG (anti-TG2, 3, and especially anti-TG6 antibodies), anti-GlyR-Abs, anti-GAD antibodies, and anti-DGP antibodies. Some of these autoantibodies are pathogenic, others-epiphenomena, and for others-there is not enough data to conclude. The opposite is also valid-it is recommended to manage strictly and follow-up patients with CD for the development of neurological dysfunction and other extraintestinal complications.

FOOTNOTES

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ORIGINAL ARTICLE

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Enhanced recovery after surgery in elderly patients with non-small cell lung cancer who underwent video-assisted thoracic surgery

Mei-Hua Sun, Liu-Sheng Wu, Ying-Yang Qiu, Jun Yan, Xiao-Qiang Li

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Abstract

BACKGROUND

This study was designed to investigate the clinical outcomes of enhanced recovery after surgery (ERAS) in the perioperative period in elderly patients with non-small cell lung cancer (NSCLC).

AIM

To investigate the potential enhancement of video-assisted thoracic surgery (VATS) in postoperative recovery in elderly patients with NSCLC.

METHODS

We retrospectively analysed the clinical data of 85 elderly NSCLC patients who underwent ERAS (the ERAS group) and 327 elderly NSCLC patients who received routine care (the control group) after VATS at the Department of Thoracic Surgery of Peking University Shenzhen Hospital between May 2015 and April 2017. After propensity score matching of baseline data, we analysed the postoperative stay, total hospital expenses, postoperative 48-h pain score, and postoperative complication rate for the 2 groups of patients who underwent lobectomy or sublobar resection.

RESULTS

After propensity score matching, ERAS significantly reduced the postoperative hospital stay (6.96 ± 4.16 *vs* 8.48 ± 4.18 d, $P = 0.001$) and total hospital expenses (48875.27 ± 18437.5 *vs* 55497.64 ± 21168.63 CNY, $P = 0.014$) and improved the satisfaction score (79.8 ± 7.55 *vs* 77.35 ± 7.72, $P = 0.029$) relative to those for routine care. No significant between-group difference was observed in postoperative 48-h

pain score (4.68 ± 1.69 *vs* 5.28 ± 2.1, P = 0.090) or postoperative complication rate (21.2% *vs* 27.1%, P = 0.371). Subgroup analysis showed that ERAS significantly reduced the postoperative hospital stay and total hospital expenses and increased the satisfaction score of patients who underwent lobectomy but not of patients who underwent sublobar resection.

CONCLUSION

ERAS effectively reduced the postoperative hospital stay and total hospital expenses and improved the satisfaction score in the perioperative period for elderly NSCLC patients who underwent lobectomy but not for patients who underwent sublobar resection.

Key Words: Enhanced recovery after surgery; Non-small cell lung cancer; Perioperative care; Propensity score; Video-assisted thoracic surgery

Core Tip: This study was designed to investigate the clinical outcomes of enhanced recovery after surgery (ERAS) in the perioperative period in elderly patients with non-small cell lung cancer (NSCLC). ERAS significantly reduced the postoperative hospital stay (6.96 ± 4.16 *vs* 8.48 ± 4.18 d, P = 0.001) and total hospital expenses (48875.27 ± 18437.5 *vs* 55497.64 ± 21168.63 CNY, P = 0.014) and improved the satisfaction score (79.8 ± 7.55 *vs* 77.35 ± 7.72, P = 0.029) relative to those for routine care. ERAS effectively reduced the postoperative hospital stay and total hospital expenses and improved the satisfaction score in the perioperative period for elderly NSCLC patients who underwent lobectomy but not for patients who underwent sublobar resection.

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INTRODUCTION

Lung cancer ranks first in all malignant tumours with respect to morbidity and mortality[1]. Surgery is the main treatment for early lung cancer[2], but the complication rate is approximately 30%-50%, resulting in delayed recovery, poor long-term outcomes, and high medical costs[3-5]. Elderly patients with lung cancer often experience a slow recovery and high complication rates after thoracic surgery and thus are a high-risk group for surgical treatment[6-8]. To reduce the postoperative complication rate and accelerate postoperative recovery, many treatment strategies and perioperative management approaches have been incorporated into the surgical field, including infection control, nutritional support, improved fluid management, and comprehensive preoperative assessment. In 2001, Henrik Kehlet, a Danish gastrointestinal surgeon, first proposed the concept of enhanced recovery after surgery (ERAS)[9]. Empirical evidence has demonstrated that effective perioperative management that incorporates ERAS reduces the stress response to surgical trauma and complications and improves surgical safety and patient satisfaction. ERAS has been proven to effectively reduce common complications and general pain in patients. In recent years, the application of ERAS after thoracic surgery has reduced the perioperative complication rate, length of hospital stay, and hospital expenses[10]. However, evidence of the effectiveness of ERAS following video-assisted thoracic surgery (VATS) is still remains uncertain. In particular, no clinical studies have been conducted to investigate ERAS in elderly patients with lung cancer who underwent VATS.

This study was designed to retrospectively analyse the clinical outcomes of ERAS in elderly patients with lung cancer who underwent VATS at Peking University Shenzhen Hospital over a 5-year period and to investigate the role of ERAS (after propensity score matching) in improving postoperative recovery.

MATERIALS AND METHODS

Clinical data

We retrospectively analysed the clinical data of 412 elderly patients with lung cancer who underwent VATS at the Department of Thoracic Surgery of Peking University Shenzhen Hospital between May 2015 and April 2017. Of these patients, 271 were men, and 141 were women; their mean age was 72.41 ± 4.7 years; and 85 patients underwent ERAS (the ERAS group), and 327 patients received routine care (the control group). Moreover, 187 patients underwent sublobar resection, and 225 patients underwent lobectomy; 330 patients were diagnosed with adenocarcinoma, and 82 patients were diagnosed with squamous cell carcinoma; and 235 patients were in tumor-node-metastasis (TNM) stage I, and 92

patients were in TNM stage II.

The inclusion criteria were as follows: (1) Patients who underwent VATS and were pathologically confirmed to have non-small cell lung cancer (NSCLC) after surgery; (2) patients aged 65-80 years old; (3) patients with NSCLC in TNM stage I to II confirmed by postoperative pathology; and (4) patients with complete clinical data. The exclusion criteria were as follows: (1) Patients with pneumonectomy; or (2) patients with pathologically confirmed small cell lung cancer.

Methods

Perioperative management: The patients were divided into the control group and the ERAS group. The control group received routine care, and the ERAS group underwent ERAS (Table 1).

Preoperative management: All patients underwent a one-stop preoperative assessment by surgeons, anaesthesiologists, and nurses to facilitate optimal preoperative preparation and were closely monitored during and after the operation for any complications. The ERAS group was given a copy of an ERAS education brochure with detailed descriptions about daily goals and was asked to complete a diary. Intraoperative management: All patients were given prophylactic antibiotics during the induction period. General anaesthesia was administered with double-lumen tracheal intubation and single-lung breathing. Intraoperative rehydration was achieved with intravenous infusion of balanced fluid, and hypertensive or antihypertensive drugs were given based on blood pressure monitoring during the operation. The indications and the feasibility for surgery were determined in accordance with the China Guidelines for the Diagnosis and Treatment of Primary Lung Cancer (2015). The scope of surgical resection was determined by the treating physician based on patient conditions. Effort was taken to make a small incision, and absorbable sutures were used to close the incision. At the end of surgery, a closed thoracic drainage tube was placed according to routine procedures. Postoperative management: Intravenous infusion was minimized, with adequate analgesia. Non-steroidal anti-inflammatory drugs and acetaminophen were used for pain management. Opioids were avoided whenever possible to prevent postoperative nausea and vomiting and other opioid-related adverse reactions. Patients were encouraged to get out of bed as soon as possible. The catheter was removed at 12 h after operation (Table 2).

Criteria for discharge and follow-up: Discharge criteria were as follows: (1) Removal of the closed thoracic drainage tube; physical mobility; (2) no difficulty breathing (no shortness of breath, wheezing or stridor; oxygen saturation > 94%); and (3) no serious complications; complications (if any) were under control.

Calculation of medical expenses: The hospital medical records were used to record and calculate the total medical expenses, including laboratory tests, physical examinations, medications, nursing, surgery, supplies, and postoperative rehabilitation.

Satisfaction: A homemade satisfaction questionnaire was used during the week after discharge to evaluate patient satisfaction. The contents included staff attitude, operating techniques, timeliness of nursing, overall hospital experience, and pain score. Quality of life was analysed, including physical performance, physical pain, mental state, and general health.

Statistical analysis: R language 3.5.3 was used for propensity score matching of pathological classification, TNM stage, and surgical approach at 1:1 between the ERAS group and the control group.

SPSS v25.0 was used for statistical analysis. Measurement data are expressed as the mean value ± SD and analysed with the independent sample *t*-test or Mann-Whitney U test; count data are expressed as the frequency and were analysed with the chi-square test or Fisher's exact test. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline data

Among the 412 elderly patients with lung cancer who underwent VATS, 327 patients were in the control group and 85 patients were in the ERAS group. No significant between-group differences were observed regarding age ($P = 0.220$), sex ($P = 0.982$), body mass index ($P = 0.540$), or forced expiratory volume in the first second ($P = 0.615$) (Figure 1). Moreover, 330 patients had adenocarcinoma, and 82 patients had squamous cell carcinoma; 290 patients were in TNM stage I, and 122 patients were in stage II; 187 patients underwent sublobar resection, and 225 patients underwent lobectomy (Table 3). After matching, the control group and the ERAS group each included 85 patients.

No patient died during the perioperative period or required blood transfusion. At the end of surgery, the tracheal intubation was removed in the operating room, and the patients were able to breathe spontaneously with normal blood gas analysis results. All patients were sent back to the general ward, and no patient required mechanical ventilation in the intensive care unit. Before discharge, any postoperative complications were alleviated and resolved with treatment.

Clinical outcome measures

ERAS significantly improved postoperative hospital stay (6.98 ± 4.3 *vs* 8.92 ± 4.42 d, $P = 0.002$), total hospital expenses (52041.86 ± 19062.33 *vs* 60760.79 ± 20511.58, $P = 0.016$), and overall satisfaction (79.66 ± 7.5 *vs* 76.26 ± 7.42, $P = 0.013$) in the lobectomy subgroup (Table 4). Postoperative hospital stay also improved in the sublobar resection subgroup (6.94 ± 4.03 *vs* 7.86 ± 3.78 d, $P = 0.09$), but the differences of total hospital expenses ($P = 0.247$) and overall satisfaction ($P = 0.621$) did not reach statistical significance. In the ERAS group ($n = 85$), 3 patients had atelectasis, 9 had pulmonary infection, 4 had

Table 1 Perioperative management

	Measures	Routine care	ERAS
Preoperative	Education	Routine preoperative education	ERAS education
	Diet	Fasting for 6 h	Drink 1000 mL of 10% glucose the night before surgery; drink 200 mL of 10% glucose 2 h before surgery
	Sedatives (to improve sleep)	Yes	Yes
Intraoperative	Indwelling catheter after anaesthesia	Yes	Yes
	Temperature maintenance	No	Yes
Postoperative	Analgesia	Patient-controlled epidural analgesia	Use of NSAIDs for 48 h
	Infusion volume	Total intravenous infusion during the first 24 h after the operation < 1500 mL, infusion rate 20-30 mL/min; vasoconstrictors may be used in the case of hypotension or urine output < 20 mL/h	Rapid intravenous drip of 250 mL of saline within 1 h; the remaining parameters were the same as those in the routine care group
	Diet during the first 6 hours after the operation	A small amount of water	400 mL of liquid food
	Promote bowel movements	No	Chewing gum
	Catheter removal	24 h after the operation	12 h after the operation
	Early exercise	Patient choice	Lower limb movements

NSAIDs: Non-steroidal anti-inflammatory drugs.

Table 2 Patient education

Patient preoperative education	
Pre-operative	Be familiar with the environment and hospitalization process
	Preoperative nutritional risk screening
	Eat a healthy diet & stay active (1-2 wk before surgery)
	Normal diet the day before surgery
	Drink moderate glucose 2 h before surgery
	Preventive use of antibiotics
Postoperative	Eating liquid food moderately within six hours after surgery & infusion
	Receive any necessary medications
	Removed catheter at 12 h after operation
Day after surgery	Normal diet
	Use mixture of non-narcotic pain medication to keep comfortable
	Get out of bed as soon as possible
	Try to cough and expectorate

atrial fibrillation, and 2 had arrhythmia; the postoperative complication rate was 21.2%. In the control group (n = 85), 4 patients had atelectasis, 12 had pulmonary infection, 4 had atrial fibrillation, and 3 had arrhythmia; the postoperative complication rate was 27.1%. The difference did not reach statistical significance (Table 5).

DISCUSSION

ERAS is a multimodal perioperative protocol based on best medical evidence. In the 1990s, Kehlet *et al*[11] first used it for

Table 3 Baseline data

Baseline data		Before the match (*n* = 412)			After match (*n* = 170)		
		Routine care (*n* = 327)	ERAS (*n* = 85)	*P* value	Routine care (*n* = 85)	ERAS (*n* = 85)	*P* value
Age		72.18 ± 4.53	72.91 ± 4.94	0.22	72.55 ± 5	72.91 ± 4.94	0.643
Sex	Male	215	56	0.982	59	56	0.624
	Female	112	29		26	29	
BMI (kg/m^2)		22.54 ± 2.69	22.73 ± 2.62	0.54	22.51 ± 2.4	22.73 ± 2.62	0.565
FEV1 (L)		3.21 ± 0.45	3.24 ± 0.41	0.615	3.24 ± 0.41	3.24 ± 0.41	0.983
Pathological classification	Adenocarcinoma	261	69	0.78	69	69	1
	Squamous cell carcinoma	66	16		16	16	
TNM stage	I	235	55	0.198	55	55	1
	II	92	30		30	30	
Surgical approach	Uniportal VATS	282	69	0.242	75	69	0.201
	Three ports VATS	45	16		10	16	
Scope of resection	Pulmonary wedge	66	14	0.64	14	14	1
	Lung segment	86	21		21	21	
	Lobectomy	175	50		50	50	

ERAS: Enhanced recovery after surgery; BMI: Body mass index; FEV1: Forced expiratory volume in the first second; TNM: Tumor-node-metastasis; VATS: Video-assisted thoracic surgery.

patients undergoing colectomy to enhance postoperative recovery[11]. It includes preoperative optimization, intraoperative stress management, and enhanced postoperative recovery, with the goal of accelerating the recovery and resumption of normal activities. It reduces the length of the hospital stay and hospital expenses without increasing the readmission rate. With the gratifying results and low surgical wound, VATS approach is recommended as the standard scheme by several international academic organizations, including the European Society of Thoracic Surgeon, the American College of Chest Physicians and Minimally Invasive Cardiothoracic Surgery[12]. In thoracic surgeries, VATS is a main part of ERAS protocols in the relevant guidelines[13]. At present, class I evidence of the effectiveness of ERAS after thoracic surgery is scarce, especially in elderly patients with lung cancer. This study showed that ERAS improved the clinical efficacy of VATS in elderly patients with lung cancer. At present, data on ERAS in patients undergoing thoracic surgery are limited. Cerfolio *et al*[14] applied ERAS in patients undergoing open pneumonectomy, with a special focus on preoperative patient education, the use of epidural anaesthesia, active standardized removal of the catheter and drainage tube after surgery, early physical movement, and a daily plan for discharge within 4 days after surgery[14]. The intervention accelerated recovery without increasing the complication or mortality rate. A small randomized controlled study also showed that preoperative food intake (no fasting), conduction anaesthesia, early postoperative food intake, and early physical movement significantly reduced the incidence of postoperative pulmonary complications[15]. Salati *et al*[16] performed propensity score matching and demonstrated that ERAS effectively reduced the length of the hospital stay. The study focused on preoperative patient education, standardized postoperative care, and active drainage tube management[16]. In recent years, thoracic surgery-specific ERAS has gradually improved. Madani *et al*[17] described their ERAS procedures for open lobectomy, including standardized care, as well as preoperative, intraoperative, and postoperative management. The study showed that ERAS significantly reduced the length of the hospital stay and complications without increasing the readmission rate. However, their procedures were relatively conservative. Recent studies have shown that paraspinal block (instead of epidural analgesia) and a more aggressive closed thoracic drainage regimen may provide greater benefits to patients[18-20]. This study showed that ERAS significantly reduced postoperative hospital stay, total hospital expenses, and postoperative complications and improved satisfaction. Subgroup analysis per surgical approach (lobectomy *vs* sublobar resection) showed that ERAS did not significantly reduce postoperative hospital stay, total hospital expenses, and postoperative complications nor significantly improve satisfaction in the sublobar resection subgroup. The scope of sublobar resection was relatively small, with less impact on postoperative recovery, which may explain the lack of a significant difference between patients with sublobar resection in the ERAS group and the control group. On the other hand, lobectomy involves a greater scope of resection and surgical trauma, and thus, ERAS was superior to routine care in postoperative recovery. These data provide a reference for the selection of an appropriate rehabilitation regime. For ERAS, clinicians must pay attention to the readmission rate. Some studies have shown that for patients with lung cancer, readmission is related to shorter survival19. However, it is not clear whether ERAS will increase the readmission rate of lung cancer patients[17]. In this study, the 30-d readmission rate was 1.2%

Table 4 Clinical outcome measures (scope of resection subgroup analysis)

Outcome Measures	Total (*n* = 170)			Pulmonary wedge (*n* = 28)			Segmentectomy (*n* = 42)			Pulmonary lobe (*n* = 100)		
	ERAS (*n* = 85)	Routine care (*n* = 85)	*P* value	ERAS (*n* = 14)	Routine care (*n* = 14)	*P* value	ERAS (*n* = 21)	Routine care (*n* = 21)	*P* value	ERAS (*n* = 50)	Routine care (*n* = 50)	*P* value
Postoperative hospital stay (d)	6.06 ± 2.07	6.61 ± 1.68	0.024	5.43 ± 1.91	6.14 ± 1.99	0.352	5.9 ± 2.51	6.29 ± 1.65	0.325	6.3 ± 1.91	6.88 ± 1.59	0.040
Total hospital expenses (CNY)	42757.63 ± 14963.16	53748.72 ± 18356.11	0.000	37812.08 ± 13327.54	41836.7 ± 13282.69	0.454	39187.44 ± 18933.83	51245.25 ± 16865.5	0.007	45641.86 ± 13016.75	58135.55 ± 18757.68	0.001
Postoperative 48-h pain score	2.38 ± 0.91	2.59 ± 0.88	0.109	2.29 ± 0.83	2.43 ± 0.76	0.667	2.33 ± 1.11	2.48 ± 0.87	0.560	2.42 ± 0.86	2.68 ± 0.91	0.135
Satisfaction score	80.65 ± 7.74	76.67 ± 7.1	0.001	80 ± 7.99	77 ± 6.86	0.427	80.29 ± 7.12	76.9 ± 5.66	0.130	80.98 ± 8.04	76.48 ± 7.79	0.003
Readmission within 30 d	0	1	1.000	0	0		0	0		0	1	1.000
Complications (*n*)	14	26	0.030	2	2	1.000	5	12	0.028	7	12	0.065
Air leakage	7	13	0.153	1	1	1.000	3	7	0.277	3	5	0.712
Atelectasis	2	4	0.678	0	0		1	2	1.000	1	2	1.000
Pulmonary infection	3	6	0.493	1	1	1.000	1	1	1.000	1	4	0.359
Atrial fibrillation	1	2	1.000	0	0		0	1	1.000	1	1	1.000
Arrhythmia	1	1	1.000	0	0		0	1	1.000	1	0	1.000

ERAS: Enhanced recovery after surgery.

(only 1 patient in the ERAS group; $P > 0.05$), which was lower than those reported by other studies.

In recent years, a large body of evidence has demonstrated that VATS reduces complications and improves the prognosis of patients with lung cancer[5,21]. At present, however, evidence of the effectiveness of ERAS following VATS is inadequate, especially evidence on the role of ERAS following VATS in elderly patients with lung cancer. This was the first study to investigate the role of ERAS in the perioperative period in elderly patients with lung cancer. We performed propensity score matching to optimize the control group and comprehensively analysed perioperative outcome measures, including postoperative hospital stay, total hospital expenses, postoperative 48-hour pain score, and satisfaction score. This study showed that for elderly patients with lung cancer, ERAS effectively improved postoperative recovery (including hospital stay and hospital expenses) and patient satisfaction and reduced the postoperative complication rates.

CONCLUSION

This is the first study to perform propensity score matching to demonstrate the effectiveness of ERAS for elderly patients

Table 5 Clinical outcome measures (age subgroup analysis)

Outcome measures	Total (*n* = 170)			Age 60-73 (*n* = 28)			Age 74-80 (*n* = 42)		
	ERAS (*n* = 85)	Routine (*n* = 85)	*P* value	ERAS (*n* = 14)	Routine care (*n* = 14)	*P* value	ERAS (*n* = 21)	Routine care (*n* = 21)	*P* value
Postoperative hospital stay (d)	6.06 ± 2.07	6.61 ± 1.68	0.024	5.96 ± 2	6.57 ± 1.7	0.057	6.18 ± 2.17	6.67 ± 1.69	0.188
Total hospital expenses (CNY)	42757.63 ± 14963.16	53748.72 ± 18356.11	0.000	42122.76 ± 13923.83	52334 ± 18206.28	0.008	43471.85 ± 16202.51	55417.37 ± 18628.5	0.001
Postoperative 48-h pain score	2.38 ± 0.91	2.59 ± 0.88	0.109	2.33 ± 0.83	2.8 ± 0.83	0.006	2.43 ± 1.01	2.33 ± 0.87	0.687
Satisfaction score	80.65 ± 7.74	76.67 ± 7.1	0.001	81.16 ± 7.52	76.78 ± 6.31	0.004	80.08 ± 8.04	76.54 ± 8.01	0.055
Readmission within 30 d	0	1	1.000	0	0		0	1	1.000
Complications (*n*)	14	26	0.030	5	11	0.109	8	15	0.071
Air leakage	7	13	0.153	4	5	1.000	3	8	0.179
Atelectasis	2	4	0.678	1	2	1.000	1	2	0.982
Pulmonary infection	3	6	0.493	1	3	0.625	2	3	0.977
Atrial fibrillation	1	2	1.000	0	1	1.000	1	1	1.000
Arrhythmia	1	1	1.000	0	0		1	1	1.000

ERAS: Enhanced recovery after surgery.

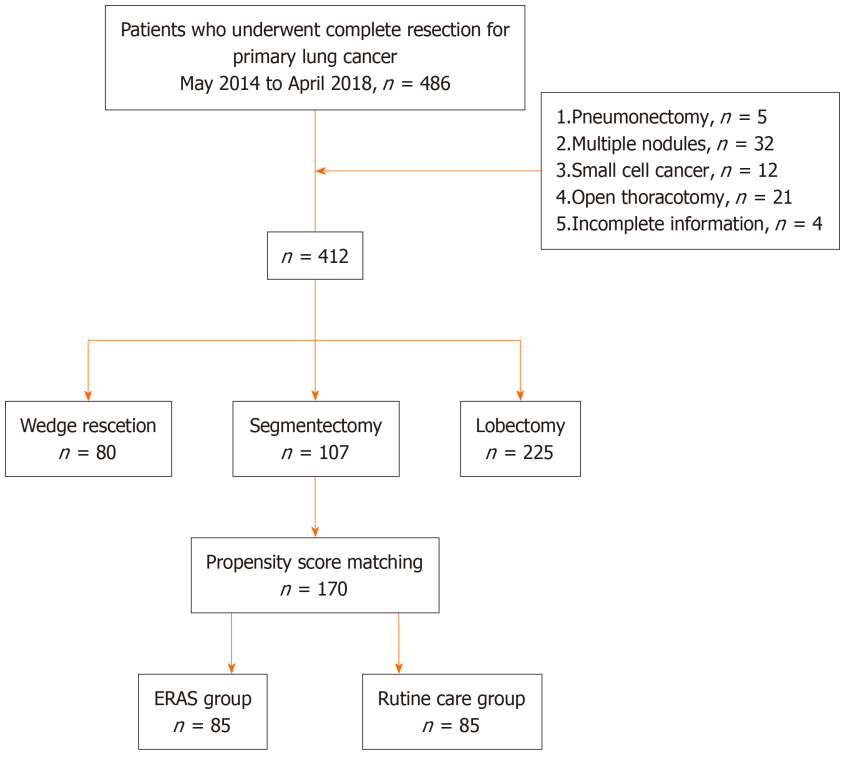

Figure 1 Include standard flow chart. ERAS: Enhanced recovery after surgery.

with lung cancer. Further subgroup analysis showed that ERAS had significant effects in the lobectomy subgroup. In summary, ERAS may be used as an effective treatment for elderly patients with lung cancer, especially patients undergoing lobectomy.

ARTICLE HIGHLIGHTS

Research background

Lung cancer is the leading cause of death worldwide, and non-small cell lung cancer (NSCLC) in the elderly accounts for a significant proportion. With the significant growth of the aging population, the need for surgical treatment of elderly patients has gradually become more prominent. Video-assisted thoracic surgery (VATS) has become an important choice for the treatment of senile NSCLC due to its characteristics of less trauma and rapid recovery. However, current systematic studies on VATS in postoperative recovery in elderly patients are relatively limited. Therefore, an in-depth understanding of the influence of VATS on elderly patients and revealing its potential role in postoperative rehabilitation are of great significance for guiding the individualized treatment of elderly patients with NSCLC and improving surgical results.

Research motivation

The aim of this study was to investigate the potential enhancement of VATS in postoperative recovery in elderly patients with NSCLC.

Research objectives

This study was designed to investigate the clinical outcomes of enhanced recovery after surgery (ERAS) in the perioperative period in elderly patients with NSCLC.

Research methods

We retrospectively analysed the clinical data of 85 elderly NSCLC patients who underwent ERAS (the ERAS group) and 327 elderly NSCLC patients who received routine care (the control group) after VATS at the Department of Thoracic Surgery of Peking University Shenzhen Hospital between May 2015 and April 2017. After propensity score matching of baseline data, we analysed the postoperative stay, total hospital expenses, postoperative 48-hour pain score, and postoperative complication rate for the 2 groups of patients who underwent lobectomy or sublobar resection.

Research results

After propensity score matching, ERAS significantly reduced the postoperative hospital stay (6.96 ± 4.16 *vs* 8.48 ± 4.18 d, P = 0.001) and total hospital expenses (48875.27 ± 18437.5 *vs* 55497.64 ± 21168.63 CNY, P = 0.014) and improved the satisfaction score (79.8 ± 7.55 *vs* 77.35 ± 7.72, P = 0.029) relative to those for routine care. No significant between-group difference was observed in postoperative 48-h pain score (4.68 ± 1.69 *vs* 5.28 ± 2.1, P = 0.090) or postoperative complication rate (21.2% *vs* 27.1%, P = 0.371). Subgroup analysis showed that ERAS significantly reduced the postoperative hospital stay and total hospital expenses and increased the satisfaction score of patients who underwent lobectomy but not of patients who underwent sublobar resection.

Research conclusions

ERAS effectively reduced the postoperative hospital stay and total hospital expenses and improved the satisfaction score in the perioperative period for elderly NSCLC patients who underwent lobectomy but not for patients who underwent sublobar resection.

Research perspectives

We look forward to more large-sample, multicenter studies to validate the recovery benefits of VATS in elderly patients with NSCLC and to further clarify the safety and effectiveness of the surgical technique. At the same time, combined with biological markers and imaging techniques, the specific mechanism of VATS on postoperative inflammatory response, immune function, and quality of life in elderly patients was further studied. With the help of advanced technical means, the individual differences of elderly patients were finely delineated to provide a more accurate basis for personalized surgical treatment. In addition, the long-term efficacy and survival rate of VATS in elderly patients were evaluated through long-term follow-up to comprehensively understand the long-term impact of surgery. These future research directions will provide an in-depth and comprehensive understanding for further promoting the development of surgical treatment for elderly NSCLC.

FOOTNOTES

Co-first authors: Mei-Hua Sun and Liu-Sheng Wu.

Co-corresponding authors: Xiao-Qiang Li and Jun Yan.

Author contributions: Yan J and Li XQ conceived and designed the study; Qiu YY screened patients to obtain clinical data and data analysis; Wu LS and Sun MH wrote the paper; All authors have read and approved the final draft. Wu LS proposed, designed, and analyzed the data and wrote the first draft of the paper. Sun MH was responsible for patient screening, enrollment, and the collection of clinical data. Both authors have made vital and indispensable contributions to the completion of the project and are therefore qualified to be co-first authors of the paper. As co-corresponding authors, Yan J and Li XQ played an important and indispensable role in project design, data interpretation, and manuscript preparation. Yan J and Li XQ applied for and were successful in obtaining funding for this

project. Yan J conceived, designed, and supervised the entire project process. Li XQ assisted and was responsible for data reanalysis and reinterpretation, graphing, comprehensive literature search, preparation, and submission of the current version of the manuscript. The cooperation of Yan J and Li XQ was critical to the publication of this manuscript.

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Institutional review board statement: The study was approved by the Institutional Review Board of Peking University Shenzhen Hospital, and all patients provided their informed consent before starting the treatment.

Informed consent statement: As it was a retrospective clinical study, all the patients were contacted by telephone to obtain verbal informed consent and it was approved by the ethics committee.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: All data collected and analyzed in this study are included in this article, and technical appendix, statistical code, and dataset available from the corresponding author at dr.lixiaoqiang@gmail.com.

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ORIGINAL ARTICLE

Clinical Trials Study

Transient elastography with controlled attenuation parameter for the diagnosis of colorectal polyps in patients with nonalcoholic fatty liver disease

Lan Wang, Yan-Fei Li, Li-Feng Dong

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Peer-review model: Single blind

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Abstract

BACKGROUND

The severity of nonalcoholic fatty liver disease (NAFLD) and lipid metabolism are related to the occurrence of colorectal polyps. Liver-controlled attenuation parameters (liver-CAPs) have been established to predict the prognosis of hepatic steatosis patients.

AIM

To explore the risk factors associated with colorectal polyps in patients with NAFLD by analyzing liver-CAPs and establishing a diagnostic model.

METHODS

Patients who were diagnosed with colorectal polyps in the Department of Gastroenterology of our hospital between June 2021 and April 2022 composed the case group, and those with no important abnormalities composed the control group. The area under the receiver operating characteristic curve was used to predict the diagnostic efficiency. Differences were considered statistically significant when $P < 0.05$.

RESULTS

The median triglyceride (TG) and liver-CAP in the case group were significantly greater than those in the control group (mmol/L, 1.74 *vs* 1.05; dB/m, 282 *vs* 254, $P < 0.05$). TG and liver-CAP were found to be independent risk factors for colorectal polyps, with ORs of 2.338 (95%CI: 1.154–4.733) and 1.019 (95%CI: 1.006–1.033), respectively ($P < 0.05$). And there was no difference in the diagnostic efficacy between liver-CAP and TG combined with liver-CAP (TG+CAP) ($P > 0.05$). When the liver-CAP was greater than 291 dB/m, colorectal polyps were more likely to occur.

CONCLUSION
The levels of TG and liver-CAP in patients with colorectal polyps are significantly greater than those patients without polyps. Liver-CAP alone can be used to diagnose NAFLD with colorectal polyps.

Key Words: Colorectal polyps; Nonalcoholic fatty liver disease; Liver-controlled attenuation parameter; Liver fibroscan; Diagnostic model

Core Tip: This study was designed to explore the risk factors associated with colorectal polyps in patients with nonalcoholic fatty liver disease (NAFLD) by analyzing liver-controlled attenuation parameters (liver-CAPs) and establishing a diagnostic model. We found that the triglyceride (TG) and liver-CAPs in patients with colorectal polyps were significantly greater than those in patients without colorectal polyps. When the liver-CAP was greater than 291 dB/m, colorectal polyps were more likely to occur. Additionally, no difference was observed in the diagnostic efficacy or specificity between liver-CAP and TG+CAP. Liver-CAP alone can also be used to diagnose NAFLD patients with colorectal polyps.

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INTRODUCTION

The global incidence of colorectal cancer, a malignant tumor, has significantly increased in recent years[1-3]. Colorectal polyps are precursors of malignant colorectal tumors whose pathogenesis involves multiple factors[1,4-7], including abnormal lipid metabolism and fatty liver[4-16]. Nonalcoholic fatty liver disease (NAFLD) is considered the main cause of chronic liver disease in most patients[17], and liver-controlled attenuation parameters (liver-CAPs) have been established to predict the prognosis of hepatic steatosis patients[13,17]. This study retrospectively analyzed liver-CAPs, lipid metabolism, and other indicators in NAFLD patients with colorectal polyps to investigate the correlation between liver-CAP, lipid metabolism, and colorectal polyps in NAFLD patients and to establish a diagnostic model.

MATERIALS AND METHODS

Patients

Patients who were diagnosed with colorectal polyps and who underwent electronic colonoscopy at the Department of Gastroenterology of our hospital between June 2021 and April 2022 were selected as the case group. Patients without important abnormalities during the same period were selected as the control group.

Inclusion criteria

The inclusion criteria for the patients were as follows: (1) Over 18 years old; (2) had undergone electronic enteroscopy during hospitalization; and (3) had NAFLD based on a liver elasticity test.

Exclusion criteria

The exclusion criteria for the patients included the following: (1) Incomplete bowel preparation or colon examination for various reasons; (2) history of inflammatory bowel disease, intestinal tuberculosis, familial adenomatous polyposis, melanosis of the colon, colorectal cancer, intestinal lymphoma, or other intestinal diseases; (3) prior liver diseases other than alcoholic fatty liver diseases, such as viral liver disease, autoimmune liver disease, genetic metabolic liver disease, or cirrhosis; (4) history of malignant tumor, metabolic syndrome, chronic kidney disease, severe infection, or other systemic diseases; and (5) use of drugs such as lipid-regulating drugs, hormones, or immunosuppressants.

Clinical parameters

After admission, general data, medical history, liver-CAP, TG, total cholesterol (TC), low-density lipoprotein (LDL), and other indicators were collected. Colonoscopies were performed by qualified senior physicians. All participants were tested for liver-CAP using FibroScan 502 Touch (Echosens). The cutoff values for the degree of lipidosis diagnosed with hepatic CAP ≥ 11%, ≥ 34%, and ≥ 67% were 238, 259, and 292 dB/m, respectively.

Statistical analysis

SPSS (version 26.0) and GraphPad (version 8.0.1.244) were used for the statistical analysis of all the data. The median values and both the 25th and 75th percentiles were associated with continuous variables. Frequencies and percentiles were associated with categorical variables. Continuous variables were compared between groups using the independent *t* test or Mann-Whitney *U* test. Multivariate analysis was performed by logistic regression, and the area under the receiver operating characteristic curve (AUROC) was used to evaluate the diagnostic efficacy. The Jorden index was calculated to obtain the cutoff value. The DeLong method was used to compare the diagnostic efficiency among the models. Differences were considered statistically significant when $P < 0.05$. The statistical review of the study was performed by Li-Feng Dong from Beijing ChuiYangLiu Hospital.

The study was approved by the Human Ethics Committee of Beijing ChuiYangLiu Hospital. The requirement for informed consent from patients was waived (No. 2024-002KY).

RESULTS

Comparison of general indexes between the case group and control group

Based on the inclusion criteria, 120 patients (76 males, accounting for 63%) were included in the case group, and 52 patients (26 males, accounting for 50%) were included in the control group. There were no statistically significant differences in terms of sex ratio, age, body mass index, TC, or LDL between the two groups. The median TG concentration in the case group was significantly greater than that in the control group (mmol/L, 1.74 *vs* 1.05, $P < 0.05$). The level of liver-CAP in the case group was significantly greater than that in the control group (dB/m, 282 *vs* 254, $P < 0.05$) (Table 1).

Logistic multivariate analysis of colorectal polyps

Logistic multivariate analysis and forest map description were used to analyze TG and liver-CAP levels (Figure 1). TG and liver-CAP were identified as independent risk factors for colorectal polyps, with ORs of 2.338 (95%CI: 1.154–4.733) and 1.019 (95%CI: 1.006–1.033), respectively ($P < 0.05$).

Comparison of receiver operating characteristic curves and DeLong tests between liver-CAP and TG+CAP for the diagnosis of colorectal polyps

Receiver operating characteristic (ROC) analysis was performed on liver-CAP and TG+CAP samples (Figure 2). The diagnosis of colorectal polyps with liver-CAP had an AUROC of 0.683, a sensitivity of 0.408, a specificity of 0.942, and a cutoff value of 291 dB/m. When the liver-CAP was greater than 291 dB/m, the probability of developing colorectal polyps increased. The diagnosis of colorectal polyps with TG+CAP had an AUROC of 0.756, a sensitivity of 0.731, a specificity of 0.694, and a cutoff value of 0.704. Taken together, the prediction probability was calculated to be 0.704.

The DeLong method was used to compare the diagnostic efficacy of liver-CAP and TG+CAP (Table 2). No difference was observed between liver-CAP and TG+CAP in diagnosing colorectal polyps in NAFLD patients, despite the lower AUROC of liver-CAP than that of TG+CAP. Hence, the diagnostic efficacy in both groups was considered the same.

DISCUSSION

Colorectal polyps gradually develop into colorectal cancer, which can substantially impact quality of life and reduce the survival rate of patients without early intervention. Therefore, early detection and treatment of colorectal polyps are essential for improving the prognosis of colorectal cancer patients and their quality of life[1,2,4-6].

Many studies have reported that NAFLD is a risk factor for colorectal polyps[4-16]. For example, the detection rate of hyperplastic polyps in the NAFLD group was significantly greater than that in the control group, and NAFLD was associated with an increased risk of hyperplastic polyps[18]. Domestic studies have also validated that colorectal adenomatous polyps are positively correlated with NAFLD[16].

Shear wave quantified ultrasound diagnosis of liver function—liver elasticity examination—is a clinically established noninvasive method for liver evaluation. Likewise, liver-CAP can determine the prognosis of patients with hepatic steatosis and fatty liver[17].

In this study, the occurrence of colorectal polyps was predicted by the liver-CAP in patients with NAFLD. Some studies have reported that the level of liver-CAP in patients with colorectal polyps was significantly greater than that in patients with noncolorectal polyps[13], and we have also confirmed it in this study. Additionally, this study demonstrated that the diagnostic efficacy of TG+CAP was relatively similar to that of liver-CAP alone.

Compared with TG+CAP, liver-CAP had greater specificity in diagnosing colorectal polyps in NAFLD patients (0.942 *vs* 0.694) and was simple, rapid, and noninvasive. The findings of this study could assist patients and attending physicians in better managing fatty liver, as we reported that liver-CAPs greater than 291 dB/m increased the likelihood of developing colorectal polyps. This threshold value is close to the threshold value of liver elasticity for the diagnosis of severe steatosis (292 dB/m) and could be a promising alternative diagnostic option for patients.

In this work, the correlations between colorectal polyps, liver-CAP, and lipid metabolism in patients with NAFLD were analyzed, and ROC analysis indicated that colorectal polyps were more common in patients with NAFLD when liver-CAP was greater than 291 dB/m or when the TG+CAP index was greater than 0.704. In this study, liver-CAP was

Table 1 Comparison of general information between the case and control groups

Parameters	Case group	Control group	*P* value
Number of Patients	120	52	NS
Male patients (%)	76 (63)	26 (50)	NS
Age (yr)	58 (48, 64)	53 (46, 62)	NS
BMI (kg/m^2)	25.58 (23.97, 28.12)	25.01 (22.98, 26.85)	NS
TC (mmol/L)	4.81 (3.99, 314)	4.86 (4.05, 5.13)	NS
LDL-C (mmol/L)	3.03 (2.38, 3.77)	3.08 (2.14, 3.42)	NS
TG (mmol/L)	1.74 (1.14, 2.38)	1.05 (0.74, 1.45)	< 0.05
CAP (dB/m)	282 (247, 314)	254 (235, 282)	< 0.05

BMI: Body mass index; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; CAP: Controlled attenuation parameter; NS: Not significant. $P > 0.05$.

Table 2 Comparison of the DeLong area under the receiver operating characteristic curves for parameter and triglyceride combined with controlled attenuation parameter

Models compared	*Z* value	*P* value
CAP and TG+CAP	-1.815	NS

TG: Triglyceride; CAP: Controlled attenuation parameter; NS: Not significant. $P > 0.05$.

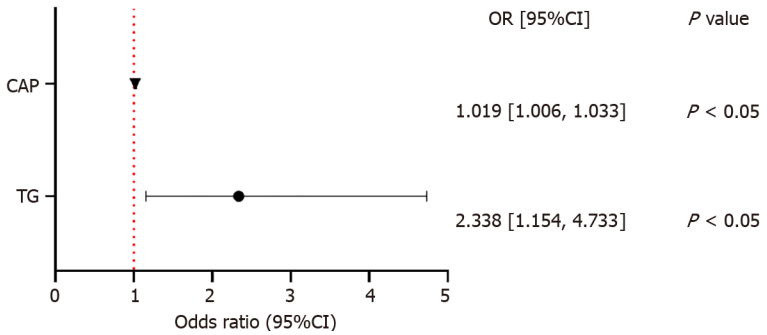

Figure 1 Forest plot of risk factors for colorectal polyps. The distance between the left and right of each plot represents the confidence interval (CI); the triangle represents the liver-controlled attenuation parameter for colorectal polyps, with an odds ratio of 1.019 (95%CI: 1.006-1.033), $P < 0.05$; the dot represents the triglyceride for colorectal polyps with an odds ratio of 2.338 (95%CI: 1.154-4.733), $P < 0.05$. CI: Confidence interval; TG: Triglyceride; CAP: Controlled attenuation parameter.

used as an indicator to predict the occurrence of colorectal polyps. Compared with those of the TG+CAP group, the AUROC (0.683) and sensitivity (0.408) in the liver-CAP group were lower, but the specificity was greater (0.942). Additionally, the diagnostic efficiency of liver-CAP alone was relatively similar to that of TG+CAP. However, further studies with larger sample sizes are still needed to verify the findings of this study.

There were several limitations to this study. This was a cross-sectional and retrospective study, and the sequence and specific time points at which fatty liver, lipid metabolism, and colorectal polyps occurred could not be distinguished. In addition, the small sample size and the place of residence of the enrolled patients could have affected the research results. Hence, it is necessary to expand the sample size and develop a prospective scheme to further verify the findings of this study.

CONCLUSION

In summary, this study revealed the correlation of both fatty liver-CAP and TG with the occurrence of colorectal polyps. In clinical practice, the findings of this study could facilitate diagnosis and treatment of colorectal polyps as well as the

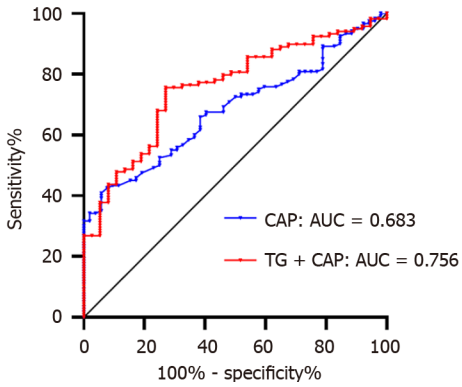

Figure 2 Comparison of the receiver operating characteristic curves of the controlled attenuation parameter and triglyceride combined with controlled attenuation parameter in the diagnosis of colorectal polyps. The red broken line represents the triglyceride (TG) + controlled attenuation parameter (CAP) for the diagnosis of colorectal polyps, with an area under the curve (AUC) of 0.756, a sensitivity of 0.731, a specificity of 0.694, and a cutoff value of 0.704; the blue broken line represents the CAP for the diagnosis of colorectal polyps, with an AUC of 0.683, a sensitivity of 0.408, a specificity of 0.942, and a cutoff value of 291 db/m. ROC: The receiver operating characteristic curve; TG: Triglyceride; CAP: Controlled attenuation parameter; AUC: area under curve.

provision of better informed advice to patients, such as dietary plans and lifestyle information. Overall, the findings of this study could improve our understanding of colorectal polyps and fatty liver, enable detection of colorectal polyps as early as possible, and help to reduce the degree of fatty liver degeneration encountered in patients.

FOOTNOTES

Co-first authors: Lan Wang and Yan-Fei Li.

Author contributions: Wang L, Li YF and Dong LF designed the research; Wang L performed the research; Li YF contributed new analytic tools; Wang L and Li YF analyzed the data; Wang L wrote the paper; all authors have read and approved the final manuscript.

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META-ANALYSIS

Systematic review and network meta-analysis of different non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis

Tao Zeng, Jian-Zhong Ye, Hui Qin, Qian-Qian Xu

Specialty type: Orthopedics

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Peer-review model: Single blind

Peer-review report's scientific quality classification

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Abstract

BACKGROUND

Various non-steroidal anti-inflammatory drugs (NSAIDs) have been used for juvenile idiopathic arthritis (JIA). However, the optimal method for JIA has not yet been developed.

AIM

To perform a systematic review and network meta-analysis to determine the optimal instructions.

METHODS

We searched for randomized controlled trials (RCTs) from PubMed, EMBASE, Google Scholar, CNKI, and Wanfang without restriction for publication date or language at August, 2023. Any RCTs that comparing the effectiveness of NSAIDs with each other or placebo for JIA were included in this network meta-analysis. The surface under the cumulative ranking curve (SUCRA) analysis was used to rank the treatments. *P* value less than 0.05 was identified as statistically significant.

RESULTS

We included 8 RCTs (1127 patients) comparing 8 different instructions including meloxicam (0.125 qd and 0.250 qd), Celecoxib (3 mg/kg bid and 6 mg/kg bid), piroxicam, Naproxen (5.0 mg/kg/d, 7.5 mg/kg/d and 12.5 mg/kg/d), inuprofen (30-40 mg/kg/d), Aspirin (60-80 mg/kg/d, 75 mg/kg/d, and 55 mg/kg/d), Tolmetin (15 mg/kg/d), Rofecoxib, and placebo. There were no significant differences between any two NSAIDs regarding ACR Pedi 30 response. The SUCRA shows that celecoxib (6 mg/kg bid) ranked first (SUCRA, 88.9%), rofecoxib ranked second (SUCRA, 68.1%), Celecoxib (3 mg/kg bid) ranked third (SUCRA, 51.0%). There were no significant differences between any two NSAIDs regarding adverse events. The SUCRA shows that placebo ranked first (SUCRA, 88.2%), piroxicam ranked second (SUCRA, 60.5%), rofecoxib (0.6 mg/kg qd) ranked third (SUCRA, 56.1%), meloxicam (0.125 mg/kg qd) ranked fourth (SUCRA, 56.1%), and rofeco-

xib (0.3 mg/kg qd) ranked fifth (SUCRA, 56.1%).

CONCLUSION
In summary, celecoxib (6 mg/kg bid) was found to be the most effective NSAID for treating JIA. Rofecoxib, piroxicam, and meloxicam may be safer options, but further research is needed to confirm these findings in larger trials with higher quality studies.

Key Words: Non-steroidal anti-inflammatory drugs; Juvenile idiopathic arthritis; Network meta-analysis; Systematic review

Core Tip: In summary, celecoxib (6 mg/kg bid) was found to be the most effective non-steroidal anti-inflammatory drug for treating juvenile idiopathic arthritis. Rofecoxib, piroxicam, and meloxicam may be safer options, but further research is needed to confirm these findings in larger trials with higher quality studies.

Citation: Zeng T, Ye JZ, Qin H, Xu QQ. Systematic review and network meta-analysis of different non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis. *World J Clin Cases* 2024; 12(12): 2056-2064
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INTRODUCTION

Juvenile idiopathic arthritis (JIA) refers to several types of chronic arthritis that appear before the age of 16[1-3]. JIA affects 294000 children in the United States, which characterized by chronic arthritis[4,5]. The pathogenesis of JIA was unknown. Clinical manifestations of JIA is joint pain, swelling, and morning stiffness[6,7]. Symptoms of JIA often persist into adulthood and are one of the leading causes of joint dysfunction in children[8]. At present, JIA is difficult to cure in the short term. The goal of treatment for JIA is to achieve sustained remission or low disease activity[9].

There are two forms of COX in the human body currently: COX-1 and COX-2[10,11]. Normally, COX-2 expression is low, but in inflammatory conditions, it is dramatically increased and thus causing a high level of inflammation[12]. Non-steroidal anti-inflammatory drugs (NSAIDs) work by blocking COX enzyme synthesis, which in turn inhibits prostaglandin synthesis[13,14]. Thus, NSAIDs have definite pain-relieving and anti-inflammatory properties. Moreover, NSAIDs is well tolerated by children and has fewer side effects. Therefore, NSAIDs are recommended drugs for symptom relief in JIA.

NSAIDs, which include traditional non-selective NSAIDS and selective NSAIDs. There are no direct comparisons of NSAIDs in current research, so it's important to evaluate their effectiveness and safety from the perspectives of healthcare providers and payers. Currently, there is a lack of systematic review and meta-analysis that comparing different NSAIDs for JIA. Network meta-analysis enables comparisons between drugs that have not been directly compared in head-to-head trials, using a common comparator like placebo[15,16]. We will use network meta-analysis to determine the best treatment for JIA and guide clinical decision-making. Our goal is to compare NSAIDs for JIA treatment through network meta-analysis.

MATERIALS AND METHODS

Search strategy

Two authors independently searched the electronic literature database of PubMed, EMBASE, Google Scholar, CNKI and Wanfang without restriction for publication date or language at August, 2023. The key words for searching can be seen in Supplement material. Articles and references were searched to prevent overlooking important sources. Previous systematic reviews, meta-analyses, and randomized controlled trials were also reviewed. Any disagreements between authors were resolved with a third independent author. Only studies involving humans were included in the search. As this study is a network meta-analysis, ethical approval was not necessary.

Inclusion criteria

The inclusion criteria were as follows: (1) Patients were diagnosed with JIA; (2) studies comparing NSAIDs therapies [meloxicam (0.125 qd and 0.250 qd), Celecoxib (3 mg/kg bid and 6 mg/kg bid)], piroxicam, Naproxen (5.0 mg/kg/d, 7.5 mg/kg/d, and 12.5 mg/kg/d), Inuprofen (30-40 mg/kg/d), Aspirin (60-80 mg/kg/d, 75 mg/kg/d, and 55 mg/kg/d), Tolmetin (15 mg/kg/d), Rofecoxib (0.3 mg/kg qd, 0.6 mg/kg), or with placebo; (3) randomized controlled trials (RCTs); and (4) studies reporting ACR Pedi 30 response and adverse events in patients.

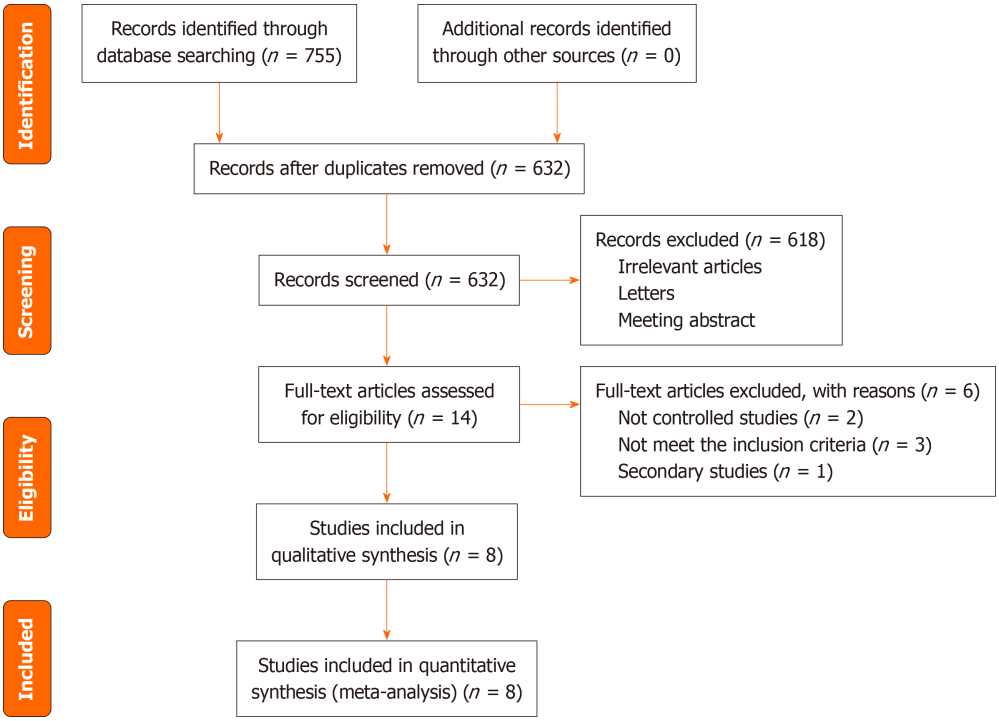

Figure 1 Literature review flow-chart.

The following studies were excluded: (1) Abstract only (insufficient data); (2) repeatedly published studies; (3) repeated studies; (4) not RCT; and (5) secondary research papers (*e.g.*, reviews, meta-analyses).

Data extraction

Two investigators independently extracted data from included trials using a standardized form, including author, publication year, country, participant characteristics, sample size, follow-up duration, and drugs. Clinical outcomes containing ACR Pedi 30 response and adverse events. In case of inconsistencies, extensive discussions were used for resolution.

Quality assessment and publication bias assessment

Two assessors evaluated the quality of individual trials based on the Cochrane Handbook, looking at factors like randomization, blinding, and reporting bias. Trials were categorized as "low risk", "high risk", or "unclear".

Statistical analysis

A network meta-analysis was performed to compare various treatments utilizing a random-effect model within a Bayesian framework. The analysis was carried out using the "gemtc" and "rjags" packages in R software version 3.5.1. Convergence was ensured through the implementation of a Markov chain Monte Carlo Bayesian approach with four chains, each consisting of 20000 iterations. Each chain generated 150000 sample iterations, with 10 thinning intervals and 100000 burn-ins. Estimates were based on median values from posterior distributions, with statistically significant differences indicated by 95% confidence intervals excluding 1 for odds ratios and 0 for mean differences. A significance level of $P < 0.05$ was used. Surface under the cumulative ranking curve (SUCRA) values were used in the network meta-analysis to rank interventions, with higher values indicating greater efficacy. A cluster-ranking plot was used to find the best outcome indicator. Heterogeneity was assessed with the I^2 test, while inconsistency within models was measured with the deviance information criterion. Node-splitting analysis and funnel plots were used to check for local inconsistencies and publication bias respectively.

RESULTS

Included studies and risks of bias assessment

The search retrieved a total of 755 articles which were identified from PubMed (322), EMBASE (189), Google Scholar (215), CNKI (20), and Wanfang (9). Of these, 123 were removed as duplicates. Based on our review of the title and abstract, 632 full-text papers were reviewed and 618 were excluded. Then, full-text articles were assessed for eligibility and 6 studies were excluded for reasons. Finally, a total of 8 studies[17-24] met the inclusion criteria and included for analysis (Figure 1).

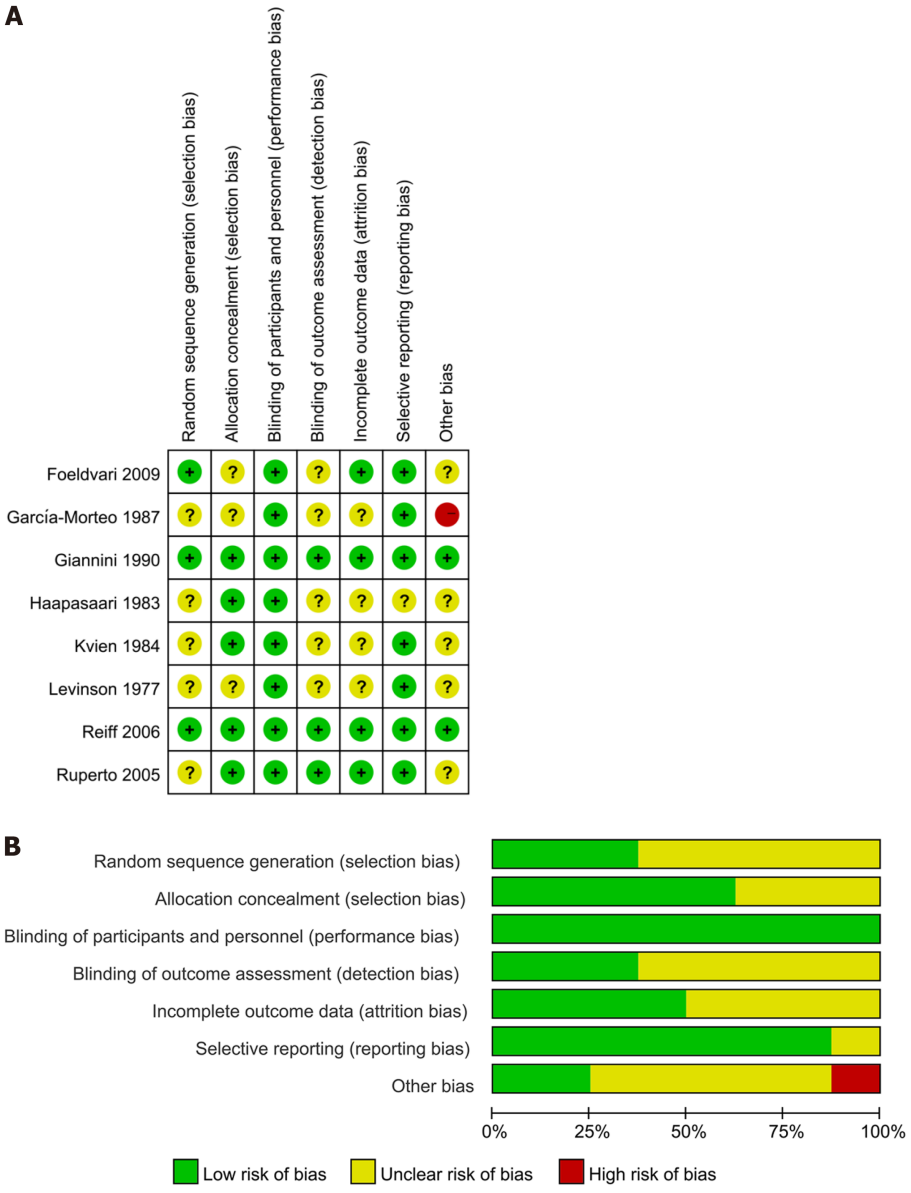

Figure 2 Risk of bias summary and bias graph. A: Risk of bias summary; B: Risk of bias graph.

Table 1 displayed the basic characteristics of the included studies. The total sample included 467 patients whose mean or median baseline age of participants ranged from 7.7 to 11.4 years and all of them were published after 1977. Subtype of JIA including polyarticular JIA, oligoarticular JIA and systemic JIA. NSAIDs including meloxicam (0.125 qd and 0.250 qd), Celecoxib (3 mg/kg bid and 6 mg/kg bid), piroxicam, Naproxen (5.0 mg/kg/d, 7.5 mg/kg/d, and 12.5 mg/kg/d), Inuprofen (30-40 mg/kg/d), Aspirin (60-80 mg/kg/d, 75 mg/kg/d, and 55 mg/kg/d), Tolmetin (15 mg/kg/d), Rofecoxib (0.3 mg/kg qd, 0.6 mg/kg), and placebo. Most trials included in the meta-analysis had unclear risk of bias, with 3 studies having adequate random sequence generation and 5 studies reporting adequate allocation concealment. Blinding of participants and personnel was adequate in all included studies, with details shown in Figure 2.

ACR Pedi 30 response

Three studies, involving a total of 770 patients, evaluated the clinical efficacy of four treatments (meloxicam, celecoxib, naproxen, and rofecoxib) in relation to the ACR Pedi 30 response. The network structure diagrams in Figure 3A illustrate the direct comparisons between these drugs in terms of their impact on the ACR Pedi 30 response. There were no notable differences in ACR Pedi 30 response between NSAIDs (Figure 3B). Celecoxib (6 mg/kg bid) had the highest ranking in SUCRA at 88.9%, followed by rofecoxib at 68.1% and Celecoxib (3 mg/kg bid) at 51.0% (Figure 3C).

Adverse events

Eight studies with ten treatments (meloxicam, naproxen, piroxicam, placebo, rofecoxib, tolmetin, aspirin, celecoxib, and diclofenac) were analyzed for adverse events (Figure 4A). The network structure diagrams showed direct comparisons between the drugs, revealing no significant differences in adverse events among any two NSAIDs (Figure 4B). The results of the SUCRA indicate that the placebo intervention achieved the highest ranking with a SUCRA value of 88.2%, followed

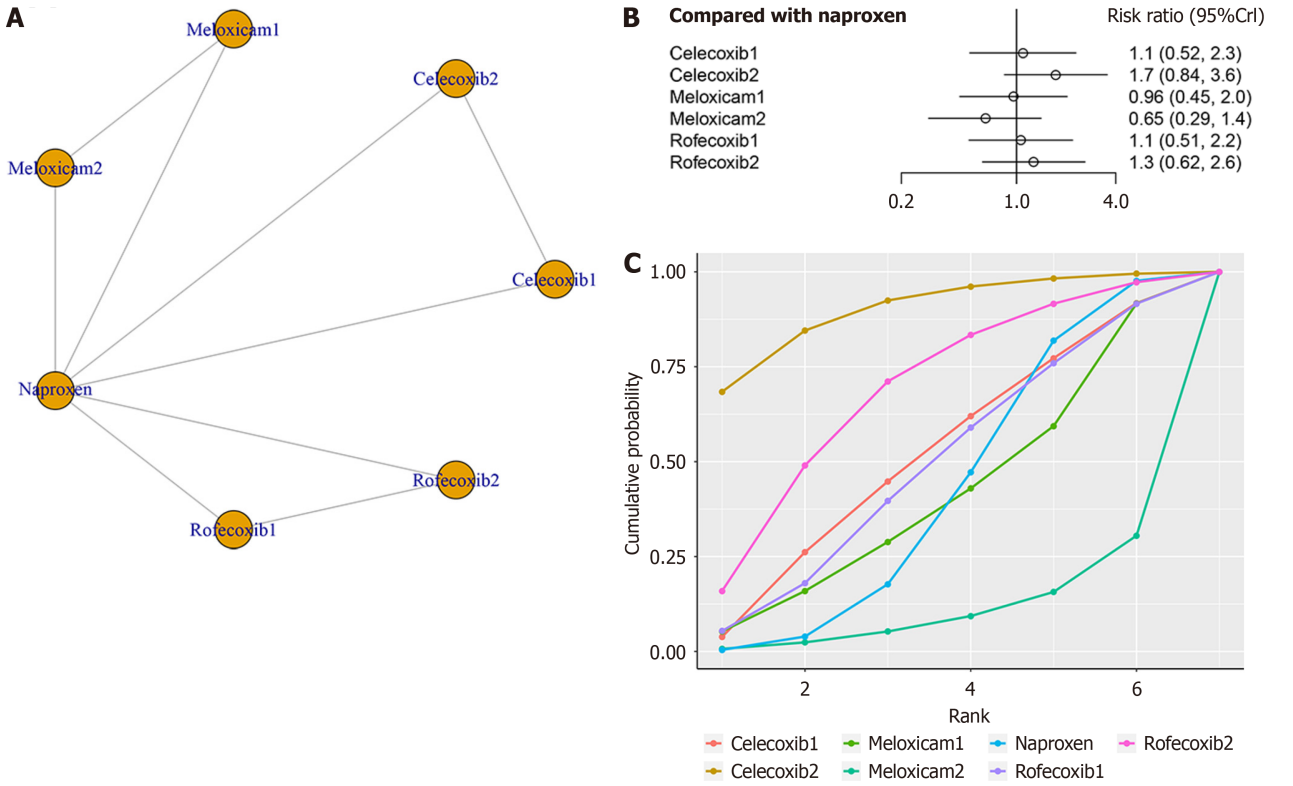

Figure 3 ACR Pedi 30 response. A: The network of evidence of all the trials for ACR Pedi 30 response; B: Forest plot comparing different treatment with naproxen for need for ACR Pedi 30 response; C: Surface under the cumulative ranking curve values of different treatment for need for ACR Pedi 30 response.

by piroxicam with a SUCRA of 60.5%. Rofecoxib at a dosage of 0.600 mg/kg per day ranked third with a SUCRA of 56.1%, while meloxicam at a dosage of 0.125 mg/kg per day and rofecoxib at a dosage of 0.3 mg/kg per day both achieved a SUCRA of 56.1%, placing them in fourth and fifth positions respectively (Figure 4C).

DISCUSSION

Main findings

The systematic review found no significant differences in efficacy or safety among NSAIDs. Celecoxib and rofecoxib were ranked highest in terms of efficacy, while piroxicam and rofecoxib were deemed safer compared to other NSAIDs.

Compared with other meta-analysis

Two relevant pair-wise meta-analyses on the topic have been published[25,26]. Our meta-analysis aligns with previous studies, but offers unique contributions. It is the first network meta-analysis comparing NSAIDs for JIA and includes a protocol for optimal treatment. Thus, our results from this network meta-analysis could help health-care professionals make clinical decisions. NSAIDs remain essential for relieving joint symptoms in JIA patients, despite the shift towards biologics-targeted therapy.

Study strengths and limitations

This review is the first to systematically analyze and compare NSAIDs in JIA patients, providing a more comprehensive assessment than direct comparisons. At the same time, SUCRA value from network meta-analysis realize the efficacy and safety of each drug global sorting. The study did not find a statistically significant difference in lowering ACR Pedi 30 response between the two drugs. Based on the SUCRA values derived from trials included in our network meta-analysis, celecoxib (6 mg/kg bid) seem to be the most efficacious drug in lowering ACR Pedi 30 response. This was similar to the finding of the previous study, where a no significant difference between NSAIDs for osteoarthritis[27].

Furthermore, NSAIDs are well tolerated and has a good safety record. The most common adverse reactions are gastrointestinal adverse effects, headache, fever rash and impairment of liver function. The main side effects of NSAIDs were gastrointestinal issues, with no serious adverse events reported. The study found no significant difference in side effects between the drugs. Placebo had the highest ranking in terms of safety, followed by piroxicam and rofecoxib. The rate of adverse event after administration NSAIDs varied from 0.7% to 70.5%[28-30]. Currently, there are fewer reports of changes in kidney function among children using NSAIDs, with the most common being reversible acute renal insufficiency. In the early stages of NSAID usage, other potential renal damages, such as nephrotic syndrome and interstitial nephritis, may also manifest.

Table 1 General characteristic of the included studies

Ref.	Sample size			Mean age			Subtype	t1	t2	t3	DMARDs (%)	Biologic agents (%)	CS (%)	Treatment duration (wk)
	t1	t2	t3	t1	t2	t3								
Ruperto *et al*[17], 2005	73	74	78	8.9	9.0	7.5	pJIA, oJIA	Meloxicam (0.125 qd)	Meloxicam (0.250 qd)	Naproxen (5.000 mg/kg)	24.7/28.4/37.2	NS	19.3/22.0/14.9	12
Foeldvari *et al*[18], 2009	77	82	83	10.4	10.2	10.4	pJIA, oJIA	Celecoxib (3.0 mg/kg bid)	Celecoxib (6.0 mg/kg bid)	Naproxen (7.5 mg/kg)	50.6/47.6/51.8	0/3.7/3.6	NS	12
García-Morteo *et al*[19], 1987	12	14		8.5	8.5		pJIA, oJIA	Piroxicam	Naproxen (12.5 mg/kg/d)		NS	NS	11.5	12
Giannini *et al*[20], 1990	45	47		7.7	7.7		pJIA, oJIA, sJIA	Inuprofen (30-40 mg/kg/d)	Aspirin (60-80 mg/kg/d)		0	0	NS	12
Haapasaari *et al*[21], 1983	15	15	15	NS	NS	NS	pJIA, oJIA, sJIA	Diclofenac (2-3 mg/kg/d)	Aspirin (50-100 mg/kg/d)	Placebo	NS	NS	NS	2
Kvien *et al*[22], 1984	40	40		11.4	9.0		pJIA, oJIA	Naproxen (10 mg/kg/d)	Aspirin (75 mg/kg/d)		0	0	0	24
Levinson *et al*[23], 1977	53	54		9.4	9.0		pJIA, oJIA, sJIA	Tolmetin (15 mg/kg/d)	Aspirin (55 mg/kg/d)		NS	0	0	12
Reiff *et al*[24], 2006	109	100	101	9.7	9.4	10.7	pJIA, oJIA	Rofecoxib (0.3 mg/kg qd)	Rofecoxib (0.6 mg/kg)	Naproxen (7.5 mg/kg/d)	53.2/51.0/45.5	NS	19.3/22.0/14.9	12

CS: Corticosteroid; pJIA: Polyarticular juvenile idiopathic arthritis; oJIA: Oligoarticular juvenile idiopathic arthritis; sJIA: Systemic juvenile idiopathic arthritis; DMARDs: Disease-modifying anti-rheumatic drugs; NS: Not significant.

Our meta-analysis has limitations, including the lack of randomized controlled trials and a small number of participants, necessitating larger clinical trials. Finally, we were unable to report other outcomes like blood loss, hospital stay relevant to this meta-analysis. The diversity in the study results may be due to differences in study quality, design, and patient characteristics. Incomplete data recording was also noted, which could introduce bias when combining the data. However, our study still offers some valuable insights for clinical use.

CONCLUSION

In summary, celecoxib (6 mg/kg bid) was found to be the most effective NSAID for treating JIA. Rofecoxib, piroxicam, and meloxicam may be safer options, but further research is needed to confirm these findings in larger trials with higher quality studies.

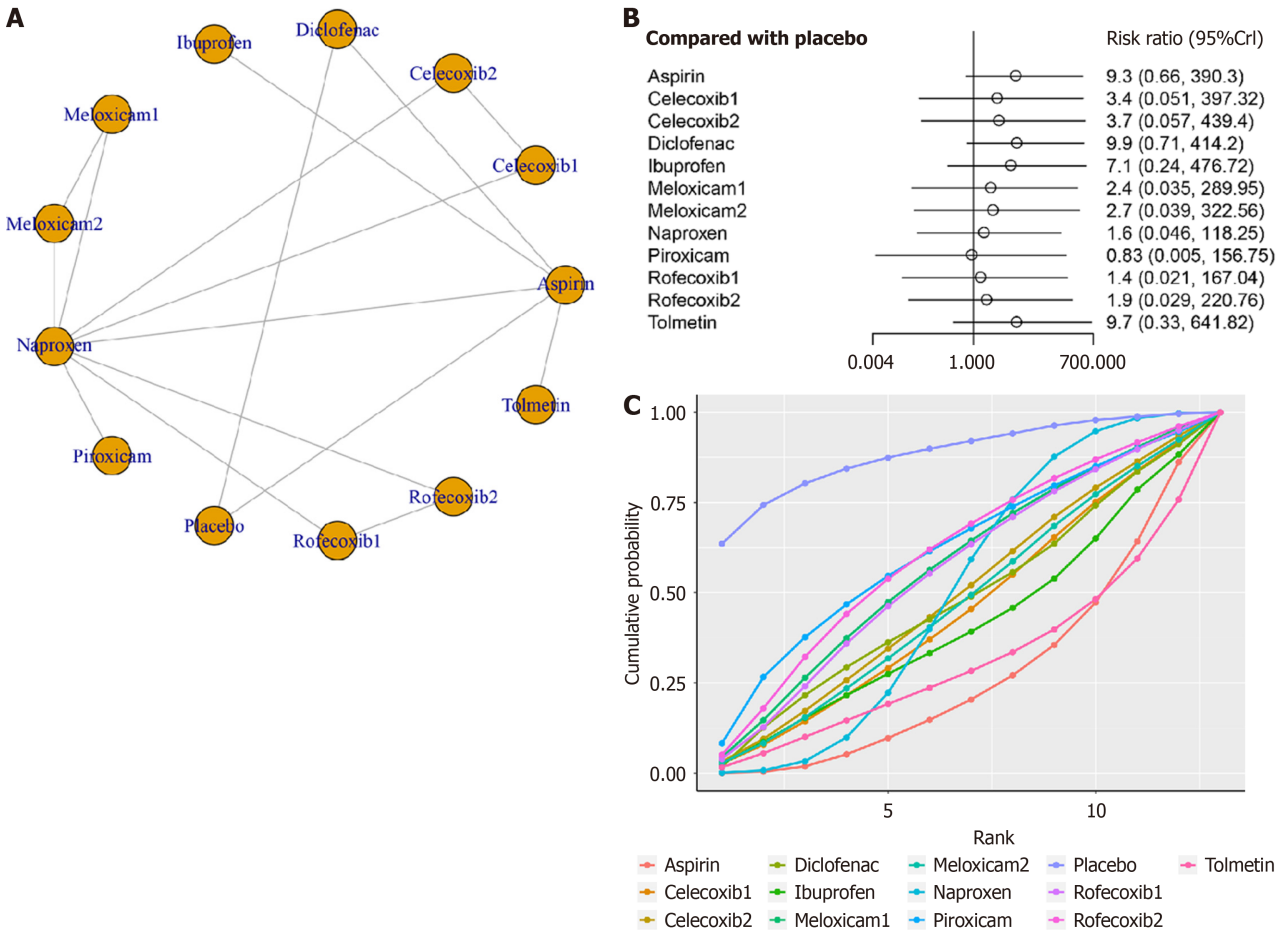

Figure 4 Adverse events. A: The network of evidence of all the trials for adverse events; B: Forest plot comparing different treatment with placebo for need for adverse events; C: Surface under the cumulative ranking curve values of different treatment for need for adverse events.

ARTICLE HIGHLIGHTS

Research background

Different non-steroidal anti-inflammatory drugs (NSAIDs) have been used for juvenile idiopathic arthritis (JIA), but the best method has not been determined.

Research motivation

To perform a systematic review and network meta-analysis to identify the most effective NSAID for JIA patients.

Research objectives

To perform a systematic review and network meta-analysis to determine the optimal instructions.

Research methods

We searched for randomized controlled trials (RCTs) from PubMed, EMBASE, Google Scholar, CNKI, and Wanfang without restriction for publication date or language at August, 2022. Any RCTs that comparing the effectiveness of NSAIDs with each other or placebo for JIA were included in this network meta-analysis. The surface under the cumulative ranking curve (SUCRA) analysis was used to rank the treatments. *P* value less than 0.05 was identified as statistically significant.

Research results

Eight RCTs (1127 patients) compared different instructions for NSAIDs, including meloxicam, Celecoxib, piroxicam, Naproxen, inuprofen, Aspirin, Tolmetin, Rofecoxib, and placebo. No significant differences were found in ACR Pedi 30 response between any two NSAIDs. Celecoxib (6 mg/kg bid) had the highest SUCRA ranking at 88.9%, followed by rofecoxib at 68.1% and Celecoxib (3 mg/kg bid) at 51.0%. There were no notable differences in adverse events between NSAIDs. Placebo had the highest ranking, followed by piroxicam, rofecoxib (0.600 mg/kg qd), meloxicam (0.125 mg/kg qd), and rofecoxib (0.300 mg/kg qd).

Research conclusions

In summary, celecoxib (6 mg/kg bid) was found to be the most effective NSAID for treating JIA.

Research perspectives

Rofecoxib, piroxicam, and meloxicam may be safer options, but further research is needed to confirm these findings in larger trials with higher quality studies.

FOOTNOTES

Author contributions: Zeng T and Ye JZ conceived and designed the study; Qin H searched and selected relevant studies; Xu QQ and Zeng T extracted and interpreted data; and all authors critically reviewed and approved the final manuscript.

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CASE REPORT

Human immunodeficiency virus-associated dementia complex with positive 14-3-3 protein in cerebrospinal fluid: A case report

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Abstract

BACKGROUND

Human immunodeficiency virus (HIV)-associated dementia (HAD) is a subcortical form of dementia characterized by memory deficits and psychomotor slowing. However, HAD often presents with symptoms similar to those of Creutzfeldt-Jakob disease (CJD), particularly in patients with acquired immune deficiency syndrome (AIDS).

CASE SUMMARY

We report the case of a 54-year-old male who exhibited cognitive dysfunction and secondary behavioral changes following HIV infection and suspected prion exposure. The patient was diagnosed with HIV during hospitalization and his cerebrospinal fluid tested positive for 14-3-3 proteins. His electroencephalogram showed a borderline-abnormal periodic triphasic wave pattern. Contrast-enhan-

ced magnetic resonance imaging revealed moderate encephalatrophy and demyelination. Initially, symptomatic treatment and administration of amantadine were pursued for presumed CJD, but the patient's condition continued to deteriorate. By contrast, the patient's condition improved following anti-HIV therapy. This individual is also the only patient with this prognosis to have survived over 4 years. Thus, the diagnosis was revised to HAD.

CONCLUSION
In the diagnostic process of rapidly progressive dementia, it is crucial to rule out as many potential causes as possible and to consider an autopsy to diminish diagnostic uncertainty. The 14-3-3 protein should not be regarded as the definitive marker for CJD. Comprehensive laboratory screening for infectious diseases is essential to enhance diagnostic precision, especially in AIDS patients with potential CJD. Ultimately, a trial of diagnostic treatment may be considered when additional testing is not feasible.

Key Words: HIV-associated dementia; Cognitive dysfunction; Creutzfeld-Jakob disease; Rapidly progressive dementia; Case report

Core Tip: In the present case report, we excluded an extremely rare patient with human immunodeficiency virus (HIV) and cerebrospinal fluid 14-3-3 protein-positive. Unlike the previously reported 7 cases, our patient had sustained improvement with anti-HIV therapy and was also the only patient in this entity to survive. Consequently, our report provided a completely different reference for managing rapidly progressive dementia in particular cases.

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INTRODUCTION

Human immunodeficiency virus (HIV)-associated dementia (HAD) is subcortical dementia characterized by memory deficits and psychomotor slowing, which occurs after the brain is infected with the HIV[1]. Cognitive dysfunction is a common symptom in patients with acquired immune deficiency syndrome (AIDS) and non-opportunistic infections caused by other viruses. Creutzfeldt-Jakob disease (CJD), also known as Cortico-striatum-myeloid degenerative disease, is characterized by mental disorders, dementia, Parkinson-like manifestations, ataxia, myoclonus, and muscle atrophy. CJD is a chronic and progressive disease caused by a rare infection with the prion protein[2]. Additionally, the cerebrospinal fluid (CSF) 14-3-3 protein is an essential marker for diagnosing CJD.

Here, a rare case is presented of a patient with AIDS and a positive 14-3-3 protein[2]. Although similar cases have been reported[3-7], this case provides new insights and is an important learning point for managing patients with rapidly progressive dementia due to its distinct diagnosis, treatment, and efficacy.

CASE PRESENTATION

Chief complaints

A 54-year-old male (Han ethnicity) presented to the neurology clinic of our institution with a 6 mo history of slurred speech that had worsened over the past 3 months.

History of present illness

The patient had suffered from memory disturbances for more than 1 year, with symptoms primarily including progressive memory loss and episodic anterograde amnesia. Additionally, he had developed an unstable gait. Initially diagnosed with brain atrophy, his symptoms had intensified after treatment at another facility, from which no case report was provided. One year prior, the patient had exhibited unclear speech, pain at the base of the tongue, and general malaise.

Additionally, dizziness, and left ear tinnitus were occasionally noted but he did not present physical signs of dysphagia or choking. The patient rejected therapy until 3 months ago when the above conditions were aggravated and the patient became unable to take care of himself. During the first consultation in our clinic on July 13, 2018, the patient demonstrated advanced manifestations of unsteady gait with one reported fall (details unavailable); severe cognitive dysfunction; hypopsychosis, which gradually became silent; and significantly decreased speech. Functionally, the patient

was unemployed and lost self-care ability.

History of past illness

The patient's past medical history was unremarkable.

Personal and family history

The patient had no history of exposure to toxic substances or family history of specific genetic diseases.

Physical examination

The patient was alert and entered the ward with a normal gait. He exhibited slurred speech, uncontrolled frowning, and pursing of the lips. Neurological deficits were noted, including impairments in memory, orientation, reasoning, and emotional expression. Meningeal signs were absent. The pharyngeal reflex was diminished, limb muscle tone was heightened, the Babinski sign was positive, and there was evident dysmetria on the finger-to-nose test (more pronounced on the left side) and the heel-to-knee test. Additionally, the patient tested positive for the Romberg sign, but there were no signs of tongue deviation or other pathological indicators.

Laboratory testing

Upon his admission, the family reported abnormality on the Mini-Mental State Examination and Montreal Cognitive Assessment tests during a previous assessment at another hospital, although the medical records from that visit were not available to us. Following his admission, an initial HIV antibody screening returned positive results, prompting us to perform a confirmatory HIV antibody test on the patient's blood (the final results were pending at that time). Laboratory tests indicated leukocytopenia with a white blood cell count of 3.2×10^9/L and lymphocytes at 0.96×10^9/L. Analysis of T cell subsets showed a T helper (TH)/T suppressor (TS) ratio of 0.1, with TH/inducer (cluster of differentiation 4 [CD4]) cells at 78/μL and TS/killer (CD8) cells at 1218/μL. In addition, the patient's CSF protein concentration was elevated at 0.73 g/L. The CSF cell count was normal, and extensive CSF testing for biochemical markers, routine cultures (including bacteria, fungi, *Mycobacterium tuberculosis*, and *Cryptococcus*), and antibodies associated with autoimmune and paraneoplastic encephalitis all returned negative results. Liver and kidney functions were normal, as were tests for anti-thyroid peroxidase antibody, anti-thyroglobulin antibody, ceruloplasmin, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, folic acid, and vitamin B12 levels. The CSF tested positive for the 14-3-3 protein, and genotyping confirmed 129 M/M and 219 E/E variants (Figure 1). An electroencephalogram (EEG) showed borderline abnormalities with periodic triphasic waves, which were not indicative of a typical disorder.

Imaging examination

Cranial computed tomography (CT) revealed cerebral atrophy and demyelination abnormalities in the white matter (Figure 2), given the multiple pinpoint hypodensities within the white matter exhibited in the bilateral basal ganglia with non-enhancement in all lesions and was initially diagnosed with lacunar infarction (Figure 2A). Medium encephalatrophy imaging accompanying white matter demyelination around the bilateral cerebral ventricle on T2-weighted images with pre-contrast c-magnetic resonance imaging (MRI) (Figure 2B). Meanwhile, 3–5 punctate hypodense lesions were identified in the bilateral basal ganglia on post-contrast MRI scans, with no evidence of enhancement (Figure 2C). Furthermore, the diffusion-weighted imaging (DWI) sequences on MRI did not display the characteristic "satin-like" high signal (Figure 2D).

FINAL DIAGNOSIS

HIV-associated dementia.

TREATMENT

The patient's condition worsened while awaiting a conclusive AIDS diagnosis. We treated the patient with symptomatic treatment and amantadine (Amantadine Hydrochloride Tablets, USP) for CJD, which was the initial diagnosis considered. Despite these measures, the patient's health continued to decline. During this period, confirmatory tests for HIV antibodies returned positive results.

The patient was subsequently transferred to a specialized local center for infectious disease control to receive targeted treatment. Over the course of 4 years, the anti-HIV regimen provided by the center consisted of efavirenz (600 mg daily), tenofovir disoproxil (300 mg daily), lamivudine (100 mg daily), and compound sulfamethoxazole tablets (480 mg twice a day). The patient experienced rapid amelioration of symptoms following the commencement of antiretroviral therapy during his hospital stay.

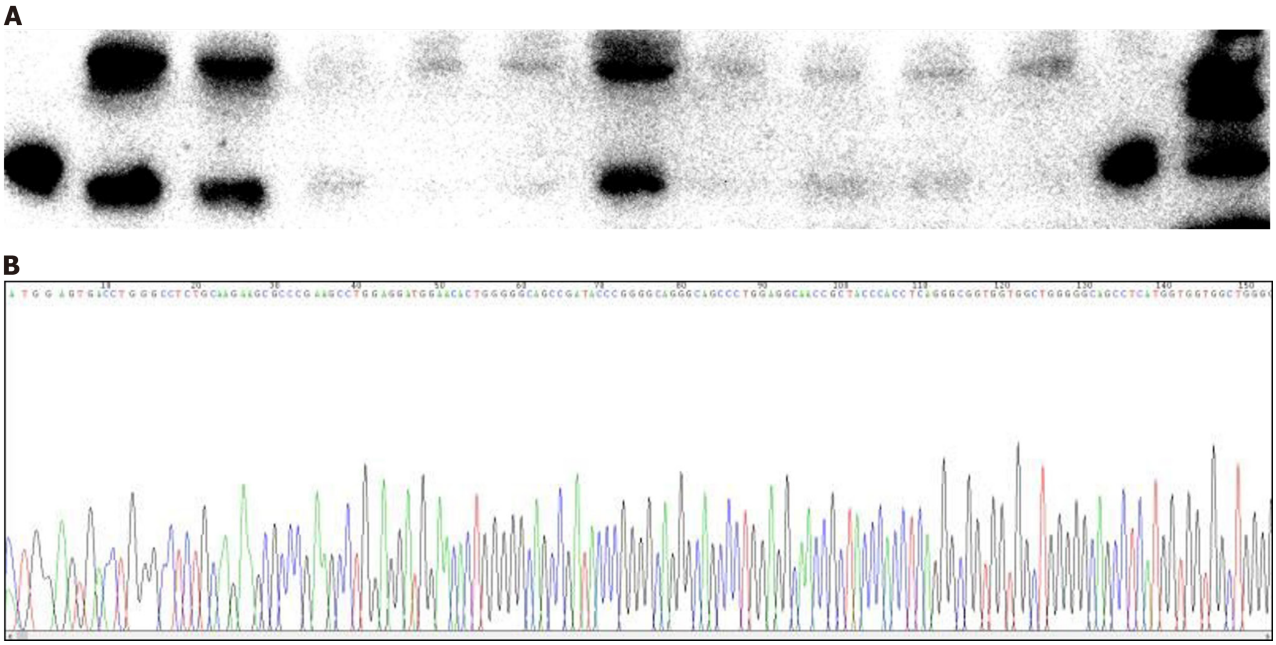

Figure 1 The 14–3–3 protein was found in cerebrospinal fluid, and 129 M/M and 219 E/E genotype was further verified. The 14-3-3 protein was positive, and the protein gene test showed M/M type.

OUTCOME AND FOLLOW-UP

Four years later, during a comprehensive outpatient follow-up assessment the patient exhibited clear consciousness and coherent speech; while recent memory and emotional expressiveness were mildly diminished, they were only marginally below the normal range; and the orientation and logical thinking functions were unremarkable. The limb muscle tension slightly increased, and the muscle strength was normal. The neurological signs and other symptoms were normal. The neuroradiological re-examination of the c-MRI (Figure 2E) revealed that the mild cerebral atrophy accompanying obvious demyelination in the white matter around the bilateral cerebral ventricle had improved than previous imaging. Additionally, several punctate hypointense lesions were spotted in the bilateral basal ganglia, exhibiting no enhancement (Figure 2F). The comparative scales and additional assessments conducted before and after treatment are summarized in Table 1.

DISCUSSION

CJD is a degenerative central nervous system disease caused by prion proteins, mainly manifested as advancing dementia, myoclonus, cerebellar ataxia, and akinetic mutism[8]. The average survival from onset to death is only a few months[3-7]. According to its etiology, CJD is mainly divided into four types: Sporadic (accounting for approximately 85%), hereditary/family (5%-15%), iatrogenic, and variant (0%-10%)[2]. Sporadic (sCJD) hinges on rapidly progressive cognitive decline, verified through neuropathological examination or supportive immunochemical or biochemical markers. For a tentative diagnosis of sCJD, clinical symptoms must be corroborated by additional tests, such as an EEG showing periodic sharp wave complexes, DWI exhibiting the ribbon sign, elevated 14-3-3 protein levels in the CSF, and a positive real-time quaking-induced conversion (RT-QuIC) test[9].

In their comprehensive review of the literature from 1995 to 2011, Muayqil *et al*[10] analyzed 38 studies involving 1849 suspected cases of sCJD with 14-3-3 protein assays conducted. Their findings indicated that the 14-3-3 protein is a valuable diagnostic marker for sCJD with a sensitivity of 92% and specificity of 80%. Furthermore, the detection of prions through RT-QuIC has demonstrated enhanced diagnostic accuracy, boasting a sensitivity of 96% and specificity reaching 100%[11,12].

MRI sensitivity is 80% in CJD[9,11,13,14], Some studies put the sensitivity as high as 92% to 98%[15-17]. At the same time, its specificity is 74%–98%[9,13].

Periodic sharp-wave complexes (PSWCs) at a frequency of 1 Hz are a hallmark EEG pattern for CJD, demonstrating a sensitivity of 64% and a specificity of 91% in diagnosis[18]. The molecular classification of sporadic CJD hinges on polymorphisms at codon 129 (M and V) and the PrP^Sc glycotype (1 and 2), leading to distinct molecular subtypes such as MM1 and MV1[9]. Crucially, a single somatic mutation in the prion protein (PRNP) gene, specifically at M129V and E2-19K, is implicated in CJD pathogenesis[19]. The frequency of this gene mutation varies across ethnicities, with the Han population showing a higher propensity for the 129 M/M genotype, which correlates with an earlier disease onset. Notably, typical PSWCs generally manifest in the later stages of the disease and are less common in MV2, VV2, and MM2 subtypes[9].

Table 1 Comparison of conditions between before and after treatment with anti-human immunodeficiency virus

Test items	Before	After
MoCA	16	25
ADL	25	70
Muscle strength	V	V
Hypertonia	(+)	Improvement
Pathological reflex	(-)	(-)
Neuroradiology	(+)	Improvement

ADL: Activities of daily living; MoCA: Montreal Cognitive Assessment.

In such cases, the diagnosis of probable CJD should meet the criteria for symptomatology, ancillary tests, and exclusion. Symptomatically: First: Rapidly progressive cognitive impairment. (1) Myoclonus; (2) Visual or cerebellar disturbance; (3) Pyramidal or extrapyramidal signs; and (4) Akinetic mutism. Ancillary criteria include: (1) Typical EEG; (2) Typical brain MRI; and (3) Positive CSF 14-3-3. Simultaneously, other possible diseases must also be excluded. Possible diagnostic criteria for CJD must meet the first and second symptoms (at least two), a positive criterion on a combined auxiliary test. Of course, other possible diseases must be ruled out to be diagnosed as probable CJD. A probable diagnosis of CJD is sufficient, in addition to meeting the criteria for the first and second symptoms (at least two), with a duration of less than 2 years. The PRNP test demonstrated M/M type, which increased the suspicion of CJD. Despite the strong consideration of HAD in this patient, the likelihood of probable CJD should still be taken into account during their hospital stay.

HAD is a common neurological complication after HIV infection and is mainly associated with memory impairment, motor coordination difficulties, cognitive deficits, difficulty performing complex tasks, and behavioral changes, including apathy and atypical reactions[1,20].

Most patients initially present with only short-term memory disorders in the early stages of AIDS; however, as the disease progresses, HIV-related chronic inflammation and immune activation may affect multiple brain regions. This can lead to dysfunctions in memory, cognition, language expression, and comprehension. With the widespread application of highly active antiretroviral therapy, the life expectancy of patients with HIV has significantly increased. Despite this, the incidence of moderate neurocognitive impairments remains high. A possible reason is that most anti-HIV drugs do not efficiently cross the blood-brain barrier to enter the central nervous system (CNS), resulting in insufficient drug concentrations in the CNS. Combined with the environmental factors within the CNS, HIV is prone to mutation, and the chronic accumulation of neurotoxicity leads to moderate neurocognitive dysfunction[20].

In this case, the diagnosis was considered infectious dementia combined with the medical history of the patient and auxiliary examination. The prime suspect was HIV, based on the following. Both HIV antibody screening test and HIV antibody confirmatory tests were positive. The apparent symptoms, including memory disorders, slowed mental processing, and behavioral disorders, were the primary symptoms of HAD, and there was a significant decrease in the patient's ability to perform daily activities. Regarding neuroradiology, CT and c-MRI revealed brain atrophy, demyelination, and white matter changes without enhancement. Consequently, the information above was consistent with HIV infection.

Four years after initiating anti-HIV treatment, we noted improved cognitive function and self-care abilities. However, memory remained worse than before; therefore, it is possible that prions may also play a role in the patient's rapid progressive dementia (RPD), Additionally, we speculate that HIV and CJD are not entirely coincidental as previously suggested[4,6].

Patients with co-infection of HIV and prions are very rare. To the best of our knowledge, only 5 cases have been diagnosed to date, and 3 others including our patient are highly suspected (Table 2). Unlike previously reported cases, our patient demonstrated sustained improvement following anti-HIV therapy and is the only known survivor. Our report provides a completely different reference for managing such cases.

The first patient was published by Babi *et al*[4] in 2016. The patient had well-controlled chronic AIDS. The elderly man passed away 3 months after a positive 14-3-3 protein test in the CSF, and a diagnosis of sCJD was confirmed histopathologically by autopsy. Subsequent reports indicate that all patients with similar conditions died within 2 months to 13 months[3,5-7,21]. In 3 of these cases, the diagnosis of sCJD was also confirmed by autopsy[3,7,21], and variant CJD in 1 case[21]. In the remaining 2 cases, autopsies were unavailable, but CJD was highly suspected[5,6]. The majority of these authors concur that there is no direct evidence linking HIV infection and prion diseases; however, further investigation is needed[4,6,7,21]. Abu-Rumeileh *et al*[3] concluded that RT-QuIC should be utilized as a specific screening tool for progressive dementia, while Dahy *et al*[5] contend that screening for sCJD should be mandatory in young patients with dementia who are living with HIV.

In our case, the patient's symptoms improved following anti-AIDS treatment, reducing the likelihood to be diagnosed with CJD (Table 1). Although 7 patients documented in previous reports shared similarities with the current case, presenting with AIDS and positive 14-3-3 protein, they were ultimately confirmed to have CJD *via* autopsy (Table 2).

In patients without routine HIV screening tests, RPD and positive 14-3-3 protein in CSF may easily lead to a misdiagnosis of CJD. Neurologists should exert every effort to determine the cause of RPD during diagnosis. Positive 14-3-3

Table 2 Difference between a previous case report about rapidly progressive dementia with human immunodeficiency virus and current report

Ref.	Pt	Sex	Age	Race/Region	Symptoms	Examination	Diagnosis	Management	Outcomes
Babi *et al*[4]	2016	Male	66	United States	Conceptual apraxia, apathy, memory impairment, and gait disturbance, ataxia with gait disturbance, chronic peripheral neuropathy	CSF: 14-3-3(+); T-Tau(+); RT-Qu IC(+); MRI: signal abnormalities in the bilateral caudate, putamen, and thalami, as well as gyriform cortical; EEG: (-); PRNP: N/A; Autopsy: CJD	Sporadic CJD	Palliative care	Passed away (3 months)
Eimer *et al*[7]	2018	Male	59	Caucasian	Mildly disoriented being insecure about the situation and location	CSF: 14-3-3(+); MRI: signal abnormalities in the caudate nuclei, frontal cortex, and parietal cortex bilaterally; EEG: periodic triphasic spike and wave complexes; PRNP: M129V; Autopsy: CJD	Sporadic CJD	Palliative care	Passed away (2 months)
Abu-Rumeileh *et al*[3]	2018	Male	62	Italy	Drowsy, with reduced verbal fluency, miotic reagent pupils, and a mask face. Axial and limb plastic hypertonia and dystonia of both hands	CSF: 14-3-3(+); MRI: cortical atrophy and multiple white matter lesions. EEG: pseudo-periodic slow spike discharges; PRNP: N/A; Autopsy: CJD	Sporadic CJD	Palliative care	Passed away (4 months)
De Carvalho Neto *et al*[6]	2019	Male	52	Caucasian	Progressive imbalance, motor and cognitive deterioration and hypersomnia	CSF: 14-3-3(+); MRI: cortical gyri_x005f form restriction on both hemispheres; EEG: triphasic PSWC; PRNP: N/A; Autopsy: N/A	Probable sporadic CJD	Palliative care	Passed away (greater than 2 months)
van de Ven *et al*[21]	2019	Male	63	Black Zimbabwean	Progressive difficulties with decision-making, obsessive compulsive disorder and visual hallucinations	CSF: 14-3-3 (weakly+); MRI: bilateral abnormal signal within the posterolateral thalami compatible with pulvinar sign; EEG: Diffuse excess of slow activity; PRNP: M129V; Autopsy: CJD	Variant CJD	Palliative care	Passed away (10 months)
Dahy *et al*[5]	2021	Male	52	Brazil	Global cerebellar syndrome, bilateral Babinski, 4-limb paratonia and release of face axial reflexes. The memory, attention and executive function deficits	CSF: 14-3-3(+); MRI: bilateral hyper intensity of images in caudal nuclei; EEG: (-); PRNP: M129V; Autopsy: N/A	Probable sporadic CJD	N/A	Passed away (13 months)
Dahy *et al*[5]	2021	Male	61	Brazil	Asthenia, lack of appetite, difficulty sleeping and occasional memory lapses, uncoordinated steps, visual delusions and bladder incontinence	CSF: 14-3-3(+); MRI: bilateral cortical ribboning in the cerebral cortex; PRNP: N/A; EEG: N/A; Autopsy: N/A	Probable sporadic CJD	N/A	Passed away (5 months)
Current report	2022	Male	54	Han/China	Progressive hypomnesis, paroxysmal anterograde amnesia, unsteady gait	CSF: 14-3-3 (weakly+); MRI: Bilateral abnormal signal within the posterolateral thalami compatible; EEG: Borderline abnormality of the periodic triphasic wave; PRNP: 129 M/M; Autopsy: N/A	Probable ADC	Anti-HIV	Improved and following-up

ADC: AIDS dementia complex; CJD: Creutzfeldt-Jakob disease; CSF: Cerebrospinal fluid; EEG: Electroencephalogram; HIV: Human immunodeficiency virus; N/A: Not available; PRNP: Prion protein gene; PSWC: Periodic sharp and slow wave complex; Pt: Publish time.

protein expression is of great value in CJD diagnosis, but it also has some limitations and presents interference. Re-evaluation of the CSF 14-3-3 protein or an RT-QuIC test should be considered to enhance diagnostic accuracy when additional examinations are not available for such rare cases.

CONCLUSION

HAD and CJD are easily misdiagnosed. In the etiological diagnosis of RPD, it is vital to exclude as many causes as possible and, if necessary, perform an autopsy to minimize diagnostic bias. The 14-3-3 protein should not be regarded as the only marker for CJD. Comprehensive laboratory screening for infection markers is essential to enhance diagnostic pre-

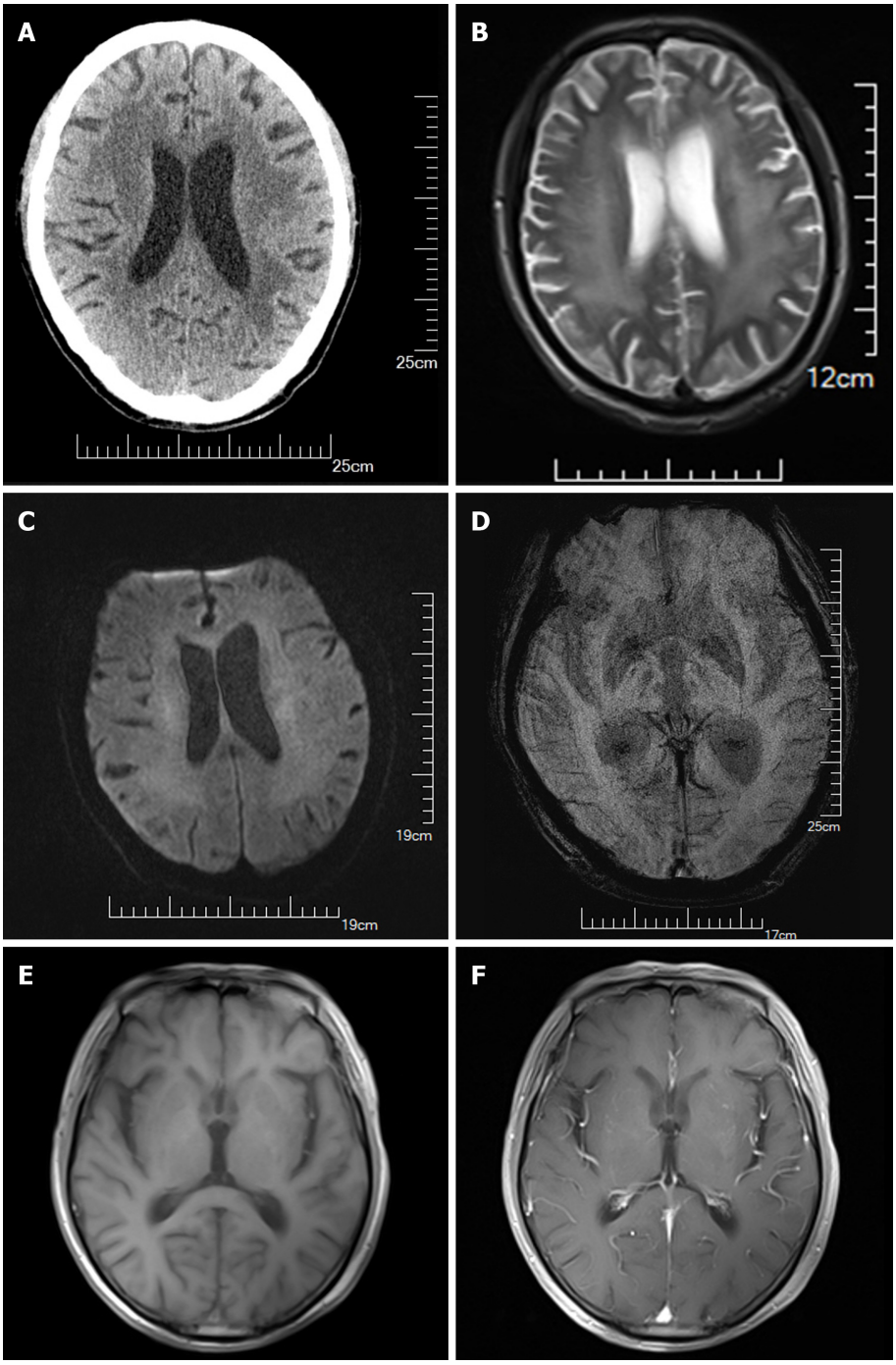

Figure 2 Pre- and post-treatment cranial imaging examinations of the patient. A-D: Neuroradiological presentation of this patient before treatment; The brain computed tomography reveals encephalatrophy and demyelination in the white matter (A); Axial T1-weighted brain magnetic resonance imaging (MRI) with pre-contrast shows mild encephalatrophy and demyelination around the bilateral cerebral ventricles (B); Axial T1-weighted brain MRI with post-contrast displays no enhancement of any lesions (C and D); E and F: Neuroradiological presentation of this patient after treatment; Axial T1-weighted brain MRI with pre-contrast illustrates slight encephalatrophy and the significantly improved demyelination in the white matter around the bilateral cerebral ventricles (E); Axial T1-weighted brain MRI with post-contrast demonstrates no enhancement in any of the lesions (F).

cision, particularly in cases where AIDS coexists with CJD. Furthermore, a trial of diagnostic treatment may be beneficial when additional diagnostic tests are not accessible.

FOOTNOTES

Co-first authors: Yun-Sen He and Xiao-Hong Qin.

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Author contributions: Min F contributed to investigation, writing – original draft, review and editing; Huang QJ, Zhang MJ, Bao MB, Tao Y, Wu B, and Dai HY contributed to writing – review and editing; He YS, Qin XH, Min F, Huang QJ, Zhang MJ, Bao MB, Tao Y, and Wu B contributed to data curation; He YS, Qin XH, Min F, and Wu B contributed to methodology; He YS, Qin XH, Huang QJ, Zhang MJ, Bao MB, Tao Y, and Dai HY contributed to the resources; Tao Y contributed to funding acquisition; Dai HY contributed to conceptualization. He YS and Qin XH contributed equally to writing the original draft and to formal analysis, and merit co-first authorship. Dai HY and Wu B have each made distinct contributions to this case report, encompassing clinical treatment and the writing of the case report, respectively, and merit co-corresponding authorship; Dai HY was involved in the clinical treatment and the extended follow-up of this case, as well as verifying the authenticity of clinical data and patient outpatient consultations; Wu B participated in the search for relevant literature, guided the writing of this case report, and was involved in editing, proofreading, and submitting the manuscript. All authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report.

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CASE REPORT

Multiorgan dysfunction syndrome due to high-dose cantharidin poisoning: A case report

Wan-Ling Xu, Wen-Jing Tang, Wei-Ying Yang, Li-Chao Sun, Ze-Qun Zhang, Wei Li, Xiu-Xian Zang

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Abstract

BACKGROUND

This report delves into the diagnostic and therapeutic journey undertaken by a patient with high-dose cantharidin poisoning and multiorgan dysfunction syndrome (MODS). Particular emphasis is placed on the comprehensive elucidation of the clinical manifestations of high-dose cantharidin poisoning, the intricate path to diagnosis, and the exploration of potential underlying mechanisms.

CASE SUMMARY

A patient taking 10 g of cantharidin powder orally subsequently developed MODS. The patient was treated with supportive care, fluid hydration and antibiotics, and hemoperfusion and hemofiltration therapy for 24 h and successfully recovered 8 d after hospital admission. Cantharidin poisoning can cause life-threatening MODS and is rare clinically. This case underscores the challenge in diagnosis and highlights the need for early clinical differentiation to facilitate accurate assessment and prompt intervention.

CONCLUSION

This article has reported and analyzed the clinical data, diagnosis, treatment, and prognosis of a case of high-dose cantharidin poisoning resulting in MODS and reviewed the relevant literature to improve the clinical understanding of this rare condition.

Key Words: Cantharidin; Poisoning; Multiorgan dysfunction syndrome; Clinical treatment and management; Case report

Core Tip: A patient taking 10 g of cantharidin powder orally subsequently developed multiorgan dysfunction syndrome (MODS). Cantharidin poisoning can cause life-threatening MODS and is rare clinically. Currently, there is no special antidote for cantharidin poisoning. Treatments mostly involve supportive care. Fluid resuscitation is essential. Hemoperfusion and hemofiltration can be applied, especially in patients with acute renal failure. Complications such as infectious pneumonia should be managed appropriately.

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INTRODUCTION

Cantharis is popularly known as the Spanish Fly. It can produce a colorless and odor-free substance, cantharidin, which is lipophilic and soluble in acetone, oil, ether, and chloroform but is insoluble in water[1]. Cantharidin is used to treat rabies, skin rash, infection, or even cancer[2-4]. It is also thought to act as an aphrodisiac[5]. However, cantharidin is also a potent toxin.

Most patients with cantharidin poisoning present clinically with irritative effects, particularly gastrointestinal discomfort, genitourinary bleeding, and renal dysfunction, but rarely with concurrent multiorgan system damage[6]. Here, we report on a patient with multiorgan dysfunction syndrome (MODS) after cantharidin ingestion. Her in-hospital clinical course was complicated by aspiration pneumonia. Finally, she was successfully treated with intravenous fluid resuscitation, antibiotics, hemoperfusion, and hemofiltration.

We discuss this case with the purpose of increasing awareness of the severity of cantharidin poisoning as well as potential treatment options.

CASE PRESENTATION

Chief complaints

A 36-year-old female presented to our hospital with a productive cough and a burning sensation in the esophagus.

History of present illness

12 h earlier, she ingested 10 g of cantharidin powder after an argument with her family.

History of past illness

She denied any past medical history.

Personal and family history

The patient denied any family history of genetic diseases or tumors.

Physical examination

Her vital signs were temperature 36.6 °C, respiration 27 breaths/min, heart rate 108 beats/min, and blood pressure 110/53 mmHg. The patient was awake and alert but in acute distress. Her mouth and throat were red and swollen. Lung auscultations revealed bilaterally diminished breath sounds and bibasilar crackles. On the first day after hospital admission, the patient developed hematuria, with a total of 600 mL of urine output over the next 24 h. On physical examination, her temperature was 38.1 °C, respirations 20 breaths/min, heart rate 135 beats/min, blood pressure 90/51 mmHg, and pulse oximetry 95% on 3 L/min oxygen provided through the nasal cannula. The patient looked lethargic; her mouth and throat showed erythema and ulcers, with yellow discharge. Cardiovascular and neurological examinations were unremarkable. On the third day following hospital admission, her vital signs improved to temperature 36.9 °C, respiration 20 breaths/min, heart rate 106 beats/min, blood pressure 119/84 mmHg, and pulse oximetry 99% on 6 L/min oxygen through the face mask. Moreover, she was awake and alert. There was improved erythema, swelling, and ulcers in the mouth and throat, with little exudate.

Laboratory examinations

Laboratory tests reported a blood white blood cell count of 12.2 × 10^9/L, neutrophil percentage of 88%, and platelet count of 145 × 10^9/L. Renal function test results were blood urea nitrogen (BUN) 3.8 mmol/L and creatinine 97.1 μmol/L. The

blood coagulation panel, hepatic function test, chemistry, and troponin results were with normal limits.

Urinalysis showed occult blood 3+, protein 1+, and a red blood cell count of 58.0 *per* high power field (HPF). Complete blood cell counts included a white blood cell (WBC) count of 30.9 × 10^9/L and a platelet count of 100 × 10^9/L.

Blood gas analysis showed pH 7.34, pCO_2 29 mmHg, pO_2 61 mmHg, lactate 5.8 mmol/L, base excess -8.8 mmol/L, and oxygen saturation 89%. Other blood test results were C-reactive protein 151.8 mg/L, aspartate aminotransferase 46.5 U/L, total protein 55.8 g/L, albumin 28.5 g/L, and procalcitonin 4.1 ng/mL. The coagulation panel was thrombin time 32.6 s, activated partial thromboplastin time 21 s, prothrombin time 13.9 s, international normalized ratio 1.2, and prothrombin activity 67%. Renal function tests showed an increased BUN of 10.4 mmol/L and creatinine 373.1 μmol/L.

On the third day following hospital admission, renal function also improved with BUN 4.6 mmol/L and creatinine 174.4 μmol/L. Blood tests reported a WBC count of 32.4 × 10^9 /L, platelet count of 52 × 10^9/L, B-type natriuretic peptide of 2590 pg/mL, myoglobin of 528.6 ng/mL, and troponin of 0.1 ng/mL. Blood gas analysis showed pH 7.48, pCO_2 33 mmHg, pO_2 123 mmHg, lactate 1.0 mmol/L, base excess 1.4 mmol/L, and oxygen saturation 99%. However, her hematuria persisted with the red blood cell count increasing to 493.2 *per* HPF in the urinalysis.

On the fourth day following hospital admission, her blood and urine cultures showed negative results, but a sputum culture grew *Klebsiella pneumoniae*.

On the sixth day, her repeat vital signs, blood cell counts, renal function, and lactate levels all returned to within normal limits.

Imaging examinations

An abdominal computed tomography (CT) scan showed bilateral perinephric fascia thickening with infiltrative changes, generalized fat stranding in the abdominal cavity and retroperitoneal space, a small amount of pelvic fluid, and mild subcutaneous exudation in the lower back. A chest CT scan reported bilateral pulmonary infiltrations, opacities in the right upper lobe and bilateral lower lobes, and small left pleural effusion. Echocardiography was normal.

FINAL DIAGNOSIS

Acute cantharidin poisoning, MODS.

TREATMENT

On admission the patient was treated with rehydration, antibiotics and 24 h hemoperfusion and hemofiltration. On the third day of admission, a 1-unit platelet transfusion and recombinant human thrombopoietin were administered due to thrombocytopenia. On the fourth day of admission, meropenem was given for *Klebsiella pneumoniae* infection based on the drug sensitivity result.

OUTCOME AND FOLLOW-UP

She was discharged from hospital on the eighth day after admission. Three months after the hospital discharge, the patient was followed up *via* telephone interview. She reported a complete recovery without any other treatment or clinical visit.

DISCUSSION

The Cantharis beetle is commonly known as the Spanish fly or blister beetle (Figure 1). Once stimulated, young Cantharis beetles produce cantharidin in the form of a milky white oral fluid, and adult Cantharis secrete cantharidin from their leg joints[7]. Depending on the beetle species, 0.2–0.7 mg of cantharidin can be exudated from each beetle. Cantharidin has the chemical formula 3, 6-epoxy-1, 2-dimethylcyclohexane-1, 2-dicarboxylic anhydride[8]. It can cause injury to various organ systems.

The immediate effect of cantharidin is its direct chemical irritation. After direct contact with the human body, cantharidin can stimulate mucosal membranes and cause skin blisters[9]. Once in the bloodstream, cantharidin can bind to albumin, which is then excreted from the renal glomeruli to induce glomerular damage and acute tubular necrosis[10]. In the cells, cantharidin can bind and inhibit protein phosphatase types 1 and 2A, which cause cell cycle arrest at the G2/M phase[11,12]. In addition, cantharidin can suppress protein expression in the endoplasmic reticulum stress pathway, leading to cell autophagy and apoptosis[13].

Clinically, patients with cantharidin poisoning can present with various symptoms[14,15]. The Direct chemical irritation can result in mouth and oropharynx burning, blisters, and ulceration, as well as abdominal discomfort, cramping, nausea, vomiting, and even hematemesis. Renal glomerular damage and tubular necrosis can present as acute renal failure and hematuria. In addition, patients can suffer cardiovascular (sinus bradycardia, junctional escape rhythm, and hypotension); neurological (seizure, dizziness, headache, altered mental status, and hallucinations); and hemato-

Figure 1 Cantharis beetles. The cantharis beetle is commonly known as the Spanish fly or blister beetle.

logical (thrombocytopenia, polycythemia) system complaints[16-18].

Postmortem autopsy examinations reveal that the gastrointestinal tract and kidneys are most frequently affected[15]. Gastrointestinal tract effects include esophageal mucosal congestion, swelling, ulceration, gastrointestinal mucosal congestion, hemorrhage, focal superficial erosion, and acute splenitis. Renal pelvis and ureter effects include diffuse petechial hemorrhage. Microscopically, Bowman's capsules and basement membranes become edematous, causing glomerular capillary constriction. The sloughed epithelial cells accumulated in the Bowman's capsules, together with the cellular debris and edematous basement membranes, to finally lead to luminal occlusion. Pulmonary involvement may include bronchopneumonia and subpleural hemorrhage[19]. Deaths from cantharidin poisoning due to cerebral edema, meningeal petechiae, and cerebral petechiae have also been reported[17,20].

Most patients start to show clinical symptoms within 2–4 h after cantharidin ingestion[14]. Our patient presented to hospital 12 h after intentional ingestion of 10 g of cantharidin powder. In the next 24 h, she started to develop symptoms of multiorgan damage, including hematuria, decreased urinary output, acute renal failure, thrombocytopenia, respiratory distress, hypotension, and lethargy.

Currently, there is no special antidote for cantharidin poisoning. Treatments mostly involve supportive care. Fluid resuscitation is essential. Antibiotics are administered following signs of pneumonia. Considering that hemodialysis cannot effectively remove cantharidin, since it binds to albumin in the circulation and has poor solubility in water, we attempted hemoperfusion and hemofiltration to remove cantharidin, inflammatory cytokines, and metabolic products, as well as to correct the electrolyte and acid-base disturbances. In addition, we initiated enteric nutrition to avoid the absorption of lipid-soluble cantharidin through the gastrointestinal tract.

CONCLUSION

Cantharidin poisoning can cause life-threatening MODS. Hence, prompt supportive care should be initiated. Hemoperfusion and hemofiltration can be applied, especially in patients with acute renal failure. Complications such as infectious pneumonia should be managed appropriately.

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FOOTNOTES

Co-first authors: Wan-Ling Xu and Wen-Jing Tang.

Author contributions: Xu WL and Tang WJ drafted the manuscript, contributed equally to this work and share the first authorship; Yang WY, Sun LC, Zhang ZQ, Li W participated in the patient management; Zang XX designed the study. All authors made a significant contribution to the work reported and approved the final version of this manuscript for publication.

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CASE REPORT

Overlapping infections of *Mycobacterium canariasense* and *Nocardia farcinica* in an immunocompetent patient: A case report

Hai-Yan Huang, Kun-Peng Bu, Jin-Wei Liu, Jing Wei

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Abstract

BACKGROUND

Infections by non-tuberculous mycobacteria (NTM) have become more common in recent years. *Mycobacterium canariasense* (*M. canariasense*) was first reported as an opportunistic pathogen in 2004, but there have been very few case reports since then. *Nocardia* is a genus of aerobic and Gram-positive bacilli, and these species are also opportunistic pathogens and in the Mycobacteriales order. Conventional methods for diagnosis of NTM are inefficient. Metagenomic next-generation sequencing (mNGS) can rapidly detect many pathogenic microorganisms, even rare species. Most NTM and *Nocardia* infections occur in immunocompromised patients with atypical clinical symptoms. There are no previous reports of infection by *M. canariasense* and *Nocardia farcinica* (*N. farcinica*), especially in immunocompetent patients. This case report describes an immunocompetent 52-year-old woman who had overlapping infections of *M. canariasense*, *N. farcinica*, and *Candida parapsilosis* (*C. parapsilosis*) based on mNGS.

CASE SUMMARY

A 52-year-old woman presented with a productive cough and chest pain for 2 wk, and recurrent episodes of moderate-grade fever for 1 wk. She received antibiotics for 1 wk at a local hospital, and experienced defervescence, but the productive cough and chest pain persisted. We collected samples of a lung lesion and alveolar lavage fluid for mNGS. The lung tissue was positive for *M. canariasense*, *N. farcinica*, and *C. parapsilosis*, and the alveolar lavage fluid was positive for *M. canariasense*. The diagnosis was pneumonia, and application of appropriate antibiotic therapy cured the patient.

CONCLUSION

Etiological diagnosis is critical for patients with infectious diseases. mNGS can

identify rare and novel pathogens, and does not require a priori knowledge.

Key Words: Overlapping infection; *Mycobacterium canariasense*; *Nocardia farcinica*; Metagenomic next-generation sequencing technology; Case report

Core Tip: Non-tuberculous mycobacteria (NTM) and *Nocardia* are opportunistic pathogens that can occur in immunocompromised patients who present with atypical clinical symptoms. *Mycobacterium canariasense* (*M. canariasense*) is a rare NTM species was first identified 20 years ago. We describe a patient with multiple lung nodules of unequal size with uneven internal density, and multiple small burrs at the edges of these lung lesions. The pathology results were inconsistent with malignancy, and metagenomic next-generation sequencing indicated overlapping infections of *M. canariasense*, *Nocardia farcinica*, and *Candida parapsilosis*. The anti-infective treatment was successful.

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INTRODUCTION

The non-tuberculous mycobacteria (NTM), also referred to as environmental mycobacteria, atypical mycobacteria, or anonymous mycobacteria, are ubiquitous species and potential causes of infectious diseases. Based on their growth characteristics determined from subculturing, the NTM are classified as rapidly growing mycobacteria (RGM; mature colonies in less than 7 d) or slowly growing mycobacteria (mature colonies in more than 7 d)[1]. Several RGM species have been identified as etiologic agents of bacteremia, especially in patients with low immunity, such as those with human immunodefciency virus (HIV) infections or malignant tumors. *Mycobacterium canariasense* (*M. canariasense*) is a rare species of RGM that is closely related to *M. diernhofer*[2,3], but has never been described separately in immunocompetent persons.

The genus *Nocardia* is also in the order *Mycobacteriales*, and includes at least 50 species that are aerobic Gram-positive bacilli which can invade the lungs, skin, or central nervous system, especially in immunocompromised persons. The symptoms of patients with *Nocardia* infections are often nonspecific, and include chronic cough, low-grade fever, fatigue and weight loss[4].

It can be difficult to diagnose infections by *Mycobacterium* and *Nocardia* from the conventional culture tests used in clinical practice, and delayed diagnosis may have serious adverse consequences. The rapid and efficient identification of the pathogen responsible for an infectious disease is a prerequisite for the effective treatment of these patients. Metagenomic next-generation sequencing (mNGS) does not require traditional microbial culture, and instead directly provides high-throughput sequencing of nucleic acids in clinical samples, which are then compared with a database. This method can rapidly and objectively detect many pathogenic microorganisms (including viruses, bacteria, fungi, and parasites) in clinical samples without the need for specific amplification, and is especially suitable for the diagnosis of acute and critical diseases and difficult infections. In this paper, we describe the use of mNGS to detect the rare co-occurrence of *M. canariasense* and *Nocardia farcinica* (*N. farcinica*) in an immunocompetent adult. This identification allowed administration of an effective treatment and led to patient cure.

CASE PRESENTATION

Chief complaints

A 52-year-old woman from Guangxi Zhuang Autonomous Region presented with productive cough and chest pain for 2 wk and recurrent episodes of moderate-grade fever for 1 wk.

History of present illness

The patient experienced a relapse of productive cough, persistent chest pain, and moderate-grade fever, but there were no chills, shivering, hemoptysis, or weight loss. She was diagnosed with pneumonia and treated with cefuroxime sodium (0.75 g/8 h) and levofloxacin (0.5 g/d) at a local hospital for 1 wk and experienced defervescence. However, the cough and chest pain persisted, and this affected her ability to work and study. The patient presented to another outpatient clinic for persistent cough and chest pain, with the possibility of malignancy unable to be excluded. Consequently, she presented at our hospital for further diagnosis and treatment.

History of past illness
This case had no specific history of past illness.

Personal and family history
The patient had a history of exposure to sheep feces 1 wk before symptom onset. She had no history of using steroids or other medications, no smoking, no tuberculosis, no malignant tumors or immunosuppressive diseases, and was unaware of any contact with persons with mycobacterial infections. She also reported no relevant family history.

Physical examination
No abnormalities were detected in the physical examination.

Laboratory examinations
Laboratory studies revealed leukocytosis, an elevated level of high-sensitivity C-reactive protein, and a high erythrocyte sedimentation rate (Table 1). After 5 d, multiple sets of blood and sputum cultures revealed no growth of bacteria or fungi. The culture of bacteria and fungi in bronchoalveolar lavage fluid (BALF), and acid-fast staining were also negative. An immunologic workup, which included HIV testing, was conducted based on suspicion of immunodeficiency, but all of the results were negative. Examination of autoantibodies and tumor markers also revealed no abnormalities. BALF and pulmonary nodular samples were subsequently sent for mNGS for the rapid identification of the causative pathogen(s). Sequencing results were compared with the sequences of bacteria in Gen Bank, and those with 100% agreement were accepted. Three days later, the pathogenic microbes in the nodular specimen were identified as *N. farcinica*, *M. canariasense*, and *Candida parapsilosis* (*C. parapsilosis*) (326 sequences), although the BALF only showed *M. canariasense* (Table 2).

Imaging examinations
A chest computed tomography (CT) scan showed multiple nodules of unequal size with uneven internal density, and multiple small burrs at the edges of the lesions, suggesting the infection of both lungs, but not excluding the possibility of a tumor (Figure 1A). A pulmonary nodular biopsy was performed, and the results indicated no malignancy, but there was evidence of non-necrotizing granulomatous inflammation (Figure 1B) and a yeast-like corpuscle in the alveolar cavity (Figure 1C). These findings are consistent with fungal infection.

FINAL DIAGNOSIS
The patient had a history of cough and chest pain, but anti-infection treatment at a local hospital led to no significant resolution of these symptoms. As an inpatient at our hospital, a CT examination showed nodular lesions of the lungs, but did not exclude malignant tumor. However, the results from puncture biopsy of the injured part of the lung and pathological examination were inconsistent with malignant tumor. Thus, combined with the mNGS results, the diagnosis in this patient was pneumonia due to overlapping infection by *M. canariasense*, *N. farcinica* and *C. parapsilosis*.

TREATMENT
Upon admission and during the evaluation period, empirical intravenous treatment consisted of broad-spectrum antibiotic agents [piperacillin sodium/sulbactam sodium (3 g/12 h) and voriconazole (250 mg/12 h)]. These antibiotics were maintained because they led to significant relief of the patient's clinical manifestations, including cough, sputum production, chest pain, and fever.

OUTCOME AND FOLLOW-UP
After 2-wk of antibiotic treatment, CT reexamination showed that the pulmonary nodules were significantly reduced (Figure 1D). The mNGS also detected a sequence of *C. parapsilosis*, and pathological staining revealed a yeast-like corpuscle in the alveolar cavity. Thus, oral voriconazole was administered at home for 3 months. An outpatient CT scan that was performed 1 month after the onset of antibiotic treatment showed that the pulmonary lesions had obviously disappeared (Figure 1E). On follow up, all the clinical symptoms had disappeared. There was also complete regression of the pulmonary consolidation after 3 months, based on a CT examination at a local hospital.

DISCUSSION
RGM are ubiquitous in the environment and commonly occur in water and soil. *M. canariasense* was described for the first time as the cause of a nosocomial infection in 17 patients during the period of January 2000 to September 2002 at a tertiary care hospital in the Canary Islands (Spain). This previous study reported that 15 of 17 patients had malignant diseases,

Table 1 Laboratory test results of blood samples collected at three times

Variable	Reference range	On admission	Antibiotic treatment	
			After 2-wk	After 1-month
Leukocytes (× 10^9/L)	3.69-9.16	10.34	5.23	7.12
Hemoglobins (g/L)	113-151	130	130	123
Platelets (× 10^9/L)	100-300	439	286	100
Neutrophiles (× 10^9/L)	2-7.7	8.49	3.17	5.2
Lymphocytes (× 10^9/L)	0.8-4	1.39	1.53	1.4
Monocytes (× 10^9/L)	0.12-0.8	0.4	0.39	0.38
ESR (mm/H)	0-20	92.8	41.4	26.5
hs-CRP (mg/L)	0-3	32.48	0.92	0.51

ESR: Erythrocyte sedimentation rate; hs-CRP: Highly sensitive C-reactive protein.

Table 2 Pathogenic microorganisms identified by metagenomic next-generation sequencing technology

Specimen	Genus			Species		
	Name	Sequence number	Relative abundance	Name	Sequence number	Cover degree
Nodular	*Nocardia*	1006	0.02%	*Nocardia farcinica*	393	18.87%
Nodular	*Mycobacterium*	9501	0.72%	*Mycobacterium canariasense*	3630	6.89%
Nodular	*Candida*	327	2.44%	*Candida parapsilosis*	326	0.23%
Bronchoalveolar lavage fluid	*Mycobacterium*	2260	42.34%	*Mycobacterium canariasense*	2020	1.75%

and all of them had central venous catheters (CVCs) at the time of diagnosis[3]. Subsequent reports identified this species from clinical specimens, including blood, and domestic water samples[5,6]. All previously reported cases presented with malignant diseases, especially hematologic malignancies, and most of them had a history of CVC. To our knowledge, there has been no previous report of infection by *M. canariasense* in an immunocompetent patient. A retrospective review showed *M. canariasense* was considered the etiologic agent of bacteremia in 12 of 17 cases[2]. de Miguel-Martinez *et al*[7] also reported *M. canariasense* in an oncohematological patient who had a long-term central device. In general, *M. canariasense* is a NTM that is only rarely pathogenic. In Türkiye, 90 NTM strains obtained from four different centers only identified 3 cases with *M. canariasense*[8]. A Japanese tertiary care center studied 5 patients with bloodstream infections due to RGM (4 with *M. mucogenicum* and 1 with *M. canariasense*) during a 5-month period. Another study showed that a blood isolate of *M. canariasense* from patient matched an isolate collected from a toilet in a 4-bed room[9]. Sun *et al*[10] found that the most commonly encountered NTM in China were *Mycobacterium intracellulare*, *Mycobacterium abscessus*, *Mycobacterium kansasii*, *Mycobacterium avium* and *Mycobacterium fortuitum*, and did not report *M. canariasense*. The symptoms of NTM infections are often nonspecific (chronic cough, low-grade fever, fatigue, and weight loss), but hemoptysis and chest pain are rare[4]. However, our patient had symptoms of chest pain, and we identified *M. canariasense* by mMGS of pulmonary nodules and BALF. We believe the chest pain may have been caused by the proximity of the lesion to the pleura.

Nocardia is ubiquitous in the environment and occurs worldwide as a saprophytic component in fresh water, saltwater, soil, dust, decaying vegetation, and decaying fecal deposits[11]. It is a Gram-positive bacillus, and has branching hyphae that are visible by microscopy. *Nocardia* infections are usually opportunistic and occur in immunocompromised hosts; infected immunocompetent patients usually develop localized cutaneous lesions. However, Beaman *et al*[12] found that 38 of 253 infected patients had none of predisposing factors contributing to opportunistic *Nocardia* infection. *N. farcinica* is related to *Nocardia asteroides*, accounts for 6.31% of *Nocardia* infections in China, mainly occurs in Gansu Province, and is considered the most virulent species of *Nocardia*[13]. Most *Nocardia* infections are pulmonary, and are usually attributed to inhalation of airborne spores or mycelial fragments from the environment. Dry, dusty, and windy conditions may facilitate the aerosolization and dispersal of fragmented *Nocardia* cells[14]. The conditions in China's Gansu Province are typically dry, dusty, and windy, consistent with the regional distribution of *Nocardia* in China. In contrast, our patient was from a wet, rainy area in southwestern China. However, our patient reported a history of exposure to sheep feces 1 wk before the onset of symptoms. This is consistent with previous reports which found *Nocardia* in decaying fecal deposits.

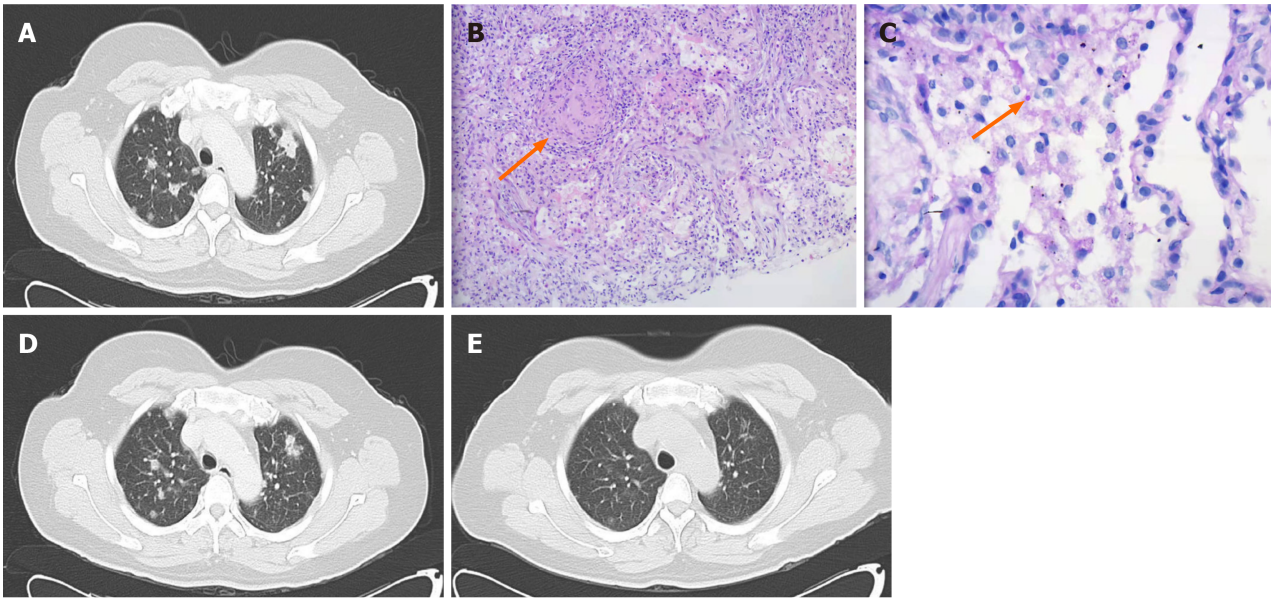

Figure 1 Changes of chest computed tomography findings and histopathology results. A: Scan at admission, revealing multiple nodules of unequal size with uneven internal density and multiple small burrs at the edges of the lesions; B: Pathology of pulmonary nodules, suggesting inflammation and granuloma formation; C: Pathology of pulmonary nodules, revealing a yeast-like corpuscle in the alveolar cavity; D: Scan after 2 wk of antibiotic treatment, showing the nodules were significantly reduced; E: Scan after 1 month of antibiotic treatment, showing the pulmonary lesions had obviously disappeared.

Identification of the etiology of an infectious disease plays an essential role in treatment of the patient, and laboratory culture is the traditional method for species identification. However, most patients with infections receive antibiotic treatment before sample collection, and this decreases the number of microbes and the sensitivity of culture. The mNGS technique is an unbiased method that can theoretically detect all kinds of pathogens, and is especially suitable for difficult and atypical infectious. Its main benefits are high sensitivity and rapid detection, and the results are less affected by prior use of antibiotics[15,16]. mNGS has a sensitivity rate that is approximately 15% higher than laboratory culture[16]. Less than 1% of the microorganisms identified by microscopy can be cultivated and characterized[17]. Our patient's negative culture results from blood, sputamentum, and BALF specimens may be due to the prior use of antibiotics. On the other hand, some research suggests that cultures of isolates from patients with suspected *Nocardia* infections should be held in the clinical microbiology laboratory for at least 2 wk for examination. We only monitored the culture results for 5 d, and this could be a reason for the negative results.

M. canariasense is a rare species of RGM that can be grown on Lowenstein-Jensen medium after about 4 d of culture at 37 °C, and is susceptible to most antibiotics[18]. Thus, antibiotic administration prior to specimen acquisition may be the main reason for our negative culture results. A limitation in China is that patients must pay for mNGS testing. Thus, for economic reason, our patient did not receive mGNS testing of blood and fecal samples.

Previous susceptibility testing of *M. canariasense* showed it was highly susceptible to amikacin, cefoxitin, ciprofloxacin, moxifloxacin, trimethoprim sulfamethoxazole, imipenem, doxycycline, minocycline, and linezolid, but only had intermediate susceptibility to clarithromycin[18]. The antibiotics previously used against *N. farcinica* include linezolid, amikacin, imipenem, and fluoroquinolone, and antimicrobial susceptibility testing demonstrated 100% susceptibility to linezolid[18-20]. A previous study described a patient who received sulphamethoxazole with linezolid and meropenem for nocardiosis, and subsequently recovered from clinical symptoms[18,21]. Other research in which all patients infected with *M. canariasense* received parenteral antibiotic therapy for 5-21 d showed that therapy guided by *in vitro* susceptibility testing did not improve patient outcome[2,18]. The 2020 NTM Guidelines proposed initiation of treatment (rather than watchful waiting) for patients who meet the diagnostic criteria for NTM pulmonary disease, but these guidelines do not mention the treatment of infections by *M. canariasense*[22]. Given the lack of high-quality evidence, the ideal treatment strategy for infection by this species remains unclear. Although we did not perform sensitivity testing, our anti-infective regimen showed high efficacy.

CONCLUSION

In summary, this is the first report of a patient who had overlapping infections of *M. canariasense* and *N. farcinica*. Infections by either of these pathogens are generally rare in immunocompetent hosts. The presence of lung nodules that are partially leafy and have burrs may lead to a misdiagnosis of lung cancer. We highlight the importance of identifying the causative pathogen by use of mNGS, a powerful tool for the detection of mixed infections, especially in patients with atypical symptoms who are infected by rare pathogens. The results from mNGS, combined with analysis of a patient underlying clinical status and laboratory indicators, provide clinicians with a more complete characterization of a disease and the causative pathogen. This case report also confirmed the potential role of *M. canariasense* and *N. farcinica* as

opportunistic pathogens. It is important to note that due to the rarity of overlapping infections by *M. canariasense* and another pathogen, empirical antibiotic treatment without mNGS results may not be adequate.

FOOTNOTES

Author contributions: Huang HY and Wei J substantial contribution to the conception and design of the work; Huang HY, Wei J, Bu KP and Liu JW contribution to the acquisition, analysis, interpretation of data for the work; Huang HY contribution to article writing and revising; Bu KP and Wei J agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approve the final manuscript and contributed to the conception and design of the work.

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CASE REPORT

Basilic vein variation encountered during surgery for arm vein port: A case report

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Abstract

BACKGROUND

Venous variations are uncommon and usually hard to identify, and basilic vein variation is particularly rare. Basilic vein variation usually presents without any clinical symptoms and is often regarded as a benign alteration. This case was a patient with congenital basilic vein variation encountered during surgery for an infusion port.

CASE SUMMARY

We documented and analyzed an uncommon anatomical variation in the basilic vein encountered during arm port insertion. This peculiarity has hitherto remained undescribed in the literature. We offer remedial strategies for addressing this anomaly in the future and precautionary measures to circumvent its occurrence. We conducted a comprehensive review of analogous cases in the literature, offering pertinent therapeutic recommendations and solutions, with the aim of enhancing the efficacy and safety of future arm port implantations.

CONCLUSION

Venous variation is rare and requires detailed intraoperative and postoperative examination to ensure accuracy, so as not to affect subsequent treatment.

Key Words: Totally implantable venous access ports; Arm ports; Venous variation; Postoperative breast cancer; Systematic review; Case report

Core Tip: Venous variation refers to structural malformations caused by abnormal development of venous vessels. At present, the etiology is still unknown. In the process of implanting the arm port for a tumor postoperative patient, we found and reported a case of successful treatment of basilic vein variation encountered during the operation, which can provide a reference for such cases in the future.

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INTRODUCTION

Breast cancer is one of the most common tumors afflicting women, and chemotherapy is an essential method of treatment. Totally implantable venous access ports are the preferred method for chemotherapy infusion in breast cancer patients[1]. In recent years, a large amount of clinical data has shown that compared with chest ports, arm ports are more suitable for breast tumors and patients with long-term infusion[2,3]. The main reasons are as follows. The infusion port catheter enters through peripheral blood vessels, which can avoid the risk of pneumothorax, hemothorax, and pinch-off syndrome caused by puncture catheterization[4]. Arm infusion ports have a short subcutaneous tunnel when implanted, and infusion and blood transfusion obstacles are significantly lower than chest infusion ports. Arm infusion ports are a better choice for breast cancer radiotherapy, chest radiography, neck and upper chest recurrence with pectoralis major muscle flap tumors, radiation dermatitis, or patients with impaired respiratory function[5].

The basilic vein is one of the superficial veins of the upper limb, on the ulnar side of the forearm. After receiving blood from the ulnar side, it gradually turns from the back of the hand to the flexor side of the forearm. It receives blood from the median cubital vein in the elbow fossa and travels up along the inside of the biceps brachii muscle. It penetrates through the fascia propria at about the midpoint of the upper arm and connects to the brachial vein or accompanies it to the axillary vein. The basilic vein has characteristics such as a straight course, few valves, gradually thickening lumen, and easy external touch[6]. However, arm venous access still poses some specific challenges, because the arm venous route has a longer implantation distance. When the guidewire is inserted into the venous circulation if the basilic vein has variant branches[7], it can cause the guidewire to jam during insertion, and if it is forcibly withdrawn at this time and the guidewire tip is of poor quality, it may cause the head end of the guidewire to be embedded, which often has no obvious symptoms and requires postoperative X-ray imaging for detection. All the surgical procedures described in this case report were performed in accordance with the relevant literature and guidelines. The purpose of this report is to describe a rare case and review the relevant literature.

CASE PRESENTATION

Chief complaints

After the right breast cancer surgery, the arm port is required to be placed for further chemotherapy.

History of present illness

The patient had previously undergone surgery to confirm right-sided breast cancer (T2N0M0), and postoperative pathology indicated a tumor size of 2.5 × 2.2 × 1.3 cm, and right axillary sentinel lymph node without cancer metastasis (0/6); immunohistochemistry indicated estrogen receptor (-); progesterone receptor (-); human epidermal growth factor receptor Her-2 (0); and Ki-67 (5%+). The patient recovered well after surgery and was admitted on July 12, 2022, for left arm infusion port implantation surgery. The puncture process encountered an obstruction, but later everything went smoothly, with an intracorporeal catheter length of 41 cm. The patient did not complain of any obvious discomfort after surgery.

History of past illness

The patient had undergone a modified radical mastectomy with sentinel lymph node biopsy for right-sided breast cancer, and had no other significant past medical history.

Personal and family history

The patient had no previous history of venous variation or personal and family history of cancer, no smoking or alcohol consumption, no special medication or exposure to toxic substances.

Physical examination

The patient had no right breast, and a surgical scar about 15 cm long was seen on the right chest wall; no obvious mass or abnormality was seen on the left breast.

Laboratory examinations

The laboratory tests for blood, urine, stool, coagulation function, infectious diseases, *etc.* were all normal.

Imaging examinations

Postoperative X-ray showed that the end of the patient's peripherally inserted central catheter was located on the right side of the T7 intervertebral foramen (Figure 1A), and an abnormal guidewire about 1.8 cm long was seen on the upper part of the left elbow (Figure 1B).

FINAL DIAGNOSIS

After the operation, imaging showed a branch of the left upper limb basilic vein, suggesting a congenital venous variation (Figure 1B).

TREATMENT

The patient underwent emergency removal of a foreign body from the left upper arm. Before the operation, a C-arm machine was used to locate the foreign body in the left upper arm and a transverse surgical incision was made. The foreign body was freed to the location position, and a guidewire about 1.8 cm long was seen during exploration (Figure 2). The guidewire was completely removed, which was confirmed by radiography.

OUTCOME AND FOLLOW-UP

The patient was considered to have basilic vein variation, and the guidewire entered the variant branch of the basilic vein during arm port insertion. Fortunately, postoperative X-ray detected it in time and handled it properly. During subsequent adjuvant chemotherapy, the arm port continued to function normally, all indicators were normal during regular examinations, and the patient did not have any obvious discomfort. After completing eight cycles of chemotherapy, the patient successfully underwent surgery under local anesthesia on February 8, 2023, and the arm port was removed (Figure 3A and B). She did not feel any discomfort during the subsequent follow-up period.

DISCUSSION

Breast cancer has become the most common malignant tumor among women worldwide, and its incidence is increasing annually. The current treatment mainly includes multidisciplinary methods such as surgery, radiotherapy, neoadjuvant therapy, and adjuvant therapy[8]. For patients who need chemotherapy, traditional totally implantable vascular access devices are installed in the chest wall, through subclavian or internal jugular vein implantation. However, as an alternative to chest ports, arm ports have become more widespread, and they have advantages such as reducing the incidence of related complications and improving patient satisfaction compared with traditional chest ports. Especially for female breast cancer patients, the breast is the most important secondary sexual characteristic and aesthetic organ. Patients with arm ports have no extra scars on their chest, and during the placement and subsequent chemotherapy process, patients do not need to expose their chest to easily install or access the port, which has cosmetic and psychological benefits[5]. Moreover, arm ports are easy to use, do not require frequent maintenance, and can significantly improve quality of life[9].

Our patient chose an arm port after consideration. Before arm port implantation, we signed relevant informed consent forms with the patient, understood the patient's past history and drug allergy history, asked the patient to undergo blood routine and electrocardiographic examination, measured biochemical indicators and coagulation function, *etc.*, and checked the skin condition of the implantation site. Finally, according to the location of breast cancer, we chose the basilic vein on the left (healthy) side as the infusion port catheter entry route. The patient was placed on the operating table in a supine position, and the target arm was kept perpendicular to the body[10]. We checked the patient's vascular condition under ultrasound guidance, and the basilic vein looked normal. We marked the pre-puncture point and pouch site and disinfected the entire arm three times. A sterile towel was placed under the punctured side limb, and the operator wore sterile clothing and gloves. The Surgical drape was spread around the puncture point to maximize the sterile area. After preparation, the vascular ultrasound probe was coated with a coupling agent and wrapped in a sterile ultrasound protective sleeve. The upper arm was tied with a tourniquet, and the coupling agent was applied again. The vascular condition was re-examined. According to the depth of the vessel, as shown under ultrasound guidance, local anesthesia (lidocaine 1%) was performed at the desired puncture point. A guidewire needle holder was selected, and blood return was seen after the puncture. During guidewire insertion, the head end encountered resistance, and when it was pulled back, it became stuck and could not be pulled back smoothly. We adjusted the guidewire needle holder position and pulled back the guidewire again. The guidewire came out of the blood vessel under strong resistance. At that time, The head end of the guidewire got stuck in the variant branch of the basilic vein. However, due to the strong stretchability of

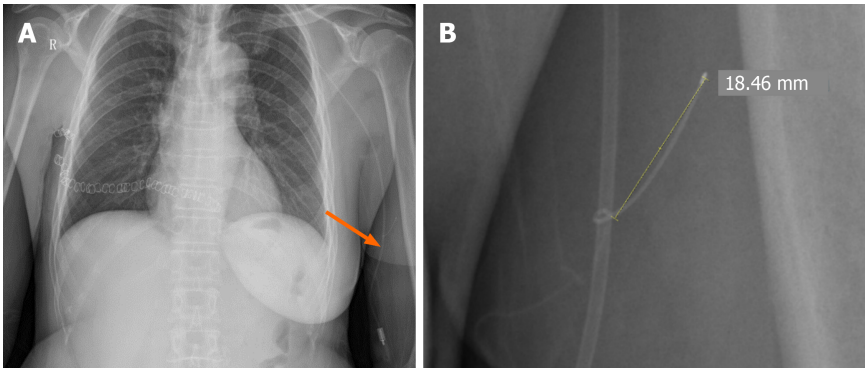

Figure 1 X-ray imaging results. A: The postoperative X-ray images indicated that the peripherally inserted central catheter was positioned correctly at the T7 cone space level on the right side; B: The postoperative X-ray images revealed that an unusual guide wire measuring around 1.8 cm in length was detectable above the left elbow.

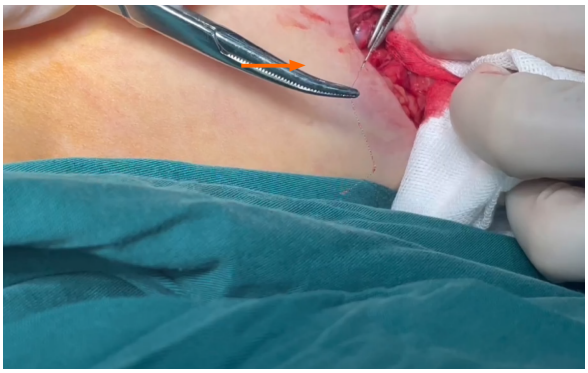

Figure 2 Abnormal guidewire about 1.8 cm long after removal.

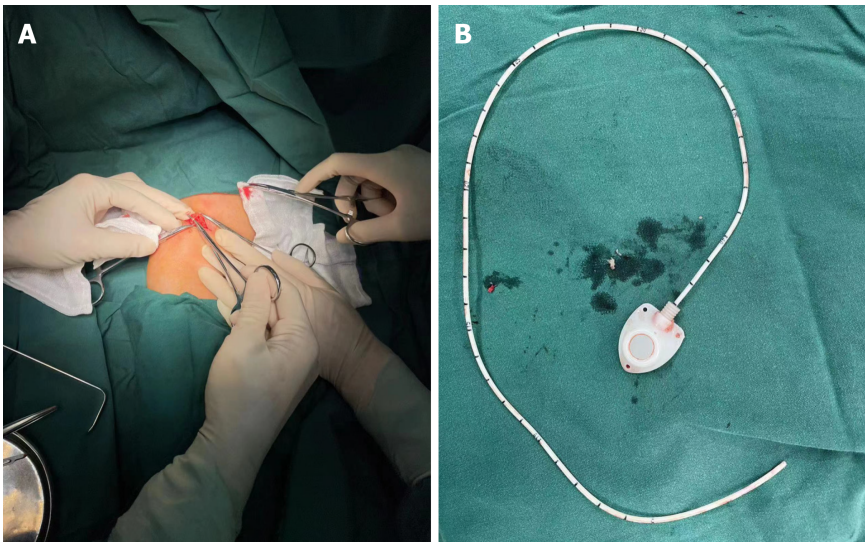

Figure 3 The patient underwent successful surgery under local anesthesia, and the arm infusion port was removed. A: Process of extracting the arm port; B: Its appearance post-extraction.

the head end, when it was pulled out, the length of the guidewire appeared to be the same as its original length. We inserted the guidewire along the needle holder again, and this time the guidewire was inserted smoothly without any resistance. All subsequent operation procedures were in accordance with relevant literature and guidelines.

We routinely performed chest X-rays after surgery, to confirm the position of the catheter. The ideal position of the catheter should be at the T5-7 level[5]. The catheter was located at the right side of the T7 intervertebral foramen level, which met the placement requirements. According to the chest X-ray, we could see an abnormal guidewire about 1.8 cm long on the upper part of the left elbow (Figure 1). We immediately consulted a hand microsurgeon, who performed

Figure 4 Guidewire removed, about 1.8 cm long, with a bent head end.

emergency removal of the foreign body from the left upper arm. The hand microsurgery procedure involved making a transverse incision of approximately 7 cm in length, according to the preoperative positioning of the C-arm machine. The incision was made through the skin and subcutaneous tissue, and the flap was then freed up to the C-arm machine positioning position. During the procedure, an abnormal guidewire measuring approximately 1.8 cm was discovered and explored (Figure 2). After removing the guidewire (Figure 4), another radiograph was taken to confirm its complete removal, and hemostasis was performed on the wound surface, and the subcutaneous tissue and skin were sutured layer by layer. During the operation, no adjustment was made that affected the infusion catheter position and the patient also underwent adjuvant chemotherapy as planned. The chemotherapy side effects were not significantly different from those in other arm port patients. The possible reason was that the basilic vein variation occurred at a place that did not affect the normal infusion catheter position, and there was no obvious impact on the absorption, distribution, metabolism, and excretion of drugs in the subsequent period. No common intraoperative complications such as air embolism or arterial injury, occurred during surgery. There was no skin soft tissue damage, catheter-related infection, catheter-related thrombosis, or other common postoperative complications. During the subsequent adjuvant chemotherapy period, the arm port continued to function normally, all indicators were normal during regular examinations, and the patient did not have any obvious discomfort. After completing eight cycles of chemotherapy, the patient successfully underwent arm port removal under local anesthesia on February 8, 2023. All indicators were normal during regular re-examination. Subsequent intermittent follow-ups showed that health status and quality of life improved significantly.

We conducted a literature search on PubMed, Web of Science and China National Knowledge Infrastructure (CNKI), and retrieved all studies published before July 2022. In many clinical case reports, the venous variations encountered had an impact on diagnosis and treatment, and the problems encountered during the treatment process, such as the impact of central venous anatomical variation on venous access, *etc*[11]. However, regarding basilic vein a variation, only one case was found in CNKI. The patient was an adult male, and variation of the left basilic vein was found during dissection. The report and discovery of this case had some significance for our operation[12].

CONCLUSION

Many studies have shown that an arm port is a feasible long-term chemotherapy option, with a high level of patient satisfaction and minimal negative impact on quality of life. These findings are important for the treatment of breast cancer, because long-term chemotherapy may have a negative impact on quality of life. The use of arm catheters can reduce pain and discomfort for patients, and improve patient satisfaction, thereby improving treatment outcomes[13]. This case report has some implications for breast cancer patients who are undergoing arm port implantation. Before clinical arm port implantation, a vascular ultrasound must be performed to confirm whether there is any abnormality in the basilic vein, whether the blood vessels have sufficient volume and whether they meet the relevant implantation conditions. Ensuring a safe vascular passage is crucial for whether the port can be successfully implanted. At the same time, it is recommended that a chest X-ray should also be taken after surgery to confirm whether the head end of the catheter is at the T5–T7 level and whether there is any residual abnormal guidewire caused by basilic vein variation at the arm port site. This rare case report aims to reduce the occurrence of postoperative complications in arm port patients, improve the safety of subsequent adjuvant chemotherapy, and achieve a safer, lower-risk, and less complicated chemotherapy process.

FOOTNOTES

Co-first authors: Cheng-Da Hu and Rui Lv.

Author contributions: Hu CD and Lv R contributed equally to this work; Hu CD and Lv R contributed to manuscript writing editing, and

data collection; Zhang MH and Mao YW validated the images and case data; Zeng HD conducted the follow-up; Zhao YX contributed to conceptualization and supervision. All authors have read and approved the final manuscript.

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CASE REPORT

Early embryonic failure caused by a novel mutation in the *TUBB8* gene: A case report

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Abstract

BACKGROUND

This study aimed to explore the relationship between gene mutations and early embryonic development arrest and to provide more possibilities for the diagnosis and treatment of repeated implantation failure.

CASE SUMMARY

Here, we collected and described the clinical data of a patient with early embryonic development stagnation after repeated *in vitro* fertilization attempts for primary infertility at the Department Reproductive Center of Zaozhuang Maternal and Child Healthcare Hospital. We also detected the whole-exon gene of the patient's spouse and parents, and conducted bioinformatics analysis to determine the pathogenesis of the gene.

CONCLUSION

A novel mutant of the *TUBB8* gene [c.602G>T(p.C201F)] was identified, and this mutant provided new data on the genotype-phenotype relationships of related diseases.

Key Words: Genes; Mutation; Embryonic development; Fertilization *in vitro*; Intracytoplasmic sperm injection; Case report

Core Tip: A clinical case (28 years old) in which a new mutation in the *TUBB8* gene caused repeated arrest of early embryonic development to expand our understanding of the genetic basis of female infertility and lay the groundwork for future genetic counseling.

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INTRODUCTION

With the development of assisted reproductive technology, an increasing number of couples are conceiving through *in vitro* fertilization (IVF) embryo transfer. However, there are still some couples who are unable to conceive successfully[1]. The normal progression of meiosis and mitosis is one of the basic conditions for oocyte maturation and early embryo development. In the process of cell division, homologous chromosomes are symmetrically arranged through the microtubule organizing center, and the chromosomes divide to form the next stage of cells under the traction of bipolar spindles. Spindle assembly and chromosome separation are inseparable from the basic role of tubulin, and *TUBB8* is a special subtype of tubulin that plays an important role in human oocytes and early embryonic cells[2,3]. Previous studies have shown that mutation of the *TUBB8* gene leads to disorders of oocyte maturation, fertilization and early embryo development stagnation[4,5]. This paper reports a clinical case in which a novel mutation in the *TUBB8* gene led to repeated early embryonic development arrest. This finding expands our understanding of the genetic basis of female infertility and lays the foundation for future genetic counseling.

CASE PRESENTATION

Chief complaints

A 2-year history of primary infertility after marriage.

History of present illness

The patient was a 28-year-old female with a 2-year history of primary infertility after marriage. Her menstrual history was as follows: menarche at age 14, a cycle of 7/-30 days, normal volume and color of menstrual blood, and no dysmenorrhea. The male partner was 26 years old. Results of the routine semen analysis were normal (sperm concentration 34.7 × 10^6; percentage of progressive motility 64.6%; sperm DNA fragmentation index: 14.38%) according to World Health Organization 5th Edition criteria.

History of past illness

In 2019, the patient underwent hysteroscopy and hysteroscopic endometrial polypectomy at another hospital due to abnormal echoes in the uterine cavity, and pathological examination of the uterine specimen indicated the presence of endometrial polyps.

Personal and family history

The patient had no pertinent personal or family history. Both partners had no bad living habits or hobbies, and were not engaged in work related to reproductive toxicity.

Physical examination

The patient had a negative vulva, a normal uterus, and a negative bilateral adnexal area. Her body mass index was 21.23 kg/m^2.

Laboratory examinations

The concentration of anti-Mullerian hormone (AMH) was 2.634 ng/mL (1 ng/mL = 7.14 pmol/L). There were no obvious abnormalities in basic hormone levels or thyroid function. The patient's karyotype was 46, XX, and the male partner's karyotype was 46, XY.

Imaging examinations

Hysterosalpingography revealed that the uterine cavity was normal, bilateral fallopian tubes were developed, and the spread of the pelvic contrast agent was diffuse and limited.

FINAL DIAGNOSIS

Primary infertility.

TREATMENT

In March 2021 and May 2021, the patient underwent two cycles of artificial insemination in the Department Reproductive Center. The first cycle was a natural cycle, and the second cycle was an ovulation induction cycle. Both cycles exhibited the development of dominant follicles and did not result in pregnancy.

From August 2021 to November 2022, 5 IVF cycles of assisted pregnancy treatment were performed in the Department Reproductive Center (Table 1).

Cycle 1: In August 2021, the short-acting long protocol in the luteal phase (GnRh-a long protocol) was used to promote ovulation. After ovulation during the mid-menstrual period, 0.1 mg of triptorelin acetate (Triptorelin®, 0.1 mg/piece, Ferring GmbH, Germany) was injected subcutaneously for 7 d, followed by 0.05 mg qd for 7 d. After 14 d, ultrasound and sex hormone examinations revealed that the ovarian follicles were in the basic state, gonadotropin (Gn) was activated, and recombinant follicle stimulating hormone was injected with recombinant follitropin β (Pouliquen®, 600 IU/piece, Merck & Co. Inc, United States) at 200 IU qd and Gn for 9 d. Three follicles were ≥ 18 mm, and nine follicles were ≥ 14 mm on the day of hCG trigger (trigger day). An intramuscular injection of 6000 IU of human chorionic gonadotropin (HCG) (2000 IU/tube, Lizhu Group, China) was administered, and 35.5 h later, oocyte retrieval surgery was performed. On the day of oocyte retrieval (D0), 12 oocytes were obtained. The male partner's semen volume on the trigger day and the sperm concentration after treatment showed no significant abnormalities, and routine IVF was performed. After 4-6 h of fertilization, the maturation of oocytes was observed after removing the extracellular granular cells: two oocytes were in the GV stage, two in the MI stage, and eight in the MII stage. However, due to the absence of second polar bodies in the perioocyte space of all MII oocytes, rescue intracytoplasmic spermatozoid injection (R-ICSI) fertilization was performed due to fertilization disorder. Five zygotes with two pronuclei (2PN) were observed on the first day (D1) after oocyte collection, and five zygotes were cleaved on the second day (D2). On the 3rd day (D3), one 8CII embryo was observed and frozen. Three 6CIII embryos and one 5CII embryo continued to incubate without forming a blastocyst. In December 2021, thawing cycle transplantation was performed, and artificial cycle preparation of the endometrium was carried out. On the second day of menstruation, 2 mg/d oral estradiol valerate (Bujiale® 1 mg/tablet, Bayer Vital GmbH, Germany) was given. On the 13th day of menstruation, ultrasound revealed 0.8 cm A-B of the endometrium, and an intramuscular injection of 40 mg qd progesterone (Xianju-®, 20 mg/piece, Zhejiang Xianju Pharmaceutical, China) was administered. Three days later, one 10CIII embryo was transferred, but no pregnancy occurred (Figure 1A and B, the embryos).

Cycle 2: In the second cycle in January 2022, the antagonist protocol (GnRH-Ant protocol) was used to promote ovulation. Beginning on the third day of menstruation, recombinant follicle stimulating hormone (Jin Saiheng®, 75 IU/piece, Jin Sai Group, China) was administered subcutaneously for nine days. On the 6th day of Gn treatment, 0.25 mg of GnRH-Ant (Orgalutran®, Merck & Co. Inc, United States) was administered by intramuscular injection until the trigger day. Six follicles were ≥ 18 mm, and eight follicles were ≥ 14 mm on the trigger day. An intramuscular injection of HCG 2000 IU and a subcutaneous injection of triptorelin acetate 0.1 mg as a double trigger were administered, and the oocytes were harvested 35 h later. Fifteen oocytes were obtained by D0. Considering the fertilization disorder that occurred in the first cycle, ICSI fertilization was performed directly. The maturation of oocytes was observed after removing the granulosa cells outside the oocytes: one in the GV stage, one in the MI stage, and thirteen in the MII stage. Ten fertilized oocytes with 2PN were observed on D1, and nine fertilized oocytes were cleaved on D2. On D3, one 8CIII embryo, two 6CIII embryos, two 4CIII embryos, one 3CIIImbryo, one 2CIII embryo, two IV embryos were observed, and no blastocysts formed after continuous feeding (Figure 1C and D, the embryos).

Cycle 3: Growth hormone (GH, Sai Zeng, Jin Lei®, 30 IU/piece, Jin Sai Group, China) at a dose of 2 IU was administered in the third cycle in May 2022. One oocyte (MII) was obtained in the natural cycle. The perivitelline space was large and the polar body was disrupted. ICSI fertilization was performed, and oocyte degeneration was observed on the first day (Figure 1E, the embryo).

Cycle 4: In June 2022, the luteal phase of the fourth cycle was designed to promote ovulation. Menotrophin (Li Zhu®, 75 IU/tube, Lizhu Group, China) was injected intramuscularly for 10 d, with four follicles ≥ 18 mm and eight follicles ≥ 14 mm on the trigger day. HCG at a dose of 6000 IU was injected intramuscularly for the trigger, and the oocytes were retrieved 35 h later. Twelve oocytes were obtained at D0, and ICSI was performed. Oocyte maturation was observed after removing the granulosa cells outside the oocytes: one in the MI stage, and eleven in the MII stage. Eight fertilized oocytes with 2PN were observed on D1, and eight fertilized oocytes with cleavage were observed on D2. On D3, there were two 6CIII embryos, four 5CIII embryos, and two IV embryos, and no blastocysts formed after continuous feeding (Figure 1F and G, the embryos)

Cycle 5: In November 2022, in the fifth natural cycle, one oocyte was obtained (MI). After continuous culture, the oocyte did not fertilized (Figure 1H, the embryo).

In August 2022, the whole exomes of the couple and the woman's parents were sequenced (Yikang Gene Testing Company). The results of high-throughput sequencing confirmed the presence of a *TUBB8* gene mutation in the woman [c.602G>T(p.C201F)], but no mutation was found in the man. Sanger sequencing of the woman's parents was used to verify the c.602G>T locus of the *TUBB8* gene. The results showed that the genotype of the patient's father was the same as that of the patient, and the patient's mother had no variation at this locus (Tables 2 and 3, and Figure 1I, the locus of the *TUBB8* gene).

OUTCOME AND FOLLOW-UP

The patient utilized donated oocytes at another hospital and is currently pregnant.

Table 1 Description and characteristics of assisted reproductive technology cycles

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
COH protocol	GnRH-A Long	GnRH-Ant	Natural cycle	Luteal phase	Natural cycle
Gonadotropin	r-FSH	r-FSH	-	HMG	-
Initiation dose (IU)	200	225	-	225	-
Total dose of gonadotropin (IU)	1975	2025	-	2025	-
Duration of gonadotropin (d)	9	9	-	9	-
E2 level on the day of HCG injection	6605.24	5822.55	189.60	2239.37	172.30
LH level on the day of HCG injection	1.54	0.57	4.87	1.86	4.04
P level on the day of HCG injection	2.05	2.56	0.28	7.38	0.21
No. of follicles (≥ 18 mm)	3	6	0	4	0
No. of follicles (≥ 14 mm)	9	8	1	8	1
Ovulation trigger (dose)	6000 IU (HCG)	2000 IU (HCG) + 0.2 mg (GnRH agonist)	0.1 mg (GnRH agonist)	6000 IU (HCG)	0.1 mg (GnRH agonist)
Interval between HCG administration and oocyte retrieval (h)	35.5 h	35 h	35 h	35 h	34 h
Number of retrieved oocytes	12	15	1	12	1
Fertilization mode	R-ICSI	ICSI	ICSI	ICSI	-
No. of MII	8	13	0	11	0
No. of GV	2	1	0	0	-
No. of 2PN	5	10	-	8	-
No. of D2 zygote	5	10	-	8	-
No. of D3 embryos	5	7	-	6	-
No. of blastocysts	0	0	-	0	-
No. of transferred embryos	1 (FET)	-	-	-	-
Pregnancy outcome	Not pregnant	No transferable embryos	No transferable embryos	No transferable embryos	No transferable embryos

COH: Controlled ovarian hyperstimulation; MII: Metaphase II; MI: Metaphase I; GV: Germinal vesicle; 2PN: 2 pronucleus; FET: Frozen Embryo Transfer.

Table 2 Results of sequencing mutation sites in the coding region of the *TUBB8* gene in the patient (female)

Gene	Chromosomal location	Variant naming	Frequency	Zygotic type	Source of variation
TUBB8	Chr 93730	NM_177987.3: c.602G>T(p.C201F)	Not included	Heterozygous	Unknown

Remarks: The variation verification result may be the complementary sequence of the reference sequence, and the variation C>A can also be expressed as G>T.

DISCUSSION

The patient suffered from primary infertility and had a history of infertility for 2 years. After excluding other infertility-related factors, she first underwent 2 cycles of artificial insemination that failed and then underwent IVF treatment. Both the number of follicles in the bilateral ovarian sinuses and the AMH levels suggested normal ovarian function. In the first cycle, the conventional short-term and long-term follicular phase scheme was used, and the fertilization disorder was remedied quickly. Despite the development of an embryo, the patient failed to conceive after transplantation. In subsequent treatments, whether an antagonist scheme, a luteal phase scheme, or the addition of growth hormone to improve the quality of oocytes was used, although the patient had mature oocytes, the subsequent cleavage of fertilized eggs and early division of embryos were not satisfactory, and the development of all embryos was still stagnant in the cleavage stage, accompanied by embryo fragmentation. After five cycles of assisted reproductive technology, we found

Table 3 Results of mutation site verification in the patient's parents

Relationship	Gene	Transcript	Verification site	Verification results
Father	TUBB8	NM_177987.3	c.602G>T	Heterozygous variation
Mother	TUBB8	NM_177987.3	c.602G>T	Without-variation

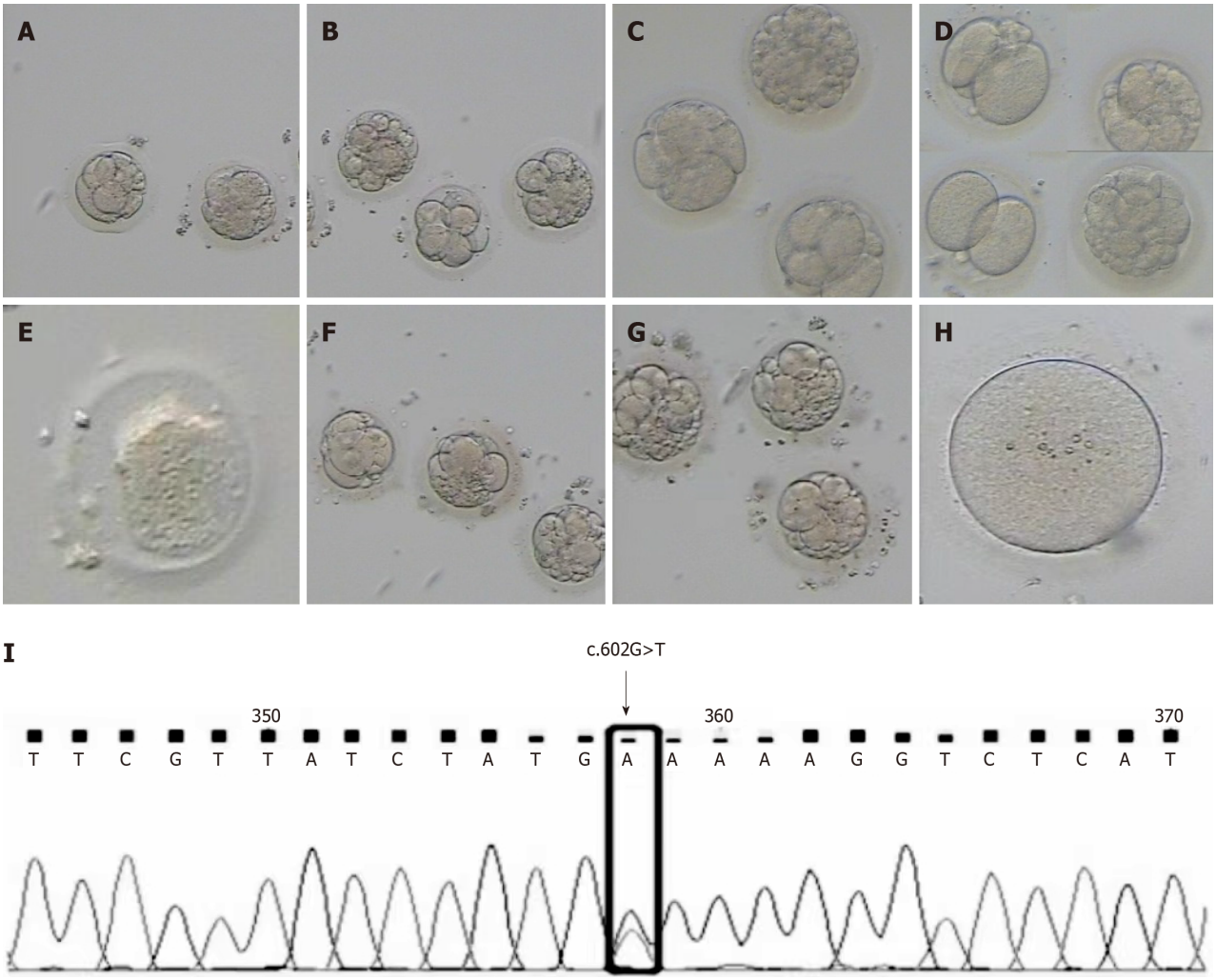

Figure 1 Embryos derived from each cycle of ovulation induction in the patient and the locus of the *TUBB8* gene mutation. A and B: Embryos of the first cycle; C and D: Embryos of the second cycle; E: Embryo of the third cycle; F and G: Embryos of the fourth cycle; H: Embryo of the fifth cycle; I: The locus of the *TUBB8* gene mutation.

that although the patient could produce mature oocytes, there were obstacles to fertilization of the oocytes and stagnation of early embryo development. By consulting the literature and tracking the results of previous similar research[6,7], we determined that maternal RNA and protein present in oocytes will still have an impact on embryo development after fertilized oocytes are formed, and maternal gene mutation may be one of the reasons for early embryo development stagnation[8]. We sequenced the whole exomes of the patient and her spouses and detected a mutation in the *TUBB8* gene [c.602G>T(p.C201F)] in the patient. The mutant gene was subsequently verified in the parents of the patient, and it was found that the *TUBB8* mutation was inherited from the father of the female patient.

The human β -tubulin family consists of nine β -tubulin isoforms[9], but TUBB8 is the only gene specifically expressed in human oocytes and early embryos[4], and spindle assembly and chromosome separation are inseparable from their basic functions during meiosis and mitosis of early embryos[2]. The *TUBB8* gene is a highly conserved genotype that exists only in primates. Missense mutations of *TUBB8* may interfere with the maturation of human oocytes, which is a key prerequisite for fertilization and subsequent embryo development. To date, 109 unique TUBB8 mutations have been reported, including 87 heterozygous mutations, 13 homozygous mutations and 9 compound heterozygous mutations, which exist in 8 families. According to these reports, TUBB8 mutations account for approximately 31.96% of all cases of primary oocyte maturation stagnation[10], and different mutant genotypes are associated with different clinical phenotypes, including the following[11]: (1) Formation of fully developed immature oocytes; (2) formation of unfertilized MII oocytes; (3) formation of a fertilized oocyte that cannot be cleaved; and (4) stagnation of early embryo development,

including: (a) Oocytes that completely stagnate at the MI stage, (b) MII oocytes that cannot be fertilized, (c) fertilized oocytes that can be fertilized but the embryo does not cleave, and (d) embryos that can be fertilized and the embryo can cleave but then stagnate at the early stage to form embryos with a normal appearance but repeated implantation failures. Therefore, our results extend the mutation and phenotype spectrum of TUBB8 in patients with oocyte maturation, fertilization and early embryonic development arrest. The heterozygous mutation of *TUBB8* described in this study c.602G>T(p.C201F) is a newly discovered variant, that has not been reported in previous literature. The clinical phenotype of this genotype is early embryonic development stagnation; that is, this mutation does not hinder the maturation and fertilization of oocytes, so we can see that this patient can form MII oocytes that can be fertilized and cleaved normally. However, the development of all the embryos stopped at the 2-8-cell stage, and they did not further develop into normal blastocysts, which was similar to the phenotypes of the mutations found by Yuan *et al*[6] and Jia *et al* [12]. Because the *TUBB8* gene plays an important role in the formation and assembly of spindles during oocyte meiosis, we speculate that the stagnation of early embryonic development in patients may be partially caused by defects in nuclear maturity[13].

There are two genetic modes of disease inheritance related to *TUBB8* gene mutations: autosomal dominant inheritance and autosomal recessive inheritance. To further explore the source of *TUBB8* mutations, we collected as much family gene information as possible. We tested the blood samples of the woman's parents (the patient was the only daughter), and it was verified that the patient's mutation was inherited from her father. Although dozens of pathogenic *TUBB8* gene mutations have been reported in the literature, there is still a lack of effective treatment methods. It has been reported that the duration of oocyte activation, the mode of calcium oscillation and calcium channel blockers affect the early embryonic development of mice[14-16]. Some studies have suggested that calcium supplementation may have a positive therapeutic effect on the embryonic development arrest caused by *TUBB8* gene mutation and ultimately overcome early embryonic development arrest[17]. Jia *et al*[12] proposed that intracellular injection of cDNA of the normal *TUBB8* gene can improve the spindle assembly of mouse cells, allowing the embryos to develop normally and enabling the birth of living offspring after injection; however the early embryo division mode of mice is different from that of humans, so there is still no experimental evidence to support the safety and effectiveness of intracellular injection of cDNA of the normal *TUBB8* gene into the human body. Therefore, for the treatment of patients, in view of the current medical means, the best choice is to use donated oocytes.

CONCLUSION

In summary, this study demonstrated that the *TUBB8* gene plays an important role in early human embryo development, and that mutation of this gene leads to early embryo development stagnation. In this patient, a novel *TUBB8* gene mutation, c.602G>T(p.C201F) was found, expanding the range of *TUBB8* gene mutations and providing new clues for genetic counseling, assisted reproductive risk prediction and optimization of the clinical treatment of infertility. This case also illustrates the importance of screening for *TUBB8* gene mutations in patients who have multicycle oocyte maturation disorder, fertilization failure or early embryo development stagnation.

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FOOTNOTES

Author contributions: Zhang XY contributed to study design and original draft preparation; Zhang XX contributed to data analysis and manuscript revision; Wang L contributed to supervision and critical review and final manuscript approval.

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CASE REPORT

Thoracic spine infection caused by *Pseudomonas fluorescens*: A case report and review of literature

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Abstract

BACKGROUND

The clinical incidence of spinal infection is gradually increasing, and its onset is insidious, easily leading to missed diagnosis and misdiagnosis, which may lead to serious complications such as nervous system dysfunction, spinal instability and/or deformity, and cause a huge burden on society and families. Early identification of the causative agent and precision medicine will greatly reduce the suffering of patients. At present, the main pathogenic bacteria that cause spinal infection are *Staphylococcus aureus*, Streptococcus, Pneumococcus, *Escherichia coli*, and Klebsiella. There are no reports of spinal infection caused by *Pseudomonas fluorescens*.

CASE SUMMARY

We report a 32-year-old female patient with spinal infection. She presented with flank pain, initially thought to be bone metastases or bone tuberculosis, and had a family background of tumors. Her clinical features and changes in imaging and laboratory tests led to the suspicion of thoracic spine infection. Histopathology of the lesion showed inflammation, tissue culture of the lesion was negative several times, and the possible pathogen - *Pseudomonas fluorescens* was found after gene sequencing of the lesion. The patient recovered completely after a full course of antibiotic treatment.

CONCLUSION

This report increases the range of pathogens involved in spinal infections, highlights the unique advantages of gene sequencing technology in difficult-to-diagnose diseases, and validates conservative treatment with a full course of

antibiotics for spinal infections without complications.

Key Words: Thoracic spine infection; *Pseudomonas fluorescens*; Spinal infection; Case report

Core Tip: Vigilance regarding unexplained spinal infection is required. Detailed physical examination, puncture biopsy, pathological examination and genetic testing can play a very important role in clinical diagnosis. Needle biopsy and genetic testing are effective methods for identifying unexplained spinal infections, and appropriate antibiotic therapy with a full course of treatment is critical to prognosis. Due to the hidden nature of unexplained spinal infections, regular follow-up over a long period of time is recommended.

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INTRODUCTION

Spinal infection is common in the thoracic spine. Spinal infections include vertebral osteomyelitis, discitis, paravertebral musculoskeletal infections, and refractory spinal abscesses[1], accounting for 2%-7% of all musculoskeletal infections[2]. Common presenting symptoms are fever and chest and back pain. Common pathogens are mainly cocci and bacilli, and infections with specific bacteria have also been reported. As bone metastasis, tuberculosis, rheumatic diseases, brucellosis, osteoporosis and other diseases can lead to different degrees of bone destruction, imaging can show abnormal manifestations of the spine; thus, spinal infection is easily misdiagnosed and missed. In the case of delayed diagnosis or surgery, potential early destructive and late disabling complications may occur[3], and can even lead to the risk of mortality, seriously affecting the normal life and work of patients, and result in serious economic burdens to society and families. If a patient has serious complications, debridement and fusion surgery can only be performed to eliminate the infected lesion and stabilize the spine[4], and if the infection is holospinal, surgery should be performed as soon as possible to achieve better neurological recovery and infection control[5]. However, regardless of the treatment chosen, antibiotics are required throughout the course of treatment. Although the optimal duration of antibiotic therapy remains controversial, it should not be less than six weeks[2].

CASE PRESENTATION

Chief complaints

A 32-year-old female patient presented with pain in her left flank of 1 wk.

History of present illness

The patient presented with pain in her left flank of 1 wk, the nature of the pain was undescribed, and was obvious at night, persistent, severe, was worse when breathing and changing position, and was slightly relieved when her position was maintained. Pain was accompanied by chest tightness and decreased appetite. No fever, chills, cough with sputum, dyspnea, or aches in other parts of the body were observed. Nausea and vomiting, abdominal pain, diarrhea, abnormal urine and bowel movements, palpitations, precordial pain, back pain, and left upper limb pain were absent. In addition, no rash was noted. From disease onset, her diet, sleep, and spirit were poor, and no significant weight reduction was observed. Self-administration of analgesic drugs (details unknown) before presentation were ineffective.

History of past illness

She was usually in good health.

Personal and family history

The patient reported a family history of malignancy.

Physical examination

Physical examination showed that she was conscious, had poor mental status, was helped into position, and supported by others. Pain was associated with breathing and trunk movement. Occasional palpable tenderness in the left flank and mild tension in the left back muscles and left flank muscles were observed with no obvious tenderness. The patient

showed no obvious deformity in the thoracolumbar segment of the spine, limited movement of the thoracic spine, interspinous tenderness at T 7-10, suspicious positive percussion pain, and a positive thoracic crush test. Examination of the cardiopulmonary tract, abdomen, and other areas showed no obvious positive signs.

Laboratory examinations

Laboratory tests showed the following: leukocytes were 10.62 × 10^9/L, neutrophil percentage was 76.80%, lymphocyte percentage was 17.80%, eosinophil percentage was 0.30%, neutrophil absolute value was 8.16 × 10^9/L, platelets were 381 × 10^9/L, C-reactive protein (CRP) was 37.35 mg/L, erythrocyte sedimentation rate was 44 mm/h, aspartate aminotransferase was 11.6 U/L, globulin was 42.0 g/L, the leukoglobulin ratio was 1.0, prealbumin was 138.7 mg/L, glucose was 6.42 mmol/L, urine ketone body 3+, urine occult blood+-, urine protein+, urine specific gravity was 1.033, urine leukocytes 32.50/μL, urine leukocytes in the high power field were 5.8/HP, liver and kidney function, blood lipids and blood glucose were not significantly abnormal. The patient underwent a tissue biopsy for bacterial culture and pathology smear. The bacterial culture of the lesion was negative, and the pathology (Figure 1) showed trabecular bone degeneration and necrosis, and the fibrous tissue of the intertrabecular granulation tissue revealed hyperplasia with inflammatory cell infiltration, and a few cytoplasmic transparent round cells were found. Symptomatic analgesic treatment was administered, but as the specific causative agent could not be identified, the patient attended Shandong Chest Hospital for inpatient treatment. After admission, re-examination of laboratory tests showed a *Mycobacterium tuberculosis* IgG antibody positive reaction, activated partial thromboplastin time of 50.6 s, albumin 37.9 g/L, creatine kinase 22 U/L, lactate dehydrogenase 116 U/L, triglycerides 1.76 mmol/L, magnesium 0.74 mmol/L, anion gap 6.8 mmol/L, and angiotensin-converting enzyme 5 U/L. Plasma D-dimer, routine blood tests, tiger red plate agglutination test, brucellosis test tube agglutination test, Brucella antibody IgG, Aspergillus galactomannan antigen, liver and kidney function, blood glucose, immunoglobulins (IgG, IgA, IgM), complement C3, complement C4, *Mycobacterium tuberculosis* IgM antibody, eight items before surgery, and the T-SPOT were also performed. There were no obvious abnormalities in the TB test, erythrocyte sedimentation rate, CRP, rheumatoid factor, anti-O, (1,3)-β-D-glucan, gram-negative lipopolysaccharide, and routine urine and bowel movements.

Therefore, a local needle biopsy of the lesion was performed again for relevant examination and culture. The results showed that no fungal or bacterial growth was found in the lesion tissue culture, and no mycobacteria were detected, and the DNA of *Mycobacterium tuberculosis* complex was also negative. The pathological evidence showed that the biopsy tissue (thoracic vertebrae) contained cartilage, bone and fibrous tissue with minimal inflammation.

Therefore, genetic sequencing (Tables 1 and 2) was performed and showed that *Pseudomonas fluorescens* had the largest number of total fragments, a small number of *Escherichia coli* and *Staphylococcus aureus*, and no mycobacteria, fungi, viruses, parasites, mycoplasma/chlamydia, and drug resistance genes were detected.

Imaging examinations

Imaging studies (Figures 2 and 3) showed that the T7-9 vertebrae were slightly flattened, and the T8 vertebra was predominant, with reduced smooth margins. The T7-9 vertebral body and adnexal bones showed patchy long T2 long T1 signals, STIR hyperintensity, and the corresponding vertebral space was slightly narrowed. Multiple bone destruction of the T7 vertebral body and T8 vertebral body, bilateral vertebral arches, left transverse process, and left rib cage with swelling of the surrounding soft tissues were thought to be caused by infectious lesions, and positron emission tomography-computed tomography (PET-CT) or needle biopsy was recommended to rule out neoplastic lesions. Mild inflammation of the middle and lower lobes of the right lung, with signs of bilateral pleural effusion were also seen.

FINAL DIAGNOSIS

Thoracic vertebral body infection caused by *Pseudomonas fluorescens*.

TREATMENT

According to the patient's symptoms, signs, imaging data and laboratory test results, and considering the inflammatory bone structural abnormalities caused by *Pseudomonas fluorescens*, antibiotic therapy with moxifloxacin 0.4 g intravenously once a day was given for 4 wk, followed by oral moxifloxacin 0.4 g once a day for 2 wk.

OUTCOME AND FOLLOW-UP

The patient's symptoms resolved after treatment, and she went through pregnancy, delivery, and breastfeeding over the next two years; thus, no second-generation sequencing was performed. After stopping breastfeeding, the patient returned to the clinic in June, 2023, and did not complain of significant back pain or oblique rib pain. Magnetic resonance imaging (MRI) of the thoracic vertebra indicated that the original lesion site was significantly improved (Figure 4).

Table 1 Precision medicine high-throughput sequencing (clinical infection gene analysis report): List of bacteria detected

Bacterial genus name (total number of fragments, abundance%)	Bacterial species name	Number of fragments detected (species)	Total fragment length (species, bp)	Homologous matching degree (%)
Pseudomonas spp. (67, 57.27%)	Pseudomonas fluorescens	44	17534	99
Escherichia coli (10, 8.55%)	Escherichia coli	10	3979	98
Staphylococci (7, 5.98%)	Staphylococcus aureus	5	2142	100

Table 2 Precision medicine high-throughput sequencing (clinical infection gene analysis report): Other list

Serial number	Name	Result
1	Mycobacterium and other important pathogens	0
2	Fungus	0
3	Virus	0
4	Parasite	0
5	Mycoplasma/chlamydia trachomatis	0
6	Drug resistance gene	0

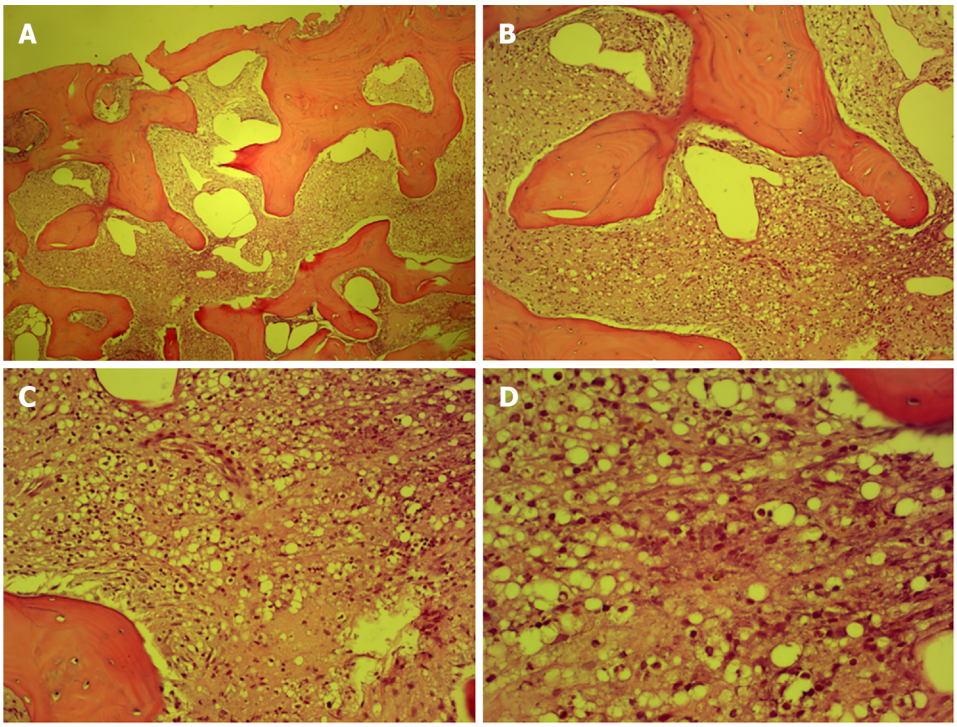

Figure 1 Pathology of the local puncture biopsy in Zibo Central Hospital. A: 4 × 10 times; B: 10 × 10 times; C: 20 × 10 times; D: 40 × 10 times.

DISCUSSION

Spinal infections are common in adults, but can also occur in younger[6] and older adults[7]. Studies[7] predict that the number of patients over the age of 80 years with spinal infections will increase rapidly in aging populations. These infections are not clinically prevalent but may lead to serious complications such as neurologic dysfunction, spinal instability and/or deformity due to skeletal destruction, and in severe cases, death[3,8]. As it is difficult to identify the causative pathogen, diagnosis is often delayed[9], resulting in a serious burden on the life and economy of patients and society. Spinal infections can occur in single-segments or contiguous multi-segments or non-contiguous multi-segments [10] and can occur throughout the spine, most commonly in the lumbosacral spine (39.1%), followed by the thoracic spine (27.1%), and less frequently in the cervical spine[11,12]. Studies have found that the occurrence of spinal infections is

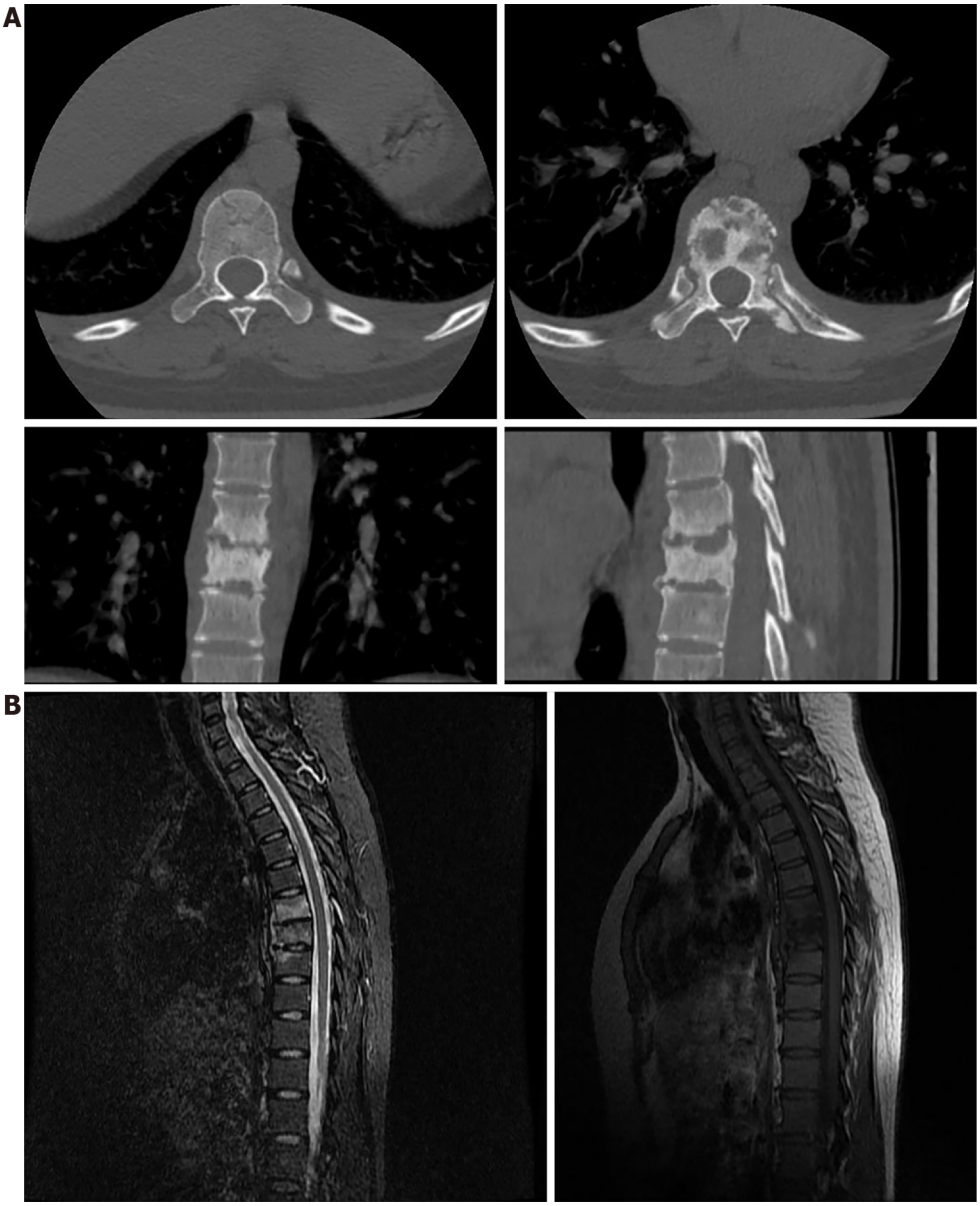

Figure 2 Computed tomography and magnetic resonance imaging of the thoracic spine. A: Thoracic vertebral computed tomography shows bone destruction in T7-9, with T8 being the most significant; B: Magnetic resonance imaging of the thoracic vertebra showed signs of bone abnormalities in T7-9, with T7 and T8 being the most significant.

mostly related to immunosuppression[13], diabetes mellitus[14], intravenous drug abuse[15], osteoporotic vertebral fractures[16], recent soft tissue infection or bacteremia[17], and spinal surgery[18]. As spinal infections often lead to morphological abnormalities of the bone and accessory structures of the spine the clinical diagnosis and differential diagnosis of tumors, tuberculosis, brucellosis, ankylosing spondylitis, *etc.*, are particularly important. With the development of MRI and PET-CT, these two techniques can distinguish between the types of spinal infections, and of these two techniques, PET-CT has shown better sensitivity and specificity in the diagnosis and treatment evaluation of spinal infections[19-21]. However, pathological analysis and bacterial culture are still important in the diagnosis of infected tissue[22]. The common pathogens in these infections[23-26] are *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus*, *Pneumococcus*, *Klebsiella*, and less commonly, *Salmonella*[27], *Aspergillus*[28], *Fungi*[29], *Actinomycetes*[30], and *Gram-positive bacteria*[25]. Due to the limitations of bacterial culture conditions and the number of samples, it is not always possible to obtain relevant pathogens even by local bacterial culture and biopsy pathology[9], which leads to challenges in clinical diagnosis and treatment. With the rapid development of genomics technology, such as high-throughput DNA sequencing, big data and gene editing technology, precision medicine is getting closer. For bacterial infections, effective treatment is only possible by accurate identification of pathogenic microorganisms. It has been found[31-33] that gene sequencing can detect pathogens that are negative using traditional cultures, is more sensitive and time-consuming than traditional cultures, and has unique advantages in the identification and detection of clinically rare bacteria, fastidious bacteria, and bacteria that do not grow in solid media. For example, Dong *et al*[34] identified 190 suspected tuberculosis sputum culture isolates by genetic technology, and found that among the 190 isolates, 186 were *Mycobacterium tuberculosis* , while the remaining 4 were non-tuberculous mycobacteria. In addition, gene sequencing technology is also used in the

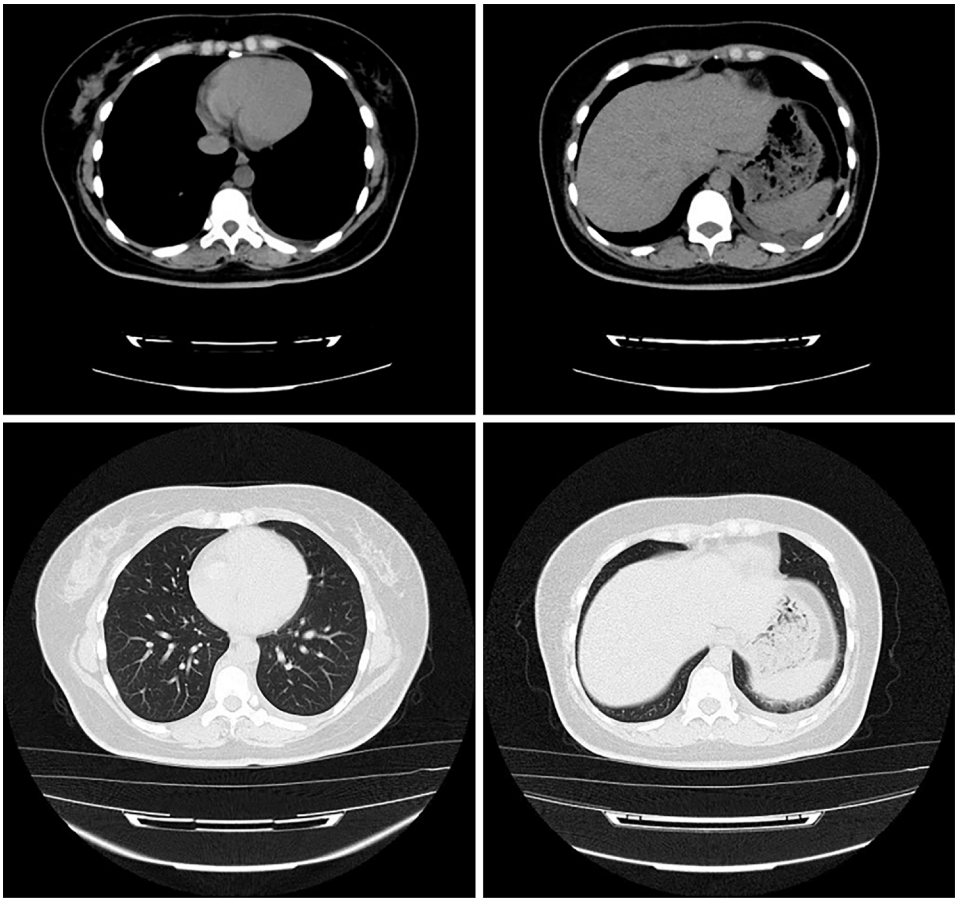

Figure 3 Computed tomography of the lungs. Chest computed tomography shows mild inflammation in the middle and lower lobe of the right lung and a small amount of pleural effusion on both sides.

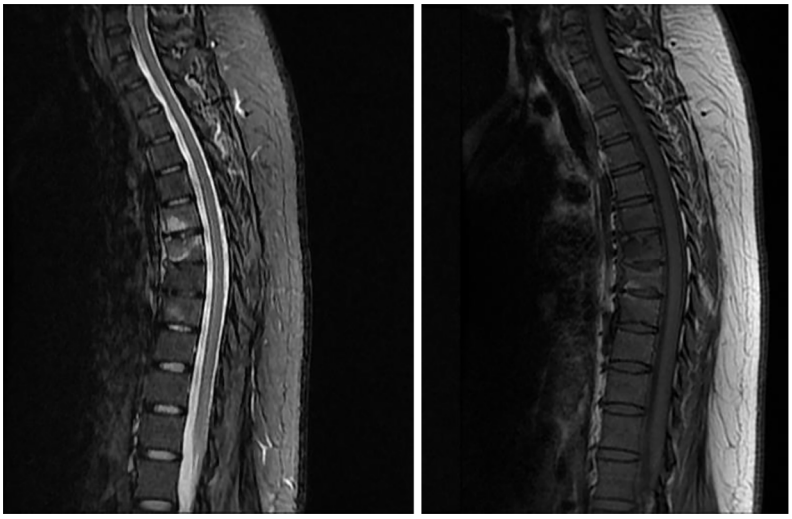

Figure 4 Magnetic resonance imaging showed that the lesions of the T7-9 vertebrae were significantly reduced after treatment.

identification of intestinal flora, the detection of tumor markers and mutant genes, the diagnosis and prognosis of diseases, and the evaluation of diagnosis and treatment effects, which is an important part of modern technologies. In the present case, gene sequencing technology was also used to detect pathogens that could not be cultured using conventional bacterial culture, in order to determine the final diagnosis and treatment plan.

Treatment of spinal infections is divided into surgical and conservative treatments, and the choice of treatment depends on whether there are clear complications. Korovessis *et al*[3] evaluated English language peer-reviewed clinical trials on purulent spinal infections published before 2009. They found that the most basic treatment for uncomplicated spondylitis was intravenous antibiotics, followed by oral antibiotics and braces. In complex cases, surgery can improve

the balance of the sagittal plane, restore nerve damage, and relieve severe pain. Duarte *et al*[22] selected the appropriate literature on spinal infections using databases from the US National Library of Medicine and the US National Institutes of Health, and stated the need for consistent antibiotic therapy, emphasizing that antibiotic use must be initiated after the etiological diagnosis is made. Surgery is used only in the presence of neurological deficits or sepsis, spinal instability and/or deformity, epidural abscess, and failure of conservative treatment. Aljawadi *et al*[35] conducted a comprehensive search of relevant literature published from 1990 to 2018 and found that adequate non-surgical treatment with antibiotics can achieve satisfactory results with low recurrence rates. In the present case, the patient had an acute onset, a short disease course, and limited lesions, and satisfactory results were achieved following non-surgical treatment with antibiotics. It is important to note that regardless of whether conservative or surgical treatment is chosen, rehabilitation at all stages has a positive effect on the improvement of neurological, motor, and sensory impairments in patients with spinal infections[36].

Compared with common spinal infections, the case reported in this article had certain specificities which were mainly manifested in the following aspects: First, the onset of symptoms was atypical. The patient did not have obvious symptoms of fever, back pain, or neurological dysfunction, but presented with severe flank pain, which was related to postural changes and breathing, and could easily be misdiagnosed as herpes zoster and visceral disease. Careful physical examination revealed tenderness and percussion pain in the thoracic spine, but no significant tenderness in the flanks, no obvious rash or paresthesia, a negative thoracic crush test, and no obvious positive signs in the lungs or abdomen. MRI of the thoracic spine and CT of the lungs were completed before the lesion was localized to the thoracic spine. Second, there was no history of obvious underlying medical conditions, immunodeficiency or suppression, and no abnormal contact or recent history of trauma, infection, and surgery. Spinal infections have been found to result from distal skin or visceral infections followed by the bloodstream route[37]. Our patient was a young woman who had previously been in good health and had no history of travel, other illnesses or unusual contacts, and no significant trauma or distal skin infection or surgery. As there was a genetic history of tumor in the family, it was not possible to determine whether the lesion was a tumor or an infection using MRI. At this time, clinicians are prone to misdiagnosis, and how to communicate with patients when there is no good and clear diagnosis, how to stabilize the patient's mental status, and what the next diagnosis and treatment plan are problems faced by clinicians. A clear source of infection was traced in this patient, and it is speculated that there may have been superficial skin lesions over a long period of time that led to colonization by the pathogen and activation of the causative agent when the body became immunocompromised, leading to morbidity. Third, pathological analysis of the biopsy and bacterial culture failed to identify the causative organism. The patient underwent biopsy for pathological analysis and bacterial culture in our hospital and Shandong Chest Hospital, and both results showed inflammatory lesions, while no obvious positive results were found in both bacterial cultures. These results are similar to those in many clinical reports[23,26], which has resulted in a bottleneck in terms of diagnosis and treatment when the true pathogen cannot be found. This poses a further challenge in the diagnosis and treatment of the disease. There were three reasons for failure to culture positive bacteria in this patient. First, few samples were obtained by puncture and the transfection rate was low. Second, a fluorescence test was not carried out. Third, culture is less sensitive than gene sequencing. Bacterial culture requires live bacterial growth, and in the progressive or active stage of the disease, the lesion site has obvious inflammatory infiltration and cytophagocytosis, inanimate bacteria or decomposed nucleic acid fragments which does not provide culture positive results or biochemical identification. For gene sequencing, the sensitivity is higher, both live bacteria and decomposed nucleic acid fragments can be detected; thus, culture and biochemical tests failed to detect *Pseudomonas fluorescens*, while gene sequencing could detect this pathogen. Fourth, the pathogenic bacteria found by gene sequencing are special. With the development of omics technology, the application of new genomics, metabolomics, and proteomic technologies has brought opportunities for clinicians to break through bottlenecks. The patient's cultures were negative, and pathology only showed inflammatory cell infiltration, and the specific pathogen was unclear. It was not until after gene sequencing was conducted that infection with *Pseudomonas fluorescens* was suggested. According to the results of gene sequencing, the presence of *Pseudomonas fluorescens*, *Escherichia coli* and *Staphylococcus* may have been due to co-infection. As the content of *Pseudomonas fluorescens* was much higher than that of the other two bacteria, *Pseudomonas fluorescens* was considered to be the main pathogen. However, this pathogen is a rare in humans, and there have been no reports of spinal infection caused by this bacterium. *Pseudomonas fluorescens* is widely distributed in nature, such as in soil, water, plant and animal environments, and can antagonize plant pathogens and promote plant growth[38], and is an important plant root growth-promoting bacterium, which is mainly used in agricultural production, and has been occasionally found to infect humans[39]. *Pseudomonas fluorescens* is an opportunistic pathogen, and the most common clinical infection is *via* blood and blood products[40-42]. From 2004 to 2006, 80 people in the United States were reported to have been infected by products contaminated with the bacterium[43]. *Pseudomonas fluorescens* can exist in urine, bile, skin and skin infected secretions[44-45], and can also enter the blood and cause pyogenic pus, osteomyelitis, pyogenic ganglitis and lung infection. It even leads to severe after-effects such as septicemia, infected huke and intravascular coagulation, with a high mortality rate[46]. *Pseudomonas fluorescens* is temperature-sensitive and does not grow below 37 °C or 42 °C during bacterial culture[47]. However, it is possible to develop transient strains that are tolerant to high temperature, for example *Pseudomonas psychrophila*, which is widely distributed in nature, and can cause human and animal disease. It has also been found[48] that *Pseudomonas fluorescens* is an important spoilage bacterium that causes spoilage of meat and can be detected in such meat. The cause of infection due pathogenic bacteria is unknown, and the source of the infection is unclear. In our patient, it may be related to the consumption of spoiled food, as the number of gene fragments of the bacterium obtained by gene sequencing was not large, but could have been due to the small amount of sampling. Fifth, the treatment of the patient was relatively smooth as she fully recovered and returned to normal work and daily life with no obvious sequelae after treatment with intravenous and oral antibiotics. This was related to the relatively young age of the patient, the short disease duration, the absence of significant comorbidities, and the use of adequate antibiotics, which is consistent with previous studies[2]. In this case, bacterial

culture was negative and drug susceptibility testing could not be performed. Ciprofloxacin was empirically selected for treatment. The Department of Pharmacology, Shantou University Medical School in China carried out a drug resistance study on the strain of *Pseudomonas fluorescens*, and found that the strain was resistant to penicillin, ampicillin, amoxicillin, cefuroxime, ceftazidime, cefotaxime, cefazolin, imipenem, meropenem, amtronam and tetracycline, and only sensitive to ciprofloxacin[49]. Liu *et al*[47] carried out a drug sensitivity test on a patient infected with *Pseudomonas fluorescens* secondary to finger skin trauma, and found that the bacterium was sensitive to ceftazidime, amiamkanamycin, amtronam, levofloxacin, ciprofloxacin, imipenem, meropenem, tobramycin, netimicin, *etc*., and resistant to piperacillin, cefoperazone, polymyxin B and ticacillin. Thus, we empirically selected ciprofloxacin in the absence of drug sensitivity, and achieved good clinical efficacy.

This case indicates that clinicians should pay attention to detailed physical and other examinations. When the patient's complaint is not consistent with their condition, appropriate physical and auxiliary examinations are important in helping to identify the cause as soon as possible. The existence of special diseases requires clinicians to continue to explore, recognize and improve, to use the continuous developments of new technologies, and to work together with multidisciplinary unity and cooperation, so that patients can obtain an early diagnosis and precision treatment, and reduce or avoid serious complications or sequelae.

CONCLUSION

This report increases the range of pathogens involved in spinal infections, highlights the unique advantages of gene sequencing technology in difficult-to-diagnose diseases, and validates conservative treatment with a full course of antibiotics for spinal infections without complications.

FOOTNOTES

Author contributions: Guo LL was the doctor in charge, and provided detailed information on the patient; Guo LL and Li L wrote the manuscript; Zhang BH provided and modified the pathological data; Cao JF provided and modified the imaging data; Guo LL, Li L, Zhang BH and Zhang LJ jointly revised the manuscript; All authors read and approved the final manuscript.

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CASE REPORT

Bone block from lateral window - correcting vertical and horizontal bone deficiency in maxilla posterior site: A case report

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Abstract

BACKGROUND

Lateral window approach for sinus floor lift is commonly used for vertical bone augmentation in cases when the residual bone height is less than 5 mm. However, managing cases becomes more challenging when a maxillary sinus pseudocyst is present or when there is insufficient bone width. In this case, we utilized the bone window prepared during the lateral window sinus lift as a shell for horizontal bone augmentation. This allowed for simultaneous horizontal and vertical bone augmentation immediately after the removal of the maxillary sinus pseudocyst.

CASE SUMMARY

A 28-year-old female presented to our clinic with the chief complaint of missing upper left posterior teeth. Intraoral examination showed a horizontal deficiency of the alveolar ridge contour. The height of the alveolar bone was approximately 3.6 mm on cone beam computed tomography (CBCT). And a typical well-defined 'dome-shaped' lesion in maxillary sinus was observed on CBCT imaging. The lateral bony window was prepared using a piezo-ultrasonic device, then the bony window was fixed to the buccal side of the 26 alveolar ridge using a titanium screw with a length of 10 mm and a diameter of 1.5 mm. The space between the bony window and the alveolar ridge was filled with Bio-Oss, covered with a Bio-Gide collagen membrane, and subsequently sutured. Nine months later, the patient's bone width increased from 4.8 to 10.5 mm, and the bone height increased from 3.6 to 15.6 mm. Subsequently, a Straumann® 4.1 mm × 10 mm implant was placed. The final all-ceramic crown restoration was completed four months later, and both clinical and radiographic examinations showed that the implant was successful, and the patient was satisfied with the results.

CONCLUSION
The bone block harvested from the lateral window sinus lift can be used for simultaneous horizontal bone augmentation acting as a shell for good two-dimensional bone augmentation.

Key Words: Sinus lift; Lateral window; Dental implant; Horizontal bone augmentation; Case report

Core Tip: The bone block harvested from the lateral window sinus lift as a shell for simultaneous horizontal bone augmentation can effectively address cases with insufficient bone height and width. This approach enables two-dimensional bone augmentation, leading to successful implant placement and restoration, as demonstrated in this case study.

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INTRODUCTION

In the edentulous maxillary posterior region, available bone heights (ABH) often decrease due to alveolar ridge resorption and progressive pneumatization of the maxillary sinus, presenting a challenge for implant restorations. The International Team for Implantology consensus recommends lateral window approach for sinus floor elevation when ABH is less than 5 mm in posterior maxilla[1].

The cortical bone tenting technique is an effective method for horizontal bone augmentation, involving the placement of a thin lamina of cortical bone over the particulate bone substitutes[2]. It is characterized by the thin cortical bone acting as a natural biological membrane, which is fixed to the alveolar ridge using titanium nails at a specific distance from the alveolar crest. Systemic review has shown that the cortical tenting technique can achieve a horizontal bone augmentation of 5.55 mm[3].

Although the maxillary sinus floor lift is a well-documented technique for bone regeneration, clinical decision-making for a maxillary sinus floor lift may become more complex when some lesions are present in the maxillary sinus[4,5]. The most commonly encountered condition during a maxillary sinus floor lift is maxillary sinus pseudocyst, with an incidence of approximately 1% to 24%[6,7]. Pseudocysts are usually detected on cone beam computed tomography (CBCT) and show a characteristic faint dome-shaped radiopacities[7]. The management of maxillary sinus cysts and the timing of bone grafting in maxillary sinus is controversial. Some scholars suggest that a period of healing is required after the removal of sinus cysts before bone grafting[8], while other scholars have achieved good results with contemporaneous bone grafting[9]. In some studies, dental implants have been placed at the same time with pseudocyst removal and bone grafting[10,11]. Some reviews have shown that the presence of pseudocysts does not affect the ultimate success of bone grafting and implant placement, but other studies have also suggested that detailed evaluation of patients is crucial to prevent undesirable complications[11,12].

This article presents a case using the bone block harvested from lateral window for sinus floor elevation/lift immediately after pseudocyst removal to correct severe vertical and horizontal bone deficiency in posterior maxilla.

CASE PRESENTATION

Chief complaints

A 28-year-old female patient consulted to Department of Oral Implantology with a complaint of a missing maxillary left upper molar several years ago due to tooth fracture.

History of present illness

The maxillary left upper first molar was extracted several years ago due to tooth fracture.

History of past illness

No significant medical history was reported. The patient denied any medical history and tobacco use.

Personal and family history

No significant personal and family history was reported.

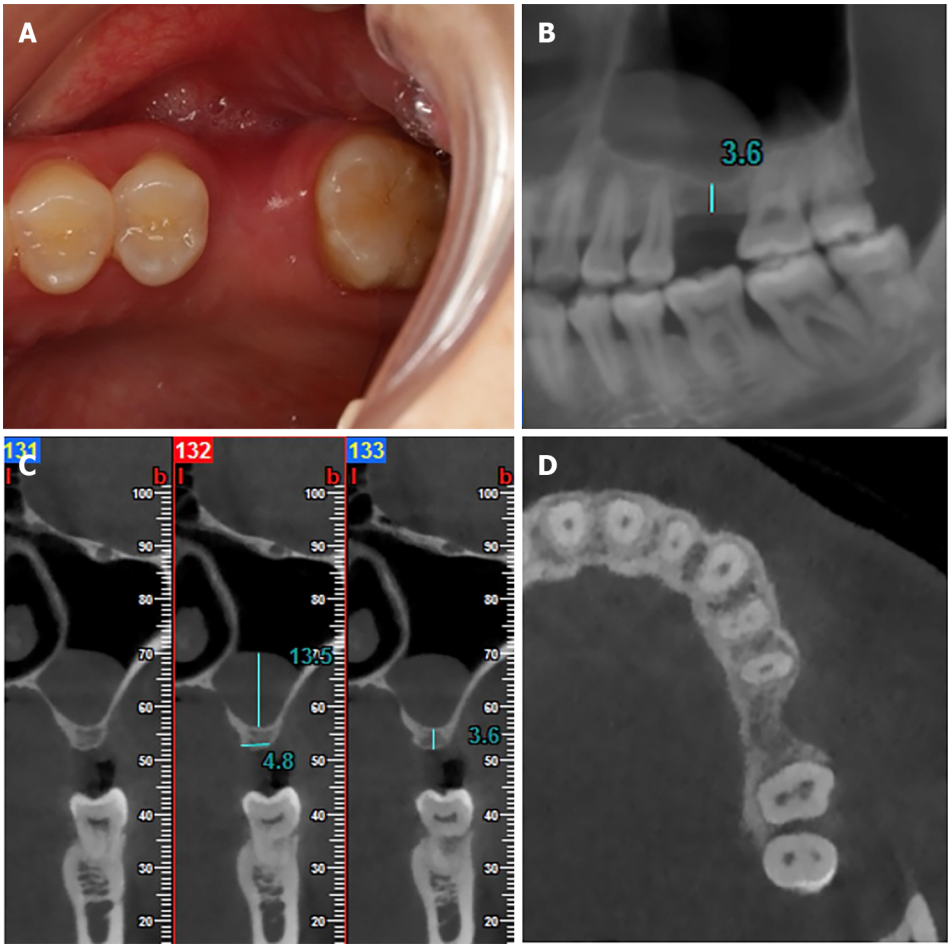

Figure 1 Preoperative occlusal view and cone beam computed tomography images of tooth 26. A: Occlusal view of tooth 26 with the horizontal bone deficiency; B: Coronal cone beam computed tomography (CBCT) image showed the mesio-distal dimensions and the region of pseudocyst; C: Sagittal CBCT image showed the available bone heights of tooth 26 and the height of pseudocyst; D: Horizontal CBCT image showed horizontal bone deficiency of tooth 26.

Physical examination

The patient's blood pressure was 112/74 mmHg with a pulse rate of 72 beats per minutes. The buccal gingival contour of tooth 26 was collapsed from the occlusal view (Figure 1A).

Laboratory examinations

The routine blood count and coagulation profile were within normal limits.

Imaging examinations

CBCT showed that the ABH of tooth 26 was 3.6 mm and available bone width (ABW) was 4.8 mm with a well-circumscribed low-density lesion in the maxillary sinus in the region from tooth 24 to tooth 26 (Figure 1B-D).

FINAL DIAGNOSIS

Maxillary dentition defect; sinus pseudocyst.

TREATMENT

A staged approach for implant placement was planned following vertical and horizontal alveolar bone augmentation and pseudocyst removal. The informed consent for treatment was signed before surgery. Immediately prior to the surgery, the mouth was rinsed three times for three minutes using 0.12% chlorhexidine mouthwash. Adrenaline-containing articaine (4% articaine 1:100000 adrenaline, 3M Espe, Seefeld, Germany) was administered for local anesthesia. A midcrestal horizontal incision and two adjacent buccal releasing incisions were made, and the full-thickness mucoperiosteal flap was reflected to expose the alveolar bone and the lateral wall of maxillary sinus. A piezo-ultrasonic (EMS, Nyon, Switzerland) device was used to prepare a rectangular bony window in the lateral wall of maxillary sinus, the

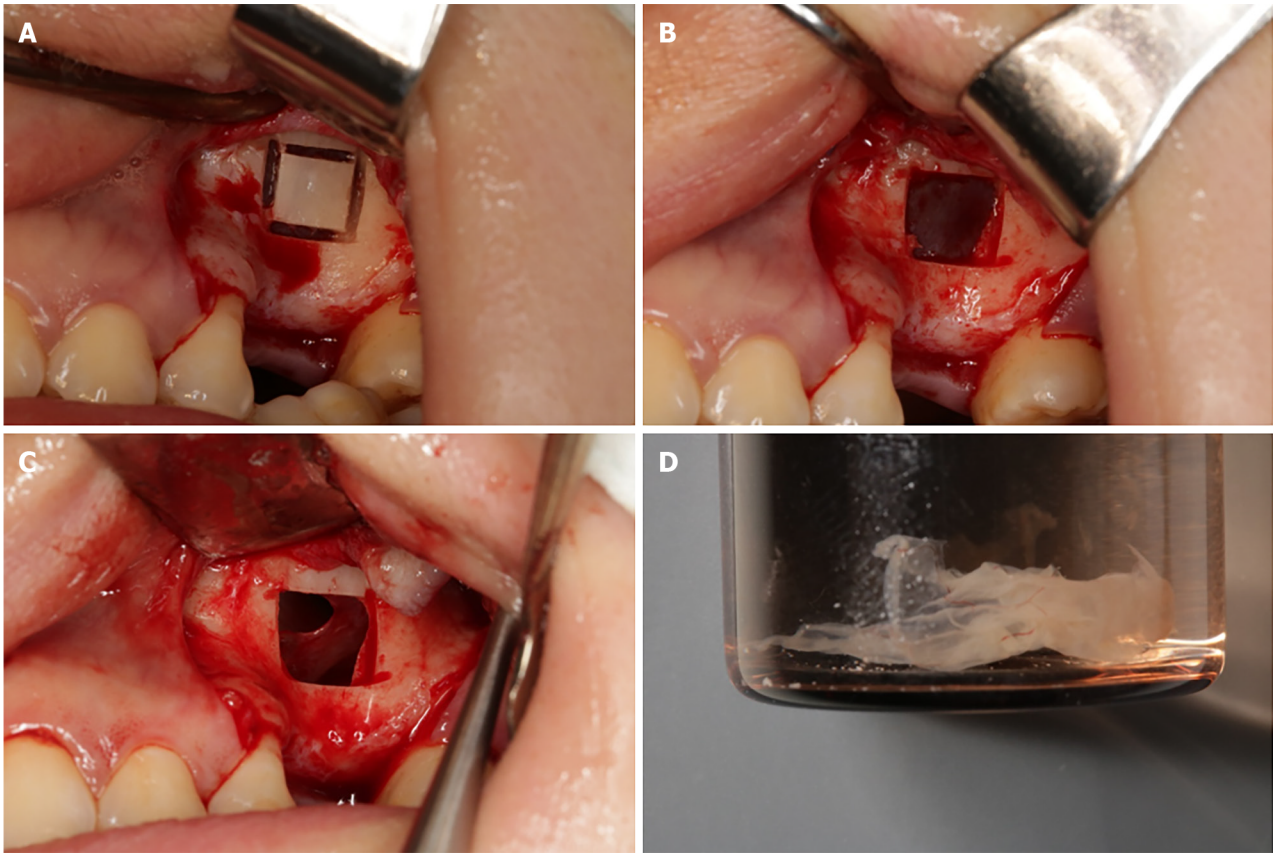

Figure 2 The surgical procedure. A: Ultrasonic bone scalpel delineating the bone window; B: Lifting the bone window to expose the maxillary sinus mucosa; C: Intentionally rupturing the maxillary sinus floor mucosa, revealing a perforation; D: Removed maxillary sinus pseudocyst.

buccal bony plate was gently detached from the maxillary sinus membrane and placed in saline for preservation. The maxillary sinus membrane was then gently and thoroughly elevated. A syringe was used to aspirate fluid from the maxillary sinus cyst by inserting it, while no visible object was extracted. The mucosa on the floor of the maxillary sinus was incised to extract the cyst, revealing perforation in the same mucosal area. The perforation in the mucosa were covered by collagen membrane (Bio-Gide, Geistlich Pharma, Wolhusen, Switzerland), and 1g bone substitutes (Bio-Oss, Geistlich Pharma, Wolhusen, Switzerland) were placed in maxillary sinus cavity (Figure 2).

A micro titanium screw was used to penetrate the center of the bony window and fixed to the buccal side of the alveolar bone in the edentulous area, the space between the bone plate and the alveolar ridge was filled with Bio-Oss bone substitutes and the bone plate were covered with collagen membrane (Bio-Gide, Geistlich Pharma, Wolhusen, Switzerland), and the incision was closed tightly with tension-free sutures (Figure 3). Postoperative instructions and antibiotics were given to the patient.

Nine months later, CBCT showed that the ABH was 15.6 mm and ABW was 10.5 mm. Also, the thickness of sinus membrane was normal and the pseudocyst was disappeared (Figure 4). A Straumann BLT dental implant (Straumann®, 4.1 mm × 10 mm, Switzerland) was placed conventionally. A screw-retained all-ceramic restoration was installed 4 months later (Figure 5).

OUTCOME AND FOLLOW-UP

The 1-year follow-up visit showed that the implant was succeeded according to the criteria proposed by Albrektsson *et al* [13].

DISCUSSION

The lateral bony window in maxillary sinus lift was opened by either a round drill or ultrasonic tips, it was usually treated in the following 4 ways: Elevated into the newly formed sinus cavity, discarded, repositioned after placing the bone graft, or utilized as a bone graft material[14].

Cortical bone tenting is a technique in which a thin cortical bone sheet is anchored to the alveolar bone by titanium nails and the space below is filled with bone graft material[2]. The thin cortical bone sheet provides a "natural biological membrane" effect and allows neovascularization to grow into the bone graft particles. The distance of the bone gain is not

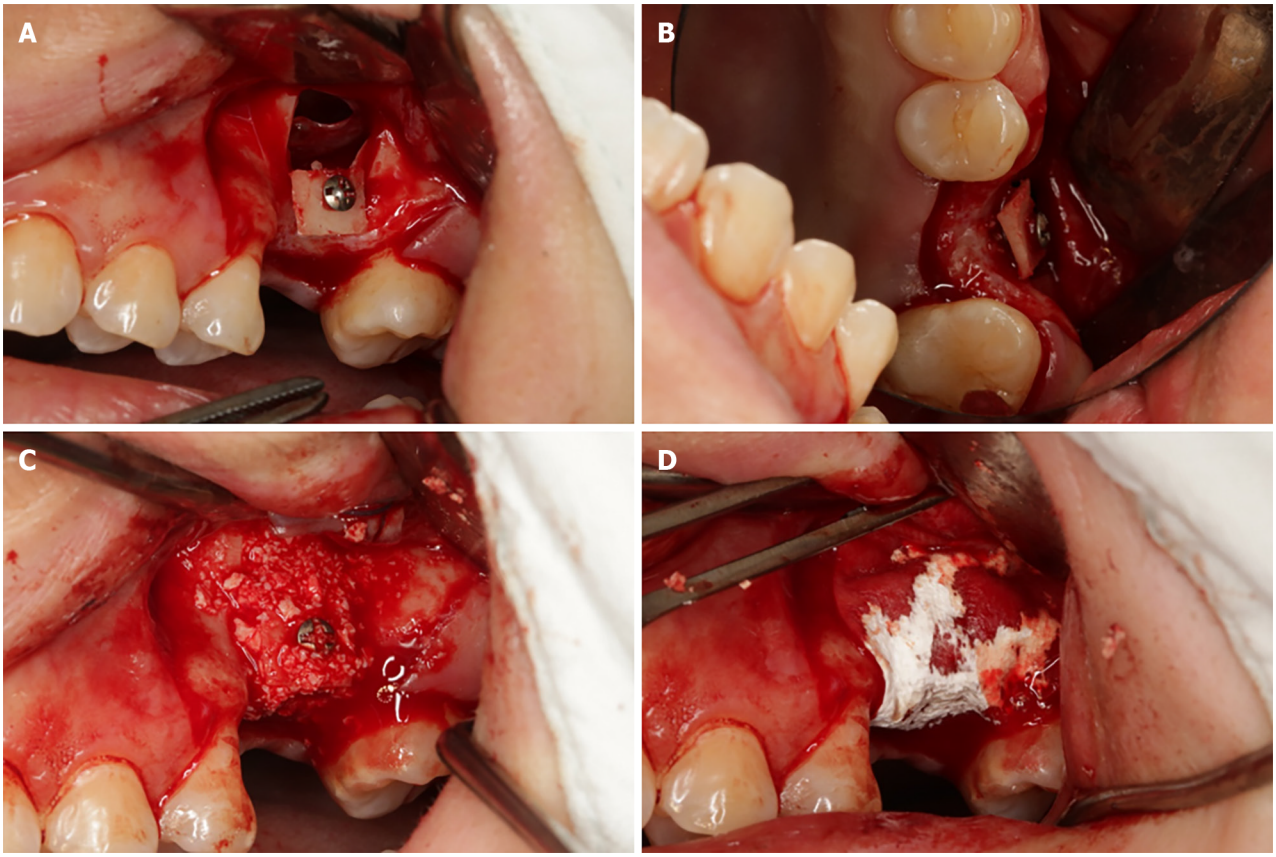

Figure 3 Intraoral photo demonstrating horizontal bone augmentation using cortical bone tenting technique. A: Fixation of the bone window with titanium screw; B: Maintaining a certain distance between the bone window and the buccal aspect of the alveolar ridge; C: Filling the gap with DBBM; D: Covering the defect area with a collagen membrane.

limited by the size of the collected bone mass as in the autologous bone grafting technique, and more bone width and less bone resorption can be achieved than with autologous bone grafting[3,15]. Traditionally, cortical bone plates are taken from the mandibular ramus or the chin. It is reported that the most frequent complication in the donor area is chin paresthesia, primarily associated with grafts harvested from the symphysis[3]. In this case, the bone plate from the lateral wall of the maxillary sinus lift was used for the cortical bone tenting technique without a separate second operative area, which not only reduced the patient's postoperative trauma, but also shortened the operative time and postoperative pain [16,17].

In this case, the largest possibility in the patient's maxillary sinus is most likely a pseudocyst, as the patient is asymptomatic, and it presents a typical well-defined 'dome-shaped' lesion on CBCT imaging. There is currently no consensus on the management regarding such pseudocysts. Some scholars believe that these pseudocysts may potentially lead to infection of bone graft material; therefore, a two-stage treatment approach is recommended[8]. This involves the removal of the cyst first, allowing for healing, followed by maxillary sinus floor elevation surgery. In contrast, studies by other scholars have shown that bone grafting can be performed during the same period of time as the removal of the cyst, with favorable results[9,11]. In this case, there were no contents in the lesion when we aspirated it during operation, and the patient did not have any symptoms preoperatively, so we chose to cover the maxillary membrane perforation with a collagen membrane directly after removing the lesion and perform bone grafting at the same time to minimize the number of surgeries and the patient's waiting period for the missing teeth. The CBCT showed that the pseudocyst was disappeared thoroughly after 9 months, indicating that the lesion had been removed. The patient had no postoperative complications and healed well.

CONCLUSION

The bone plate from lateral window approach for sinus augmentation can be an alternative donor site for severe horizontal bone augmentation in maxillary posterior region. In asymptomatic preoperative pseudocysts in the maxillary sinus and in which no specific intraoperative contents were aspirated, removal of the lesion for simultaneous maxillary sinus floor elevation can also yield good results.

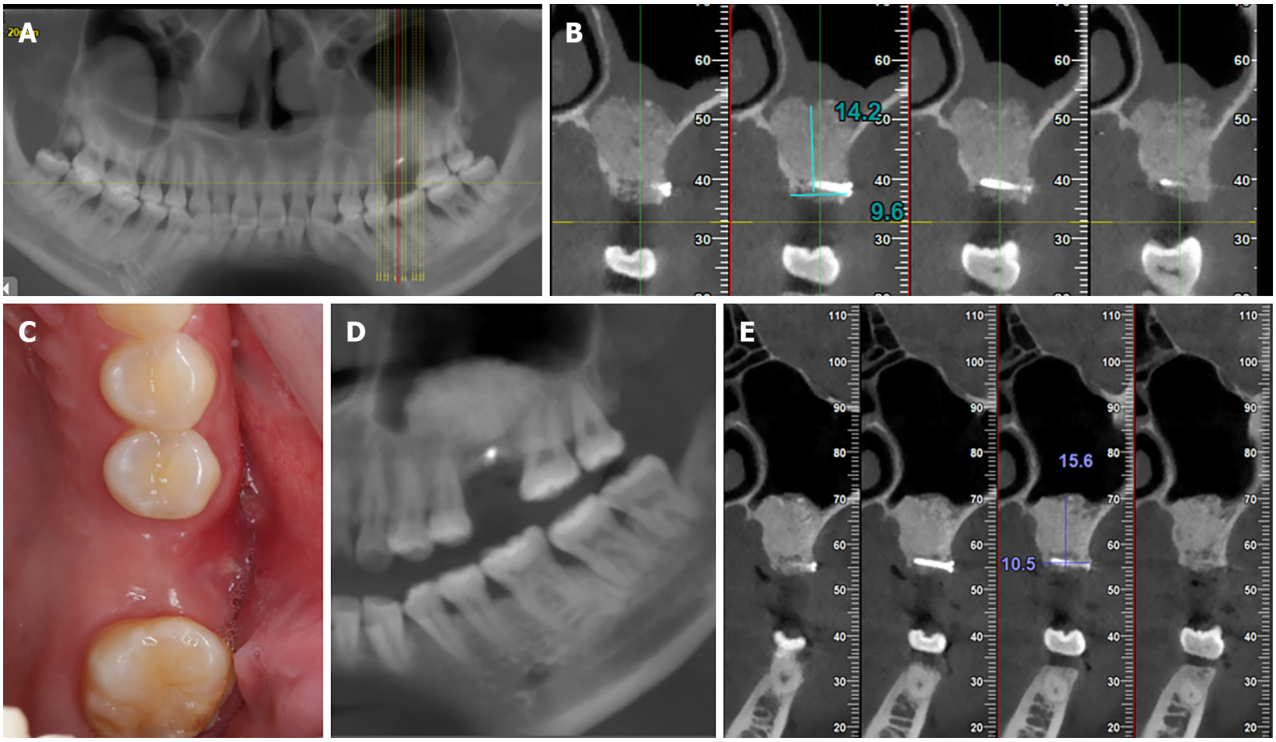

Figure 4 Immediate postoperative and 6-month follow-up. A: Immediate postoperative sagittal cone beam computed tomography (CBCT) image showing the overall condition of the maxillary sinus; B: Immediate postoperative Coronal CBCT image showing the disappearance of the maxillary sinus floor mucosal pseudocyst, with a bone height of 15.8 mm and a bone width of 10.8 mm; C: At 9 months postoperative, adequate alveolar bone width can be observed intraorally; D: A: At 9 months postoperative, sagittal CBCT image showing the overall condition of the maxillary sinus; E: At 9 months postoperative, Coronal CBCT image showing the disappearance of the immediate postoperative maxillary sinus floor mucosal pseudocyst, with a bone height of 15.6 mm and a bone width of 10.5 mm.

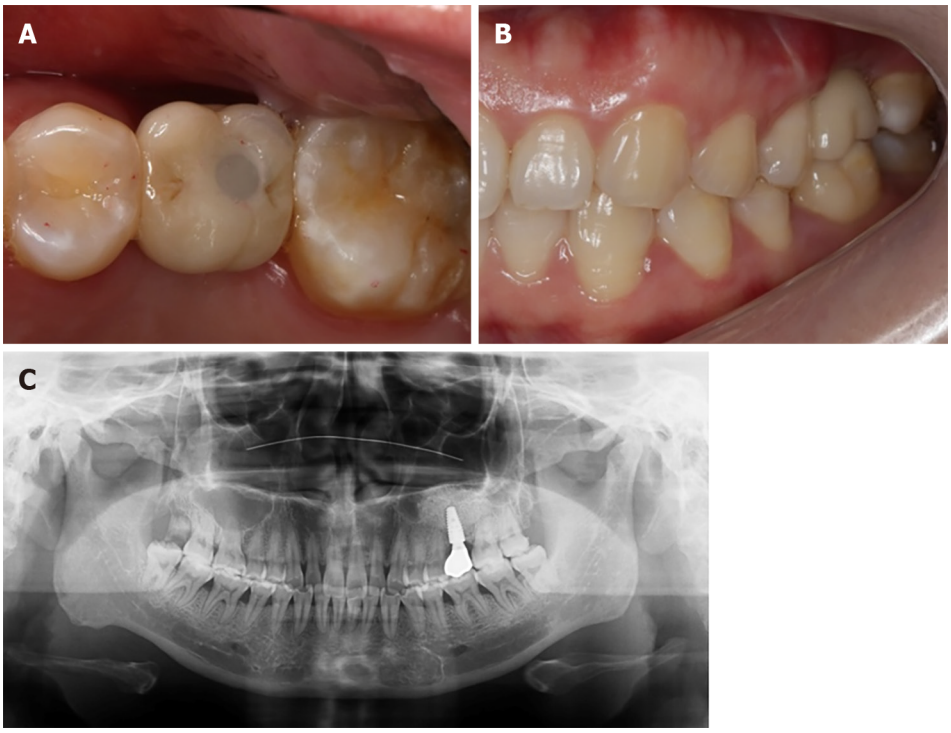

Figure 5 Clinical photos and imaging with final restoration. A: Occlusal view of screw retained all-ceramic restoration; B: Proper occlusion after all-ceramic restoration; C: Panoramic view after restoration showed sufficient bone volume around dental implant.

FOOTNOTES

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follow-up and manuscript writing; Shao WJ contributed to data collection, photo collection, and organization. All authors have read and approve the final manuscript.

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CASE REPORT

Small intestine angioleiomyoma as a rare cause of perforation: A case report

Teng-Yuan Hou, Wei-Juo Tzeng, Pei-Hang Lee

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Abstract

BACKGROUND

Angioleiomyoma is a rare and benign stromal tumor typically found in subcutaneous tissue. It rarely occurs in the gastrointestinal tract. Among the reported cases, the most common complication was gastrointestinal bleeding. Perforation has only been reported as a complication in the last few decades.

CASE SUMMARY

This case report detailed the discovery of intestinal angioleiomyoma in a 47-year-old male presenting with abdominal pain that had persisted for 3 d. After suspecting hollow organ perforation, surgical intervention involving intestinal resection and anastomosis was performed.

CONCLUSION

The report underscores the significance of early surgical intervention in effectively treating angioleiomyoma while emphasizing the pivotal role of timely and appropriate measures for favorable outcomes.

Key Words: Angioleiomyoma; Intestinal perforation; Abdomen; Acute; Diarrhea; Case report

Core Tip: Here we report the first case of angioleiomyoma in the small intestine with a complication of perforation. This type of complication is extremely rare as the last published report of a perforation complication related to angioleiomyoma was published 30 years ago in Russian.

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INTRODUCTION

Angioleiomyomas are a vascular subtype of leiomyomas, categorized as benign smooth muscle tumors. The tumor itself is characterized by inclusion of vessel and smooth muscle cells[1]. Angioleiomyomas mostly arise from the wall of a vein. The majority of cases occur at 30 years to 60 years of age, with female predominance and location in a lower extremity[2]. Although, angioleiomyomas have been found in different organs[3-5]. Within the gastrointestinal tract, occurrences of angioleiomyomas are exceptionally rare[6]. This case report presents the inaugural instance documented in the English literature and details a patient who exhibited hollow organ perforation attributable to angioleiomyoma.

CASE PRESENTATION

Chief complaints

A 47-year-old male presented with lower abdominal pain and diarrhea.

History of present illness

The patient reported that his symptoms started 3 d prior to presentation, with both gradually progressing over that period. He also reported having a fever that would go up to 39 °C for 1 wk.

History of past illness

The patient had a medical history of controlled hypertension for many years.

Personal and family history

The patient's personal and family history was unremarkable.

Physical examination

The physical examination revealed the following: Body temperature, 36.7 °C; heart rate, 105 beats/min; respiratory rate, 18 breaths/min; and blood pressure, 125/80 mmHg. The skin and mucous membranes were free of yellow staining, rash, bleeding spots, liver palms, and spider nevus. Chest breathing was normal. However, the tenderness over the low abdomen and rebounding pain was mentioned.

Laboratory examinations

Laboratory tests indicated elevated C-reactive protein (335 mg/L; normal range: < 5 mg/L) and increased creatinine (1.81 mg/dL; normal range: 0.64 mg/dL-1.27 mg/dL).

Imaging examinations

Computed tomography (CT) showed pneumoperitoneum and a mass over the pelvic area (Figure 1).

FINAL DIAGNOSIS

Ileum angioleiomyoma with complications of perforation and pneumoperitoneum.

TREATMENT

We initially suspected a perforation associated with sigmoid colon cancer. Therefore, surgical intervention was initiated approximately 7 h after admission. An exploratory laparotomy revealed a tumor, measuring 8 cm × 5 cm, located 70 cm from the ileocecal valve. It was surrounded by an abscess formation (Figure 2). A thorough examination of the stomach,

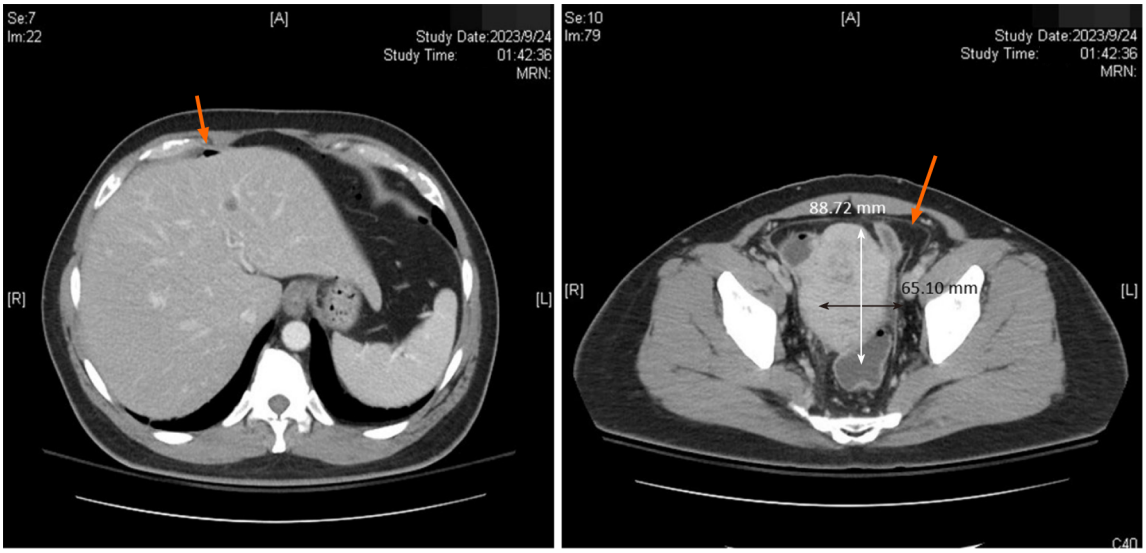

Figure 1 Computed tomography before the operation. A: Pneumoperitoneum (orange arrow); B: One 6.8 cm × 6.5 cm mass over the pelvic area (orange arrow).

intestine, and colon did not reveal additional perforation. The tumor was excised followed by end-to-end anastomosis.

OUTCOME AND FOLLOW-UP

Postoperatively, the patient was transferred to the ward for continued care and was discharged 2 wk after the operation. The patient returned to our clinic for follow-up after 2 wk without complaint of abdominal pain, nausea nor vomiting. The immunohistochemical analysis of the resected specimen corroborated the diagnosis of angioleiomyoma.

DISCUSSION

Leiomyomas are most frequently located in the uterine myometrium (95.0%), followed by the skin (3.0%) and the gastrointestinal tract (1.5%)[6]. In 1969, the World Health Organization defined leiomyomas as well-circumscribed benign tumors composed of bundles of mature smooth muscle cells. The World Health Organization classification includes three main groups: Solid leiomyoma; vascular leiomyoma (angioleiomyoma); and epithelioid leiomyoma (leiomyoblastoma) [7]. Angioleiomyoma, initially described by Stout[8] in 1937, commonly affects the skin and subcutaneous tissue of the lower extremities. Its presence in the gastrointestinal tract is exceptionally rare. Angioleiomyomas in the gastrointestinal tract occur predominantly in the jejunum (44%), followed by the ileum (37%) and the duodenum (19%).

Four distinct subtypes of angioleiomyoma have been identified[2]. The first type is capillary or solid angioleiomyomas. They are characterized by a rich stratification of smooth muscle cells surrounding a few slit-like vascular channels. This subtype is the most common. The second type is venous angioleiomyomas, which is distinguished by more vascular channels and walls that are thicker compared to capillary angioleiomyomas. The third type is cavernous angioleiomyomas, and this subtype features widened vascular channels surrounded by a thin layer of smooth muscle cells. The fourth type is combined capillary and venous angioleiomyomas[9,10].

Our patient was diagnosed with cavernous angioleiomyoma based on histological findings. Sections showed ileal tissue with a well-circumscribed subserosal tumor composed of proliferative spindle smooth muscle cells bearing brightly eosinophilic cytoplasm and arranged in fascicles, punctuated by variable-sized vascular channels. The vessels were irregularly dilated with attenuated walls. There was also a lack of a thick muscular wall (Figure 3).

The clinical presentation of angioleiomyoma is diverse. Uncomplicated cases are typically asymptomatic. However, a limited number of reported cases exhibit rare clinical presentations. Therefore, it is challenging to establish comprehensive clinical features and complication rates. Only 10 cases of gastrointestinal angioleiomyoma have been documented in the literature. Table 1 compares these cases with our own.

Gastrointestinal bleeding is the most commonly reported complication associated with angioleiomyoma. Past cases have reported other complications, such as intussusception and prolapse. Notably, our case represents the first reported instance of angioleiomyoma-related perforation in the English literature.

In our case, preoperative imaging, specifically CT, revealed a lesion located in the pelvic region accompanied by pneumoperitoneum. We initially suspected malignancy-related hollow organ perforation. Despite the absence of tarry or bloody stool reported by the patient, CT indicated a tumor of 9.5 cm × 6.5 cm × 6.4 cm in size that was surrounded by abscess.

Table 1 Case list of angioleiomyoma in the gastrointestinal tract

Ref.	Age, sex	Location	Complication	Diagnosis	Treatment
Valnicek[11], 1959	NA	Small bowel	GIB	NA	NA
Gădăleanu and Popescu [12], 1988	31, female	Duodenojejunal flexture	GIB	Laparotomy	2 stages: (1) Tumor vascular pedicle ligation; and (2) Resection
Sapelkin[13], 1989	NA	Small bowel	Perforation	NA	NA
Pidoprigora *et al*[14], 1995	NA	Small bowel	GIB	NA	NA
Sadat *et al*[9], 2007	58, female	Ileum	GIB	Angiography	Resection
Nakatani *et al*[15], 2010	45, female	Ileum	GIB	Capsule endoscopy + double-balloon enteroscopy	Resection
Turan *et al*[16], 2010	Age not known, female	Ileum	Intussusception	CT	Resection
Stanojević *et al*[17], 2013	40, female	Rectum	Prolapse	Clinical	Tumor excision
Gachabayov and Mityushin [18], 2016	21, male	Jejunum	GIB	CT	Resection
Shao *et al*[19], 2018	42, male	Jejunum	GIB	Double balloon enteroscopy	Resection
Our case	47, male	Ileum	Perforation	CT	Resection

CT: Computed tomography; GIB: Gastrointestinal bleeding; NA: Not available.

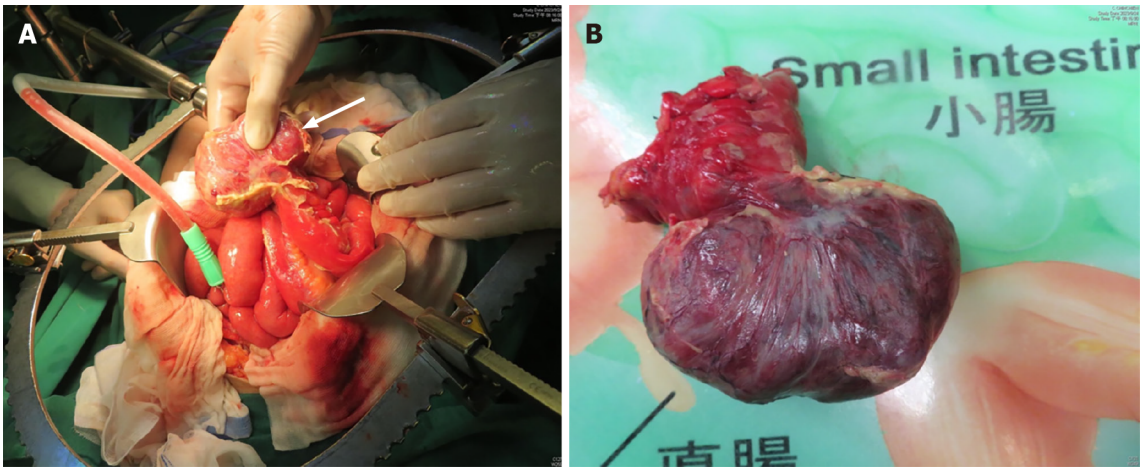

Figure 2 Gross appearance during the operation. A: Pelvic mass surrounded by an abscess (white arrow); B: The tumor and a small section of the ileum was resected.

Surgical resection of the affected bowel segment is the typical treatment to manage the angioleiomyoma and any accompanying complications. Resection is typically followed by side-to-side anastomosis, which was also performed in our case. Given the initial suspicion of hollow organ perforation, a comprehensive inspection of the entire abdomen was essential to identify potential perforations caused by other etiologies. This thorough examination was crucial to ensure an accurate diagnosis and appropriate intervention.

CONCLUSION

In summary, small bowel angioleiomyoma is a rare occurrence. Perforation is also a rare complication related to angioleiomyoma. Nonetheless, early surgical intervention plays a crucial role in the effective treatment of angioleiomyoma. Timely and appropriate surgical measures are pivotal for a favorable outcome in such cases.

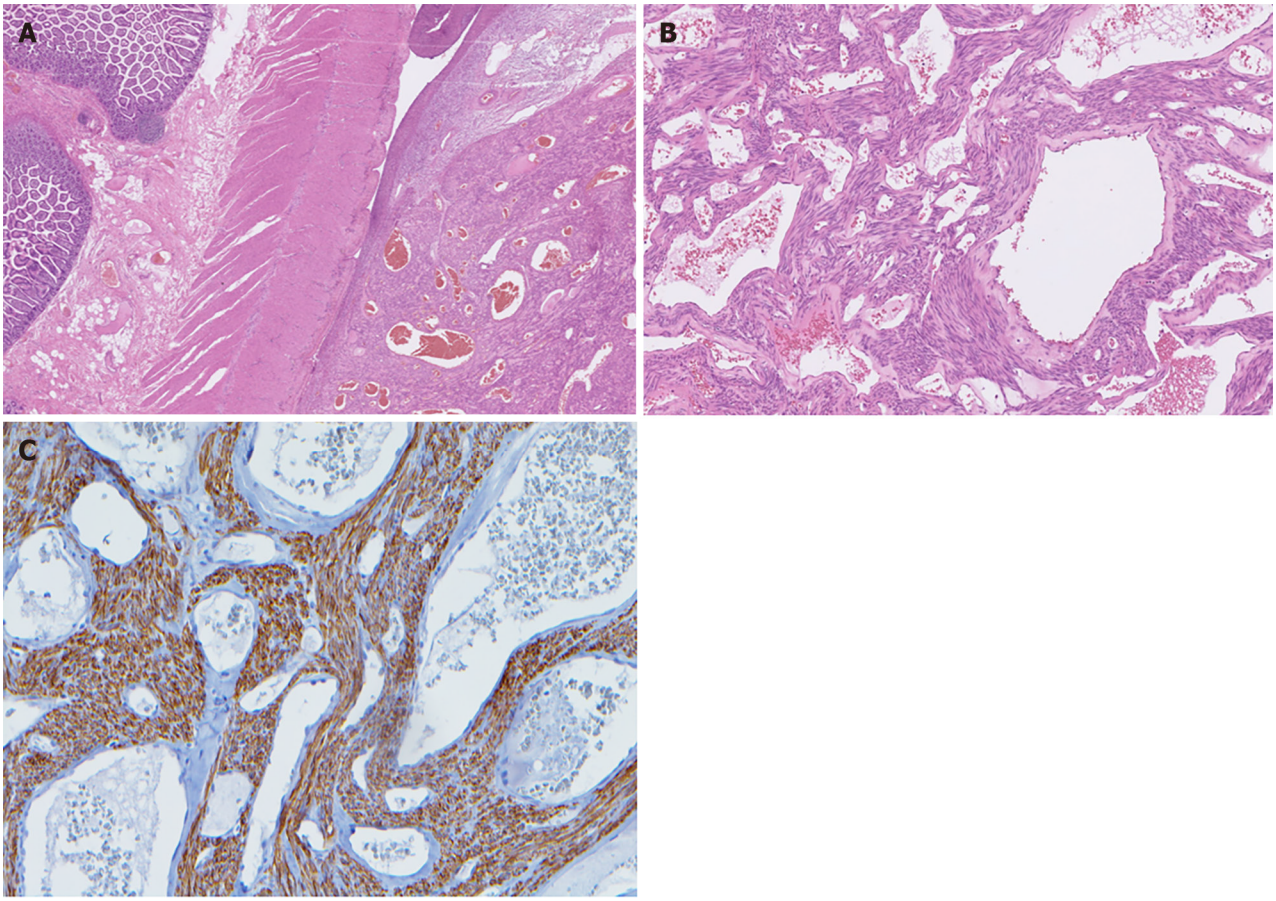

Figure 3 Histopathology of angioleiomyoma. A: Ileal tissue with a well-circumscribed subserosal tumor; B: Proliferative spindle smooth muscle cells bearing brightly eosinophilic cytoplasm and arranged in fascicles, punctuated by variable-sized vascular channels. The vessels were irregularly dilated with attenuated walls; C: The proliferative smooth muscle cells were highlighted by desmin immunostaining, while the cavernous vascular channels lacked a well-formed muscular wall.

FOOTNOTES

Author contributions: Hou TY designed the report; Lee PH analyzed the histological images; Tzeng WJ analyzed the data and wrote the paper; All authors read and approved the final manuscript.

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CASE REPORT

Crossed renal ectopia with rectal cancer: A case report

Zhen-Wei Tang, Hui-Feng Yang, Zhao-Yu Wu, Chang-You Wang

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Abstract

BACKGROUND

Crossed renal ectopia (CRE) occurs when one kidney crosses the midline from the primary side to the contralateral side while the ureter remains on the primary side. Rectal cancer, one of the most common malignant tumors of the digestive tract, refers to cancer from the dentate line to the rectosigmoid junction. The concurrent presentation of CRE alongside rectal cancer is an uncommon clinical observation.

CASE SUMMARY

Herein, we report a 69-year-old male patient with rectal cancer who was diagnosed with CRE *via* computed tomography during hospitalization. Following thorough preoperative evaluations, the patient underwent Dixon surgery.

CONCLUSION

We performed laparoscopic radical resection of rectal cancer and adequate lymph node removal in a patient with CRE with no postoperative discomfort.

Key Words: Rectal cancer; Crossed renal ectopia; Anatomy; Laparoscopic surgery; Case report

Core Tip: Rectal cancer is a common malignant tumor in clinical practice, and current treatment methods mainly include surgery and chemotherapy. The occurrence of rectal cancer in conjunction with crossed renal ectopia (CRE) is exceedingly rare. We reported a patient with rectal cancer who underwent CRE and Dixon surgery.

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INTRODUCTION

Crossed renal ectopia (CRE) involves the translocation of one kidney from its original side across the midline to the contralateral side. Contrary to what the term might suggest, the kidneys do not actually "cross" each other; instead, one kidney shifts to the same side as the other. Any colon surgery for such patients must take into account possible anatomical abnormalities, such as abnormalities in the renal vessels and variations in the position of the ureter. For patients with CRE, in addition to ensuring an adequate resection margin of the tumor, attention should be given to the protection of blood vessels and nerves in the surrounding organs, and appropriate enlarged combined resection may be performed when necessary. Consequently, conducting a thorough preoperative assessment and formulating a meticulous surgical strategy are of paramount importance. In Japan, Nakai *et al*[1] reported the laparoscopic treatment of a patient with CRE complicated with sigmoid carcinoma; however, instances of combined laparoscopic treatment for CRE complicated by rectal cancer have yet to be documented.

In this paper, we report a case of CRE with rectal cancer treated by laparoscopic surgery without any postoperative complications.

CASE PRESENTATION

Chief complaints

A one-month history of frequent bowel movements and the passage of dark red bloody stools, with no apparent cause.

History of present illness

A 69-year-old male experienced an increase in the frequency of defecation-approximately 2-3 times/d-mainly due to no obvious cause before 1 month-dark red stool with blood.

History of past illness

The patient had lost 10 pounds in weight in the past five months.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

On physical examination, the vital signs were as follows: body temperature, 36.5 °C; blood pressure, 135/78 mmHg; heart rate, 74 beats per minute; and breathing, 15 breaths per minute. The abdomen was soft, no mass was palpated, and no obvious abnormalities were found on anal examination.

Laboratory examinations

Routine laboratory tests showed no abnormal values, and evaluation of tumor markers revealed a high level of carcinoembryonic antigen of 10.1 ng/mL (standard value 0-3.4 ng/mL) and no other significant abnormalities.

Imaging examinations

Colonoscopy revealed a peripheral mass approximately 12 cm away from the anal margin (Figure 1A); gastrointestinal angiography revealed space-occupying lesions in the rectum (Figure 1B); colonoscopy revealed moderately differentiated adenocarcinoma. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) of the rectum suggested local thickening of the rectum and neoplastic lesions in the middle and upper parts of the rectum, which was considered rectal cancer (T3) (Figure 1C and D). Multiple nodules were observed in the mesorectum, presacral fascia, and bilateral iliac vessels and were considered metastatic lymph nodes (N+), but contrast-enhanced CT also revealed no renal shadow in the right kidney area; additionally, no renal shadow was found in the left lower abdomen or pelvis, and the shape of the kidney was irregular (Figure 2A and B). Subsequently, we performed enhanced MRI of the abdomen and pelvis of the patient, first, to rule out the possibility of liver metastasis that could not be detected by CT, and second, to take a closer look at blood vessels. There was no renal shadow in the right kidney area, and a shadow in the left abdominal or pelvic kidney was considered. A CRE with malrotation and an abnormal internal signal was considered. The left renal vein ran behind the abdominal aorta, suggesting posterior nutcracker syndrome (Figure 2C).

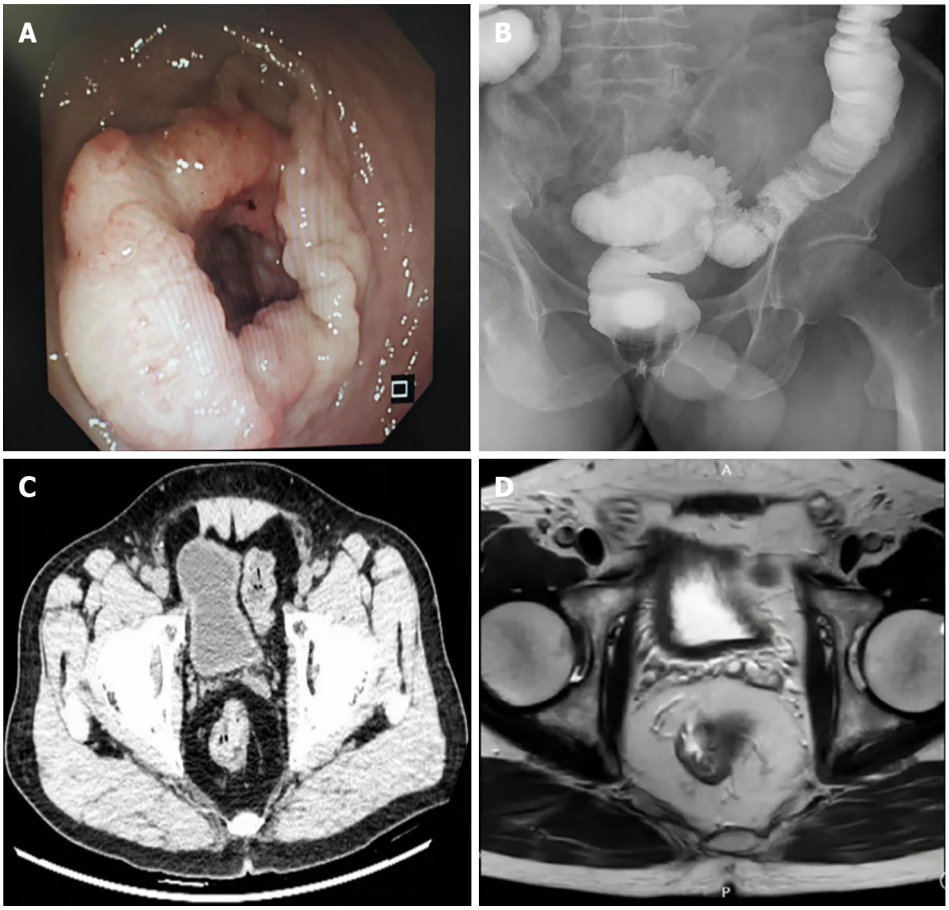

Figure 1 Imaging and endoscopic examination of rectal cancer. A: Colonoscopy shows a continuous intestinal mass 12 cm away from the anal margin; B: Digestive tract imaging shows rectal space-occupying lesions; C: Abdominal contrast-enhanced computed tomography shows rectal mass; D: Abdominal enhanced magnetic resonance imaging shows rectal mass.

Further diagnostic work-up

The patient was diagnosed with rectal cancer (cT3N + M0) combined with CRE and underwent laparoscopic radical resection of rectal cancer combined with D3 Lymph node dissection. During Toldt's space separation, a blood vessel very similar to the inferior mesenteric artery (IMA) was found. At the time, given the patient's anatomical variations, the surgeon opted not to dissect the blood vessel. Instead, the separation was conducted laterally and anteriorly to Gerota's fascia, proceeding from the exterior towards the interior, and the posterior kidney and ureter were protected during the operation. With internal and lateral penetration, we found that the blood vessels that were not severed at the beginning were the veins of the ectopic kidney. Then, we safely severed the IMA, protected the hypogastric nerves on both sides, ensured a sufficient tumor resection margin, severed the intestinal tube, and sent specimens for pathology. The remaining descending colon and rectum were moved toward the pelvis, and the descending colon and remaining rectum were anastomosed end to end. The operation time was 190 min, and the blood loss volume was 20 mL. Postoperative pathological findings revealed that the tumor was a moderately differentiated rectal ulcerative adenocarcinoma with a size of 5 cm × 3.5 cm × 1.5 cm. The tumor penetrated deep myometria and reached the peri-intestinal fat (pT3), nerve invasion and vascular cancer thrombus were visible, and no lymph node metastasis (pN0) was observed around it, corresponding to stage pIIA. The immunohistochemical results were as follows: MLH1 (+), MSH2 (+), MSH6 (+), PMS2 (+); the Ki-67 index was 80%.

FINAL DIAGNOSIS

Based on the patient's medical history, the final diagnosis was rectal cancer with CRE.

TREATMENT

The patient was discharged from the hospital on the 7th day after surgery. Considering the risk factors associated with neuroaggression, the patient was advised to receive XELOX chemotherapy after surgery.

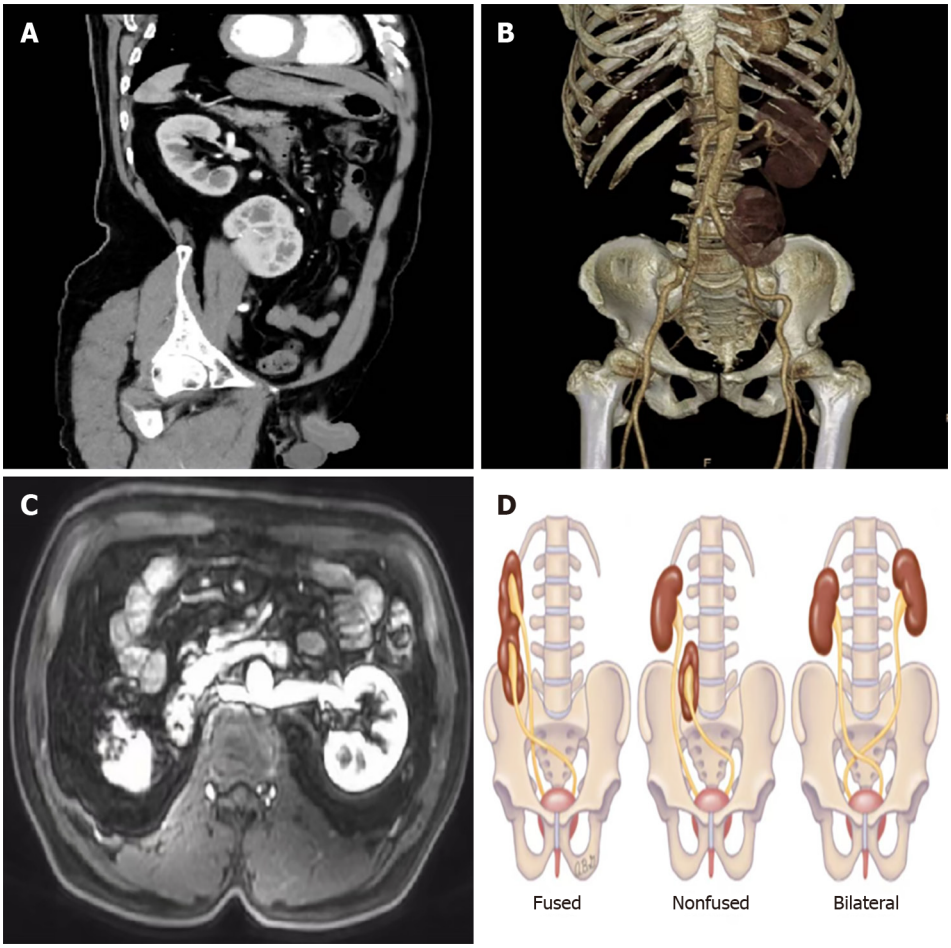

Figure 2 Imaging examination and example images of crossed renal ectopia. A: Abdominal contrast-enhanced computed tomography Indicating crossed renal ectopia (CRE); B: Three dimensional imaging shows both kidneys on the left side; C: The left renal vein is located behind the abdominal aorta; D: Schematic diagram of CRE.

OUTCOME AND FOLLOW-UP

Currently, the follow-up patients are still alive.

DISCUSSION

CRE is a rare congenital genitourinary malformation. Its reported incidence is approximately 1 in 2000 individuals, with most cases being identified at autopsy[2]. There is a male-to-female ratio of approximately 3:2[3] and CRE can be classified into fusion type, nonfusion type and bilateral type. The nonconfluent type refers to an ectopic kidney that crosses the midline but does not integrate with the normal kidney parenchyma. The ureter of the ectopic kidney descends and crosses the midline, but the ureter drains into the bladder in a normal position. In the fused type, the ectopic kidney is usually fused below the normal kidney. Approximately 90% of these lesions are fused, which is commonly observed in the left kidney to the right ectopic fusion[4]. In the bilateral type, both kidneys are ectopic and cross the midline with the ureter to maintain normal bladder insertion (Figure 2D). This patient rarely had a right kidney to the left that was not fused, and some CREs can be accompanied by renal tumors, which are more common in adults. Clear cell carcinoma is the most common histological type and is rare in children, with the main type being Wilms tumor[5].

CRE is usually found incidentally during the investigation of other genitourinary problems, and approximately half of the patients experience other complications, such as kidney stones, hydronephrosis, and frequent urinary tract infections, for which surgical treatment may be the best choice[6]. Fortunately, none of the above symptoms were present in this patient.

Therefore, for patients with CRE, anatomical variation increases the risk and difficulty of colon surgery. The most important difference between the IMA and both kidneys is the difference in treatment because, for rectal surgery, 253 lymph nodes located at the root of the IMA sometimes need to be dissected to ensure the quality of D3 Lymph node dissection in rectal cancer patients. Therefore, the anatomical relationship between them must be clarified[6]. Maeda *et al* [7] reported a patient with a horseshoe kidney with sigmoid colon cancer who benefited from preoperative three dimensional (3D) angiography. Because a horseshoe kidney is usually accompanied by abnormalities in blood vessels or

the ureter, angiography helps determine the location of these structures. Giani *et al*[8] performed anterior rectal resection surgery on patients with cross-fusion ectopic kidneys using 3D laparoscopy, and 3D laparoscopy technology also provided assurance of surgical safety. In our patient, the location of the IMA during the operation was unclear. For safety, the lateral approach was decisively changed to ensure that there was no wrong vessel. If necessary, open surgery may be considered to ensure a safe radical operation.

During intestinal surgery on patients with CRE, it is imperative to exercise caution to prevent injury to the ectopic kidney, ureter, renal vessels, genital vessels, and other structures located behind the peritoneum. Typically, the appropriate anatomical space for intervention is Toldt's space anterior to Gerota's fascia. If the dissection is too deep, there is a risk of damaging retroperitoneal structures, whereas if it is too superficial, it may result in tumor leakage. Additionally, special attention should be paid to safeguarding the bilateral hypogastric nerves adjacent to the bilateral common iliac vessels to minimize the impact on urinary and reproductive functions.

CONCLUSION

We recommend that patients with CRE or other renal malformations undergo a comprehensive preoperative evaluation to formulate a detailed surgical plan, and relevant angiography should be performed if necessary before surgical treatment in accordance with the above principles.

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FOOTNOTES

Author contributions: Tang ZW contributed to manuscript writing and editing, and data collection; Yang HF contributed to data analysis; Wu ZY and Wang CY contributed to conceptualization and supervision. All authors have read and approved the final manuscript.

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CASE REPORT

Systemic lupus erythematosus in a 15-year-old female with multiple splenic nodules: A case report

Mi Il Kang, Hyeok Chan Kwon

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Abstract

BACKGROUND

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease primarily affecting young females. SLE can invade any organ, and various forms of splenic invasion have been reported. Manifestations include splenomegaly and splenic infarction, rupture, and calcification. The study encountered a rare case of splenic involvement, with nodules of various sizes without calcifications or ruptures.

CASE SUMMARY

A 15-year-old girl presented with arthralgia, weight loss, fever, increased levels of inflammatory markers, and positive antinuclear antibody test results. The patient was diagnosed with SLE. She was asymptomatic while taking steroids and hydroxychloroquine. Ten months after discharge, the patient developed a fever and abdominal pain. Lupus enteritis was suspected, and abdominopelvic computed tomography (AP-CT) was performed. There were no specific findings in the gastrointestinal tract, but multiple splenic nodules were observed. Infection or hemangioma was considered; however, no specific radiological findings were observed. A biopsy of the spleen was performed to determine the possibility of malignancy. The histological findings of the spleen included extensive periarteriolar necrosis with hematoxylin bodies and numerous karyorrhectic debris. Based on the biopsy results, the patient was diagnosed with an SLE flare-up and was maintained on high-dose steroids and immunosuppressants.

CONCLUSION

As disease activity increased, multiple nodules in the spleen that were previously unseen were observed using AP-CT and histologically confirmed. Spleen invasion by SLE can appear in multiple nodular forms and patterns. Therefore, physicians should consider these findings when differentiating these nodules from infections

and malignancies.

Key Words: Multiple nodules; Spleen; Splenectomy; Systemic lupus erythematosus; Differential diagnosis; Case report

Core Tip: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease primarily affecting young females. Here, the study reports a rare case of a 15-year-old female with SLE. During follow-up, the patient developed splenic involvement with nodules of various sizes, which are not typical manifestations. The patient was diagnosed with an SLE flare-up and was maintained on high-dose steroids. The study emphasizes the importance of an accurate diagnosis and careful observation of rare splenic manifestations of SLE.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease mainly affecting young females, including those of childbearing age[1]. SLE is commonly observed in children, and less than 20% of all cases occur at a young age[2]. SLE can invade organs of the body, resulting in various symptoms. Spleen invasion often manifests as splenomegaly, splenic infarction, and rupture[3]. Similar to other rheumatic diseases, such as rheumatoid arthritis and systemic sclerosis, splenic calcification may occur in SLE[4]. It is often necessary to differentiate SLE from other diseases, such as infections or malignancies; thus, understanding the various clinical findings in the affected organs is crucial. Herein, the study reports a rare case of splenic involvement with nodules of various sizes in a 15-year-old girl with SLE.

CASE PRESENTATION

Chief complaints

A 15-year-old female patient presented to the Department of Rheumatology with a 3-month history of multiple articular pain and weight loss.

History of present illness

The patient was admitted to our hospital. Approximately 3 months before admission, she experienced weight loss of 6 kg and pain in both shoulders and knees. She had left pleural pain and a fever of up to 38.3 °C that began 2 wk before admission. She also had bilateral pelvic pain that began 1 wk before admission.

History of past illness

She had no relevant medical history.

Personal and family history

Personal or family history was unremarkable.

Physical examination

Physical examination revealed a blood pressure of 100/66 mmHg, pulse rate of 115 beats/min, and respiratory rate of 20 breaths/min. Her body temperature was 36.5 °C at the time of admission.

Laboratory examinations

Laboratory results showed normal levels of white blood cells (3.89 × 10^3/μL); lymphocytes (0.65 × 10^3/μL); hemoglobin (8.6 g/dL); platelet (331 × 10^3/μL); C-reactive protein (1.25 mg/dL); erythrocyte sedimentation rate (63 mm/h); serum creatinine (0.43 mg/dL); antinuclear antibodies (1:1280 with a homogeneous pattern); anti-double-stranded DNA antibodies (2470.4 IU/mL) (normal range < 7); complement component 3 (70.6 mg/dL) (normal range: 70-206); and complement component 4 (6.3 mg/dL) (normal range: 11-61). The patient tested positive for anti-cardiolipin IgG (46.0 GPL) (normal range < 23), anti-Ro (2.43 AI) (normal range ≤ 0.90), anti-La (6.60 AI) (normal range ≤ 0.90), anti-Smith (1.93 AI) (normal range ≤ 0.90), and anti-RNP antibodies (6.69 AI) (normal range ≤ 0.90). Proteinuria was not observed on urinalysis. All bacterial cultures and tuberculosis yielded negative results.

Imaging examinations

Left costophrenic angle blunting was observed during chest examination, and electrocardiography showed sinus tachycardia.

FINAL DIAGNOSIS

SLE was diagnosed based on clinical symptoms, antibody test results, and blood test results, according to the 2012 Systemic Lupus International Collaborating Clinics criteria[5].

TREATMENT

High-dose steroids, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs were administered, and almost all symptoms improved. After the prednisolone dose reduction to 20 mg, outpatient follow-up was performed every 2 or 4 wk. Afterward, the prednisolone dose was gradually reduced to 5 mg. Additionally, the interval between outpatient visits was increased to 2 months. Topical tacrolimus was administered because of facial malar rash and photosensitivity.

OUTCOME AND FOLLOW-UP

Two months after the last visit, she presented to the hospital with nausea, abdominal pain, weight loss of 3 kg, and a fever of up to 38.2 °C. Abdominopelvic computed tomography (AP-CT) was performed to rule out lupus gastroenteritis or other infections. Imaging revealed no specific findings in the gastrointestinal tract. However, splenomegaly with a maximum diameter of 11.8 cm was observed. Additionally, several round, low-density nodules with a maximum diameter of 4 cm were observed in the spleen (Figure 1). The results of the interferon-gamma release assay, cytomegalovirus polymerase chain reaction, and Epstein-Barr virus polymerase chain reaction were all negative, and reticulocytes were normal. According to the radiologist, it was necessary to differentiate between hemangiomas and hematologic malignancies in the splenic nodules. First, a red blood cell single-photon emission computed tomography (CT) was performed to discriminate between hemangiomas. Cold lesions were found, and hemangiomas were excluded. Hematologic malignancy could not be ruled out; therefore, positron emission tomography-CT (PET-CT) was performed, and the left sternoclavicular lymph node [maximum standardized uptake value corrected for lean body mass (SULmax), 3.6], right axillary lymph node (SULmax, 2.7), and splenic fluorodeoxyglucose (FDG) uptake (SULmax, 3.1) increased (Figure 2). A sternoclavicular lymph node biopsy was performed because the possibility of lymphoma could not be ruled out. Histological findings revealed extensive subcapsular necrosis with hematoxylin bodies, suggesting a high possibility of SLE (Figure 3), and a scheduled splenectomy was performed after the pneumococcal vaccination was administered. Macroscopic examination of the spleen revealed round nodules without calcification or rupture of approximately 13 cm × 8 cm in diameter (Figure 4). The histological findings of the spleen included extensive periarteriolar necrosis with hematoxylin bodies and numerous karyorrhectic debris. These findings were diagnostic of SLE activation; however, there were no findings suggestive of infection or malignancy (Figure 5). Subsequently, the patient was diagnosed with an SLE flare-up, and high-dose steroids and immunosuppressants were administered. Since then, the overall symptoms have improved, and she has been undergoing follow-up without any specific symptoms.

DISCUSSION

SLE can invade multiple organs and presents with various clinical symptoms and imaging findings. Previous case reports have described calcified fibrotic nodules of various sizes in the spleen of patients with SLE[4,6]. Splenic calcifications form granulomas caused by histoplasma infection; other causes include tuberculosis, Brucella infection, and auto-infarction[6]. However, there were no suggestive findings or history of infection in this case. Splenomegaly is common in patients with SLE. It is associated with lymphoid hyperplasia, enlarged lymphoid follicles, and SLE activation. The activation of macrophages and plasma cells around the arterioles also contributes to splenomegaly[3]. In this case, the previously reported splenic calcifications, ruptures, and atrophy were not observed. As far as we know, there have been no splenic multiple nodules that were not accompanied by these changes. Instead, AP-CT revealed round, low-density nodules of various sizes and splenomegaly. Lymphoma could not be ruled out because of the increased FDG uptake in the spleen and various lymph nodes observed on PET-CT. PET-CT has also shown lymphadenopathy and increased FDG uptake in patients with SLE[7]. Furthermore, the risk of non-Hodgkin lymphoma has been reported to increase in patients with SLE[8,9]. Additionally, because changes in the shape of nodules of various sizes in the spleen were not previously known to be associated with SLE flare-ups, a biopsy was performed to confirm the diagnosis. One study reported a low-density splenic nodule in a patient with lupus. However, aseptic necrosis and infarction were also observed[10]. Many SLE patients show positive antiphospholipid antibodies, and these antibodies are involved in splenic infarction and necrosis through the upregulation of surface adhesion molecules and the release of proinflammatory cytokines and procoagulants[11-13]. In this case, periarteriolar necrosis was observed during histological examination, but infarction,

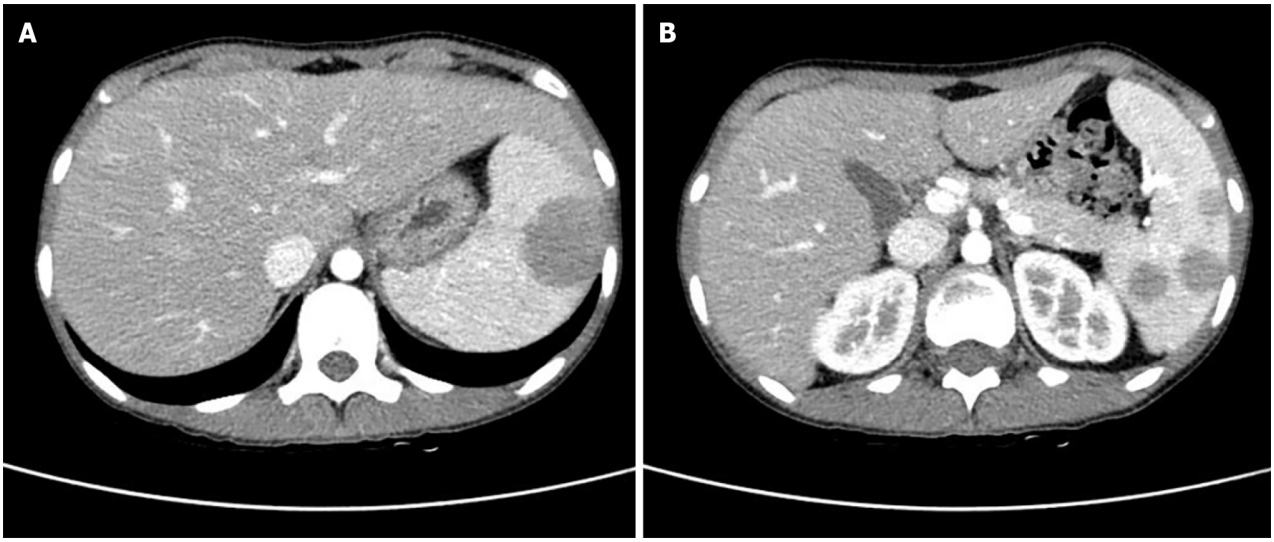

Figure 1 Abdominopelvic computed tomography images of the patient. A and B: Multiple low-density nodules up to 4 cm in the spleen.

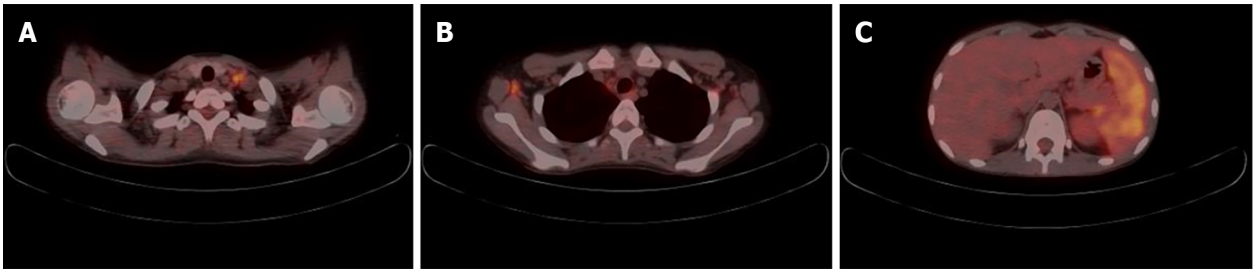

Figure 2 Positron emission tomography-computed tomography images of the patient. A: Multiple hypermetabolic lymph nodes of various sizes along the left supraclavicular lymph node (SULmax, 3.6); B: Right axillary lymph node (SULmax, 2.7); C: Uneven hypermetabolic activities (SULmax, 3.1) observed in the spleen.

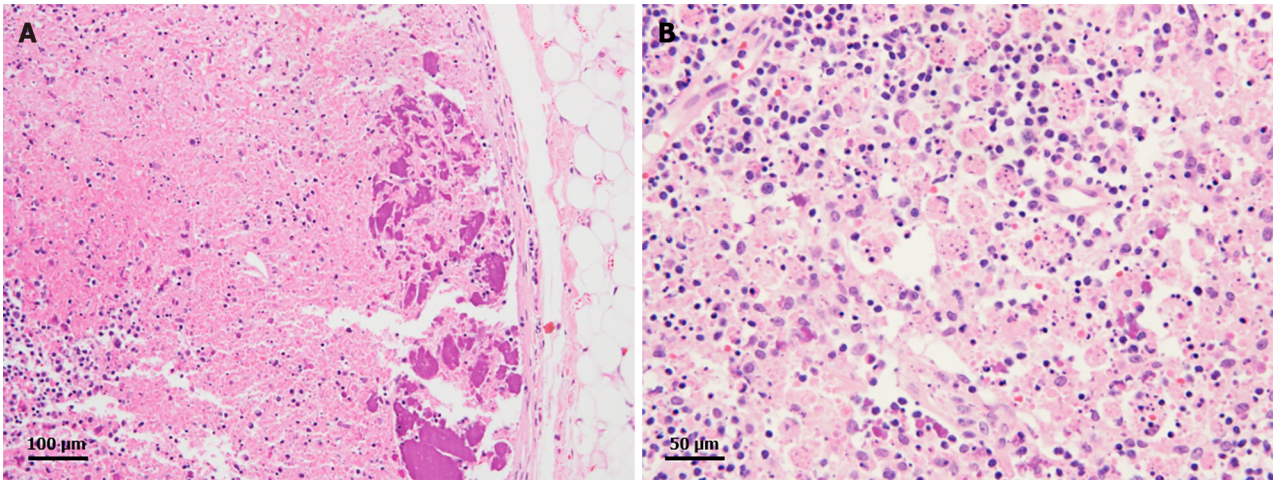

Figure 3 Histopathological findings of the lymph node. A: Lymph node biopsy reveals extensive subcapsular necrosis with hematoxylin bodies (hematoxylin and eosin stain, × 200); B: Higher magnification shows abundant crescentic histiocytes, abundant karyorrhectic debris, and small hematoxylin bodies (hematoxylin and eosin stain, × 400).

necrosis, and calcification were not clearly observed during imaging. The histological examination revealed hematoxylin bodies, crescentic histiocytes, and abundant karyorrhectic debris.

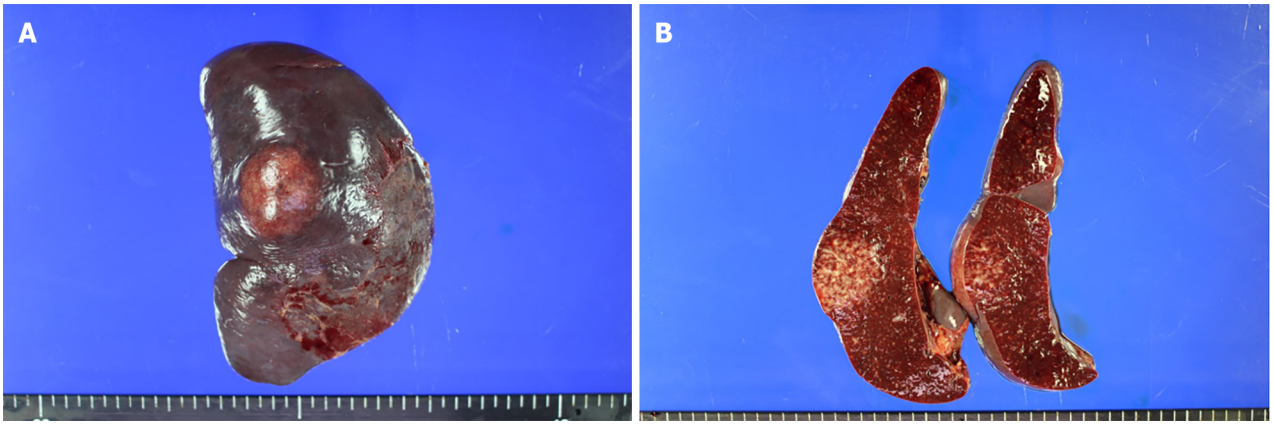

Figure 4 Gross findings after laparoscopic splenectomy. A and B: Multiple nodules observed on the surface of the spleen. No other specific findings were noted.

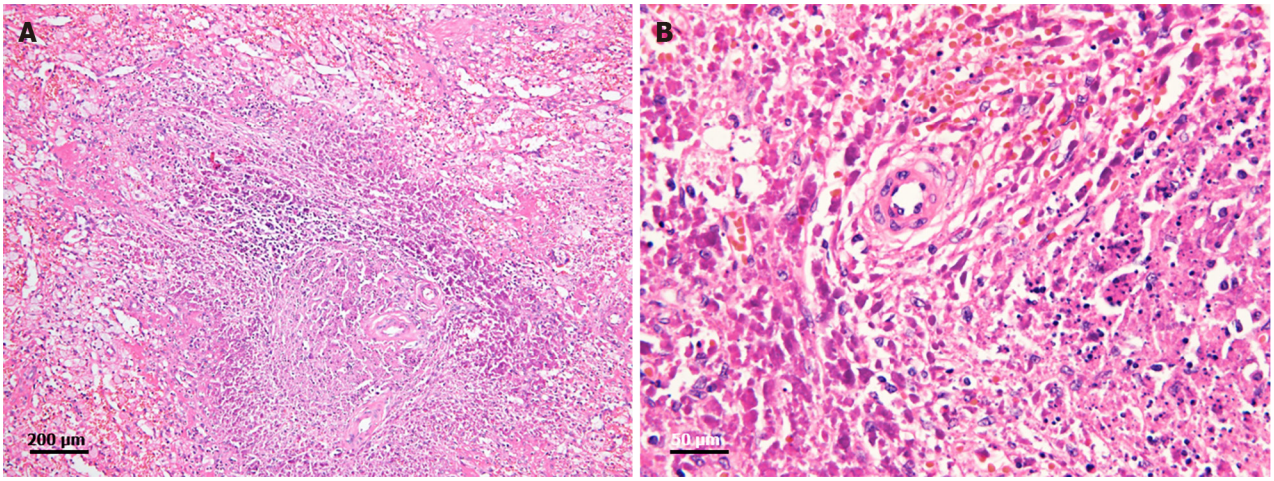

Figure 5 Histological findings of the spleen. A: Extensive periarteriolar necrosis with hematoxylin bodies (hematoxylin and eosin stain, × 100); B: Higher magnification of hematoxylin bodies and abundant karyorrhectic debris (hematoxylin and eosin stain, × 400).

CONCLUSION

In this case, as disease activity increased, multiple nodules in the spleen that were previously unseen were observed on AP-CT and histologically confirmed. Thus, the invasion of the spleen by SLE can appear in multiple nodular forms and patterns without calcifications or ruptures. Physicians should consider these findings in order to differentiate them from other infections or malignancies.

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LETTER TO THE EDITOR

Machine learning in liver surgery: Benefits and pitfalls

Rafael Calleja, Manuel Durán, María Dolores Ayllón, Ruben Ciria, Javier Briceño

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Abstract

The application of machine learning (ML) algorithms in various fields of hepatology is an issue of interest. However, we must be cautious with the results. In this letter, based on a published ML prediction model for acute kidney injury after liver surgery, we discuss some limitations of ML models and how they may be addressed in the future. Although the future faces significant challenges, it also holds a great potential.

Key Words: Machine learning; Liver surgery; Artificial intelligence; Random forest; Prediction model

Core Tip: Artificial intelligence is trending topic in healthcare research. Machine learning classifiers have been explored in the field of liver surgery and liver transplantation. However, despite of promising results, a real applicability is limited by several factors.

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TO THE EDITOR

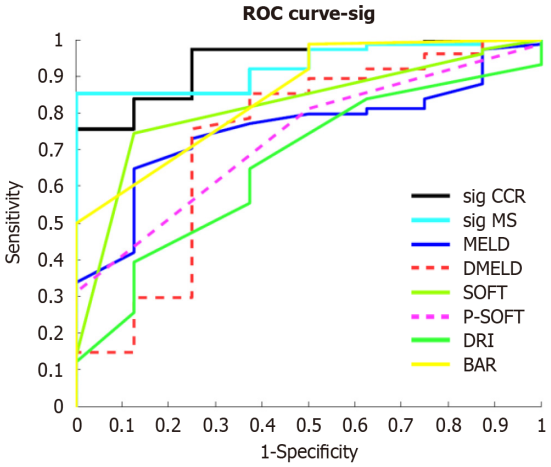
We read with interest the retrospective study by Dong *et al*[1] that developed a machine learning (ML) prediction model for acute kidney injury (AKI) following liver

resection (LR). We thank the authors for their work and contribution in this field. LR is the first-line treatment of various liver lesions. However, the reported incidence of AKI after LR ranges from 10% to 15%[2], significantly impacting patient morbidity and mortality. Hence, identifying factors that may lead to the development of AKI is relevant. Dong *et al*[1] explored the potential contribution of ML classifiers to this issue.

The authors analyzed a retrospective cohort of 2450 patients and trained and validated four ML classifiers (logistic regression, random forest, support vector machine, extreme gradient boosting, and decision tree). The training methodology (10-fold cross-validation) and validation (a holdout technique with 30% patterns) were adequate. Random forest exhibited the highest performance [area under the curve (AUC) = 0.92] among the classifiers. Although the results were satisfactory, certain considerations must be addressed.

First, the rate of missing values should be reported because it can affect model training, subsequently affecting model performance and generalizability. Hence, random forest classifiers are the best algorithms for a significant rate of missing values[3]. Conversely, if this rate is low, artificial neural networks (ANNs) could offer promising dataset results. Second, several factors reported in the literature are associated with AKI after LR, such as major hepatectomy, surgery duration, hepatojejunostomy, increased Model for End-Stage Liver Disease score (MELD), and blood transfusion[2,4-8]. Among these factors, only surgery duration was included in the baseline characteristics. The inclusion of these variables may have increased the robustness of the model. Finally, performing external validation is challenging. Differences between the training and external validation cohorts may impact model accuracy. Therefore, a prospective validation may be an alternative.

Some recent studies in ML applications ranges from protein structure prediction or COVID-19 diagnosis from X-ray images to optimizing donor-recipient matching to reduce waitlist mortality or improve post-transplant outcomes[9-11]. Our experience in the field of ML in liver surgery started from liver transplantation and efforts primarily focused on improving donor-recipient matching. Using graft survival as the endpoint, we developed an ANN model that achieved an AUC of approximately 0.8212[12]. This method was validated in an external cohort and improved AUC by 15%[13]. This ANN was integrated into a rule system with the MELD score to prioritize graft allocation. Although this method was explored in the United Network of Organ Sharing database, limited results were obtained because of a significant proportion of missing values were found[14]. Dong *et al*[1] found that the model performance was better than the current scores for AKI prediction. Similarly, we reported the difference of ML models that outperformed traditional scores, such as MELD, Survival Outcomes Following Liver Transplantation score, Donor Risk Index score, and Balance of Risk score (Figure 1). In medicine, certain variables do not necessarily have to assume a linear relationship. Hence, ML models are superior to statistical methods (linear regression), from which most of these scores are derived[15]. However, these findings may be attributed to model overtraining; therefore, validation is required.



KCH (train) -> KCH test 3-month	CCR gener.	MS gener.	AUC gener.
MELD	0.7683	0.5000	0.7517
DMELD	0.8659	0.3750	0.7297
SOFT	0.8902	0.1250	0.8159
P-SOFT	0.9024	0.0000	0.7230
DRI	0.9024	0.0000	0.6571
BAR	0.8780	0.5000	0.8446
sig CCR	0.9024	0.0000	0.9375
sig MS	0.6585	0.6216	0.9274

Figure 1 External validation of artificial neural network models[13]. The performance obtained by these models is compared to other published score in terms of area under curve. A receiver operating characteristic curve depicts these metrics. Artificial neural network models based on the concept of minimum sensitivity and correct classification rate are represented such as sig minimum sensitivity and sig correct classification rate respectively. These models outperformed other traditional scores such as Model for End-Stage Liver Disease, Model for End-Stage Liver Disease score excluding exception points and donor age, Survival Outcomes Following Liver Transplantation, Preallocation Survival Outcomes Following Liver Transplantation, Donor Risk Index or Balance of Risk. CCR: Correct classification rate; MS: Minimum sensitivity; MELD: Model for End-Stage Liver Disease score; DMELD: Model for End-Stage Liver Disease score excluding exception points and donor age; SOFT: Survival Outcomes Following Liver Transplantation score; P-SOFT: Preallocation Survival Outcomes Following Liver Transplantation score; DRI: Donor Risk Index score; BAR: Balance of Risk score; AUC: Area under curve; KCH: Kings College Hospital; ROC: Receiver operating characteristic. Citation: Ayllón MD, Ciria R, Cruz-Ramírez M, Pérez-Ortiz M, Gómez I, Valente R, O'Grady J, de la Mata M, Hervás-Martínez C, Heaton ND, Briceño J. Validation of artificial neural networks as a methodology for donor-recipient matching for liver transplantation. *Liver Transpl* 2018; 24: 192-203. Copyright© The Authors 2018. Published by Wolters Kluwer Health, Inc.

The most significant lesson learned from using these models is their high dependency on the datasets on which they were trained. This issue affects the practical applicability. Retrospective data, external validation, the "black box issues" in ANN, and data-protection policies are considered significant contributing factors. To overcome these barriers, better

data-handling policies are needed. Applicability relies on the clinicians' confidence in using these models. Therefore, if external validation is impossible (region-specific rather than universal models), prospective validation should be considered. Moreover, the databases must be updated regularly to reinforce the learning of these models. Clinical scenarios are dynamic, and models must change accordingly.

Recently, interest in artificial intelligence and ML has increased. They can handle large amounts of data quickly and yield accurate results. However, we must note the limitations of these models and address them to achieve a real integration.

FOOTNOTES

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