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EDITORIAL

Advances and future directions in keloid research: Pathogenesis, diagnosis and personalized treatment strategies

Song-Yun Zhao, Dan Wu, Chao Cheng, Jia-Heng Xie

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Abstract

Keloids, which are abnormal manifestations of wound healing, can result in significant functional impairment and aesthetic deformities. The pathogenesis of keloids is multifaceted and complex and influenced by various factors, such as genetics, the environment, and immune responses. The evolution of keloid treatment has progressed from traditional surgical excision to a contemporary combination of therapies including injection and radiation treatments, among others. This article provides a comprehensive review of keloid pathogenesis and treatment, emphasizing the latest advances in the field. Ultimately, this review underscores the necessity for continued research to enhance our understanding of keloid pathogenesis and to devise more effective treatments for this challenging condition.

Key Words: Keloids; Pathogenesis; Diagnosis; Treatment; Personalized therapy

Core Tip: This article provides a comprehensive review of keloids, which are abnormal outcomes of wound healing. Keloids can lead to dysfunction and aesthetic deformities pathogenesis is influenced by genetic, environmental and immune responses. The evolution of keloid treatment has shifted from traditional surgical excision to modern therapies, including injections and radiation therapy. The article emphasizes the need for continued research to better understand keloid development and improve therapeutic strategies for this complex condition.

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INTRODUCTION

Keloids are a common yet challenging type of skin lesion that can cause significant physical and emotional distress[1]. These irregular growths are the result of an overgrowth of fibroblasts and can occur after various skin injuries, such as surgical incisions and acne[2,3]. Although keloids are not life-threatening, their occurrence in vital or functional areas can greatly impact a patient's appearance and functionality and potentially restrict their mobility[4,5].

Over the years, considerable progress has been achieved by both researchers and clinicians in understanding the fundamental mechanisms of keloid formation and developing effective treatment options[6]. Advances in diagnostic imaging and molecular biology have improved our ability to identify and characterize keloids, while innovative therapeutic approaches, including laser therapy and cryotherapy, present promising alternatives to traditional surgical excision[7-10].

This review focuses on recent advancements in the pathogenesis, diagnosis, and treatment of keloids, emphasizing pivotal research that contributes to our understanding of this intricate disorder. By incorporating the latest findings from both basic research and clinical studies, our aim is to offer a comprehensive overview of the current status of keloid management while also highlighting avenues for further investigation and innovation in this critical field.

THE IMMUNE MICROENVIRONMENT OF KELOIDS PROMOTES THEIR GROWTH

Immune cells present within the keloid microenvironment, including macrophages, T cells, and mast cells, play a crucial role in the initiation and persistence of keloids[11-13]. Macrophages, which are key players in the inflammatory response, exhibit an M2-like phenotype in keloids, which is linked to anti-inflammatory reactions and tissue mending[14]. However, these M2-type macrophages also generate substantial levels of transforming growth factor-β1 (TGF-β1) and vascular endothelial growth factor (VEGF), potentially contributing to the excessive deposition of extracellular matrix (ECM) and the observed angiogenesis in keloids[15].

T cells, which are present in the keloid microenvironment, can produce cytokines that contribute to disease development and progression[16]. Research has revealed the presence of CD4+ and CD8+ T cells in keloids, and there is a predominance of CD8+ T cells[16]. These cells produce cytokines such as interferon-γ, tumor necrosis factor-α, and interleukin (IL)-10, which stimulate fibroblast proliferation and collagen synthesis[16].

Mast cells, which are involved in immune responses, can produce a variety of mediators, including histamines, cytokines, and growth factors, that contribute to keloid development. Studies have shown that mast cells in keloids produce high levels of TGF-β1, thereby promoting fibrosis[17].

Within this immune context, keloid fibroblasts also undergo significant alterations. In comparison to normal skin fibroblasts, these cells exhibit heightened antiapoptotic capabilities and faster proliferation rates[18]. Keloid fibroblasts release various cytokines, including IL-6, IL-8, VEGF-A, and basic fibroblast growth factor, which mediate angiogenesis, fibroblast proliferation, and the deposition of ECM[19]. Furthermore, keloid fibroblasts exhibit a more contractile phenotype than fibroblasts in normal tissues, contributing to the excessive deposition of collagen in keloids[20].

The ECM also plays a significant role in the development of keloids[21]. The ECM has a complex composition involving collagen, elastin, and proteoglycans and offers structural support for the skin[21]. Keloids are characterized by excessive deposition of ECM proteins, particularly collagen, leading to increased tension and firmness in keloid tissues [21].

NUMEROUS SIGNALING PATHWAYS CONTRIBUTE TO THE GROWTH AND MAINTENANCE OF KELOIDS

One critical signaling pathway implicated in the development of keloids is the TGF-β pathway[22]. TGF-β cytokines participate in and promote various cellular processes, including growth, differentiation, and the generation of the ECM [23]. In keloids, there is an abnormal increase in TGF-β expression, leading to increased collagen production and reduced

degradation. Consequently, excessive deposition of collagen occurs in the keloid tissue, resulting in a raised and thickened scar.

Another signaling pathway involved in keloid formation is the mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway regulates the proliferation, differentiation, and survival of keloid cells[24]. In keloids, the MAPK pathway is activated, contributing to enhanced cell proliferation and collagen production.

The Wnt/β-catenin pathway is also closely associated with keloids[25]. This pathway regulates cell proliferation and differentiation and is activated in keloids, leading to increased cell proliferation and collagen production, which contribute to the growth and maintenance of keloid tissue[25].

Finally, the Notch signaling pathway is involved in keloid formation. Notch, which is a transmembrane receptor, regulates cell fate and differentiation. In keloids, the Notch pathway is activated, leading to increased cell proliferation and collagen production[26].

ADVANCES IN THE DIAGNOSIS AND TREATMENT OF KELOIDS

The diagnosis of keloids primarily relies on clinical presentation and can be confirmed through biopsy. Keloid treatment can be challenging, and no single method is universally applicable. Treatment options include conservative approaches such as pressure therapy, silicone gel sheets, corticosteroid injections, and more invasive methods such as surgery, cryotherapy, laser therapy, and radiation therapy[1-5].

Conservative measures are typically the initial step in treating keloids[27]. Pressure therapy involves applying pressure to keloids using materials such as pressure bands or patches, which can help flatten keloids, reduce tension, and decrease the risk of recurrence[27]. Intralesional corticosteroid injections can help minimize inflammation and slow the growth of keloids[28].

Surgical removal of keloids is another treatment option; however, the risk of recurrence is high[29]. To mitigate the risk of recurrence, postoperative adjuvant therapies, such as intralesional corticosteroid injections, radiotherapy, or cryotherapy, may be used[29]. Cryotherapy involves freezing keloids with liquid nitrogen, while radiotherapy primarily involves exposing keloids to low doses of radiation, thereby inhibiting the growth and secretion of keloid fibroblasts[30]. Laser therapy can also be used to treat keloids[31]. By using high-intensity lasers to break down scar tissue and promote the growth of new, healthy tissue, this method is less invasive than surgery and carries a lower risk of recurrence[31]. It is worth noting that combination therapy may be more suitable for treating keloids in some cases. For instance, a combination of surgery, radiation, and intralesional corticosteroids may be used to treat large or recurrent keloids.

In summary, the diagnosis of keloids relies on the clinical presentation, and treatment selection depends on factors such as the size, location, and severity of the keloid, as well as the patient's medical history. Despite significant advancements in understanding and treating keloids, the overall therapeutic results remain unsatisfactory. Future research in the field of keloids may concentrate on various areas, including identifying new therapeutic targets, developing more effective treatments, and clarifying the underlying mechanisms of keloid formation and growth.

FUTURE RESEARCH DIRECTIONS IN THE KELOID FIELD

Keloids, which are characterized by excessive scar tissue growth, are thought to have a genetic component, and single nucleotide polymorphisms (SNPs) in various genes have been studied for their potential associations with keloid formation[32]. Candidate genes involved in wound healing, inflammation, collagen production, and ECM regulation, such as TGF-β, ILs, matrix metalloproteinases, and collagen genes, have been investigated for SNPs[33]. Genetic variations in immune response genes, cytokines, and growth factors have also been explored. Ethnic and geographic differences in keloid prevalence may be influenced by genetic factors[34]. However, the genetic basis of keloids remains complex and multifactorial, and while specific genetic markers have been associated with keloids in some studies, the precise mechanisms and markers are not fully understood, and genetic testing is not yet a routine diagnostic tool for keloids. Clinical management primarily involves various treatment options.

A prospective focal point in the field might involve the development of innovative therapies for keloids, such as the use of growth factor inhibitors, immunomodulators, or gene therapies targeting specific signaling pathways implicated in keloid formation and growth. Additionally, the advancement of more efficient drug delivery systems, such as nanoparticles, could enhance the effectiveness of existing therapies[35,36].

Another area of potential exploration is the use of tissue engineering techniques to treat keloids. Exploring the use of stem cells, growth factors, and scaffolds to regenerate healthy tissue and facilitate the healing of keloids could yield promising outcomes[37]. Further advancements in tissue engineering may enable the implementation of personalized therapies tailored to individual patients.

The development of novel diagnostic tools and biomarkers may significantly contribute to the diagnosis and treatment of keloids. Incorporating imaging methods such as magnetic resonance imaging or ultrasound could facilitate improved visualization of keloid tissue and the monitoring of treatment progress[38]. The identification of specific biomarkers, such as cytokines or growth factors, could also aid in the diagnosis and monitoring of keloids. Researchers can determine the underlying mechanisms of keloid formation and growth at the molecular and cellular levels. The identification of key genes, proteins, and signaling pathways involved in keloid formation may lead to the creation of innovative therapies and diagnostic tools. Advancements in genomics, proteomics, and other high-throughput technologies might contribute to the discovery of new targets and pathways[35].

CONCLUSION

In conclusion, the field of keloids is poised for significant advancements in the future with the emergence of new treatments, diagnostic tools, and biomarkers. Progress in tissue engineering, genomics, and other technologies may pave the way for personalized, targeted treatments for keloids.

FOOTNOTES

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OPINION REVIEW

Mental health implications of suicide rates in South Africa

Nkechinyere C Edeh, Chiedu Eseadi

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Abstract

Mental health challenges are a severe issue that could lead to suicide if not properly addressed. South Africa has a significant burden of mental health issues, which contributes to the soaring rate of suicide. Adequate mental health-care provision could reduce the high suicide rate in South Africa. Since the apartheid regime, the country has made a series of efforts to improve mental health. This study aimed to review and examine available literature on mental health and suicide issues in South Africa and demonstrate the policy implications. This study adopted a narrative review approach. Electronic databases (PubMed, Scilit, Google Scholar and Semantic Scholar) were used to identify published articles in the English language with crucial search terms that included mental health, South African mental health policy, South Africa, suicide and policy. Literature suggests that at the provincial level, there are no adequate mental health policies, and the implementation of the country's mental health policy is faced with many challenges, such as a shortage of professionals and finances. The review also showed that task sharing and counselling have been pilot-tested and shown to be effective methods for the prevention of mental illness and promotion of positive mental health. This study concludes that the mental health treatment gap still exists in South Africa, and this needs to be tackled using effective, multi-level counselling interventions and policy initiatives. Adequate mental health-care provision and effective implementation of mental health policy could reduce the high rate of suicide in South Africa.

Key Words: Counseling; Mental health policy; Suicide; South Africa; Task-sharing

Core Tip: A mental health challenge is a severe issue that could result in suicide if it is not addressed correctly. Mental health issues are prevalent in South Africa, contributing to the increasing suicide rate. Currently, South Africa still has a mental health treatment gap that ought to be addressed through effective, multi-level counseling interventions and policy initiatives to reduce the high suicide rate.

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INTRODUCTION

A high suicide rate is seen as a global concern that needs to be controlled, especially in low- and middle-income countries. It has been documented that Africa's mental health is gloomy and if not adequately solved, could lead to a health emergency[1]**.** Suicide is seen as death caused by injuring oneself with the intent to die[2]. It is a significant cause of mortality worldwide, accounting for 800000 deaths each year all over the world[3]. Suicide is responsible for 11% of non-natural deaths; the youth suicide rate is 9.5%, almost as high as the adult suicide rate[4]. It was also observed that suicide is the second leading cause of death among youth all over the world, with low- and middle-income countries accounting for 78% of all suicide rates[5]. People who sometimes get discontented with issues around them and who lose hope commit suicide by jumping from high places, burning, hanging, overdosing, using sharp objects, gassing, drowning, poisoning, electrocutions, and shooting, among others[4].

Many factors predispose people to suicide. People exposed to violence are at risk, and people who have access to health-care have less chance of committing suicide[3]. Violence exposure among adolescents can result in exposure to other types of violence, implying that experiences of victimization could amass over time[6]. When people face a series of troubles, social isolation, and anxiety, they may slip into depression and begin to think of terminating their lives. This study aimed at reviewing and examining available literature on mental health and suicide issues in South Africa, and further demonstrating the policy implications thereof.

Mental health in South Africa

Mental health disorder is a severe problem in South Africa. Mental illnesses such as depression, anxiety disorders, mood disorders, and substance abuse disorders are most prevalent in South Africa[7]. A person-centered approach to mental health-care in the country involves building rapport, rekindling hope, empathic listening, and empowering patients to cultivate their own social and internal resources for recovery[8]**.** However, mental health is influenced by the interplay of many factors, including genetic, biological, environmental, economic, political and socio-cultural[9]. Mental illness affects all strata of the South African population – the pregnant, prisoners, adults, children, adolescents and occupational groups [10,11]. Studies report high levels of mental disorders among different components of the population. For instance, high rates of mental disorders were detected among South African prisoners[11]. A study on the mental health of pregnant women showed that most of them in South Africa are at risk of mental illness[10].

South African adolescents are at increased risk of psychological maladjustment. This is a result of the country's alarmingly high rates of crime and violence, which may lead to suicidal thoughts and suicide, hence the need for mental health interventions[12,13]. The mental health of students at universities is considered one of the most pressing public health areas in South Africa[14]. According to study estimates, one out of every three South Africans will suffer from a mental illness during their lifetime, an incidence that is greater than that of most nations with low and middle incomes [15]. In addition, about 75% of individuals with mental illness in South Africa may not receive sufficient mental healthcare[16].

Mental disorders predict the onset of suicide ideation[17]. Hence, there is a need to investigate the connection between trauma and suicidal thoughts, particularly in low-income nations where traumatic disorders seem to be more pervasive than in developed nations[18]. Also, despite the fact that mental health is recognized as a public health priority in South Africa, mental health-care remains largely underfunded[19,20]. Research shows that one of the most efficient and cost-effective methods to expand access to mental health care in South Africa is to integrate it into existing health systems[15].

MENTAL HEALTH POLICY AND STATE OF MENTAL HEALTH-CARE IN SOUTH AFRICA

The Minister of Health often seeks input from various stakeholders when developing national health legislation and policy in South Africa. Implementation plans with clearly defined indicators, targets, timelines and budgets are prepared by the provincial Departments of Health[21]. Since the end of the apartheid reign in South Africa, the country has made several efforts to promote mental health, which led to the promulgation of the 2004 Mental Health-Care Act. According to the South African Ministry of Health, 2004 was a significant departure from the past apartheid health policies. It set out to expand access, place primary health-care as the first point of contact of mental health-care with the health system, and facilitate the incorporation of mental health-care into general health services and the establishment of community-based services.

The adoption of the Mental Health Policy Framework (MHPF) for South Africa and the Strategic Plan 2013 – 2020 by the National Health Council, emerged from a series of consultations, including provincial and national mental health summits. A progressive agenda was set with the first national MHPF, the "National Health Policy Guidelines for Improved Mental Health in South Africa", drafted in 1997. The policy considers mental health issues to be an integral part of general health-care issues. It was South Africa's first officially endorsed national mental health policy, with the country previously relying on instruments such as White Papers to inform policy choices[22]. The mental health policy was based on several existing policy and legislation mandates in South Africa, including the White Paper for the Transformation of the Health System in South Africa, 1997; the National Health Policy Guidelines for Improved Mental Health in South Africa, 1997; the National Health Act, Act 63 of 2003; Mental Health-Care Act, Act 17 of 2002; Prevention of and Treatment for Substance Abuse Act, No. 70 of 2008; and Child and Adolescent Mental Health (CAMH) Policy Guidelines, 2003[23,24].

Despite the formal adoption of the CAMH policy, a comprehensive CAMH policy implementation plan is still lacking across the South African provinces[21]. In South Africa, there is poor mental health even when individuals show depressive symptoms as risk factors for future suicide attempts and have attempted suicide in the past[25,26]. Mental health policy implementation has not been effective due to lack of adequate attention, limited staff for policy and planning and neglect of responsibilities by some provincial authorities for driving implementation[27]. The South African children and adolescents still suffer from poor mental health, and this group seems to be neglected according to a study conducted on CAMH[21]. Furthermore, facilities in most psychiatric hospitals are outdated, mental health professionals are limited in number, and community mental health and psychosocial rehabilitation services are still undeveloped, which makes them inefficient and less functional[22,28]. It is also worth noting that there is a significant gap in the screening and treatment of maternal mental disorders due to the lack of collaboration between providers of maternal health services, child health services, and mental health services in primary care[10].

The responsibility for health-care lies with the South Africa national department, whereas, using the public health-care model, the provinces administer and oversee comprehensive health-care *via* district delegation[29]. The South Africa Human Rights Commission's report on the mental health-care status clearly states that there were significant challenges in the implementation of the national policy. These challenges included insufficient funding for mental health-care services, limited human resources or disparities in the allotment of mental health personnel across the private and public sectors, and urban and rural communities, and lack of collaboration between government departments[22,30]. This shows that a lot of work is still required in our schools. It is therefore necessary to promote mental health in South Africa to curtail the high suicide rate. Although there have been significant developments in mental health policy and legislation in South Africa, the inequality between provinces in available resources for mental health-care remains an issue[14].

SUICIDE IN SOUTH AFRICA

Suicide is a leading cause of death in South Africa. In a 2018 study, the female suicide rate in South Africa was 4.5 per 100,000, and women reported twice as many suicide attempts as men[25]. However, a 2020 study on Trends in Suicide Mortality in South Africa reported a higher proportion of suicide rates among South African men[31]. This study conducted in 2020 did not observe an overall decline in suicide mortality despite the high rate of decline in suicide rates in other parts of the world[31].

It is important to note that the high incidence of suicidal behavior in South Africa has significant implications for mental health facilities[4]. In consensus with research data from most countries, mental disorders are highly predictive of suicidal behavior[17]. As a result, it is not surprising that the suicide rate in South Africa is high due to increasing mental illness. The adolescent experience of revictimization can cause mental stress that may result in suicide[6]. Youth social stress was significantly associated with suicide attempts[5].

Some regional suicide prevention initiatives exist, including the South African Depression and Anxiety Group, Life Line Southern Africa, and the South Africa Federation for Mental Health. The others are the Mental Health Information Centre of South Africa, and the International Association for Suicide Prevention[4]**.** However, that significant progress has yet to be made in the planning and implementation of coordinated, targeted suicide prevention interventions in South Africa[8].

OBSERVATIONS BASED ON LITERATURE ANALYSES

This study adopted a narrative review approach, and electronic databases (PubMed, Scilit, Google Scholar and Semantic Scholar) were used to identify published articles with crucial search terms that included mental health in South Africa, South African mental health policy, and South Africa and suicide rate. The inclusion criteria for articles in Table 1 were articles on suicide and mental health outcomes in the South African context, whereas those articles focusing on other regions of the world were excluded. The outcome of the literature search and analyses are presented in Table 1.

The literature shows that mental illness, which could lead to suicidal thoughts and behavior, is a significant concern in South Africa, and there have been limited interventions and policies aimed at addressing this issue[32-37]. It has been reported that South Africa is far from implementing the right to health for individuals with mental health challenges[38]. Studies show that common mental health disorders in South Africa include substance use disorders and depression[39]. Therefore, it is clear that to reduce the suicide rate in South Africa, efforts should be targeted at effective treatment of substance use disorders, depression and other mental conditions. Reviewed studies further showed that challenges are

Table 1 Summary of suicide-related and mental health studies in South Africa

Ref.	Objectives	Methodology	Participants	Results
Goldstone *et al*[8], 2018	To explore mental health-care providers' context- and population-specific suggestions for suicide prevention when providing services or PWSUDs in the Western Cape, South Africa	Qualitative data were collected *via* in-depth, semi-structured interviews with 18 mental health-care providers providing services to PWSUDs in the public and private health-care sectors	18 mental health-care providers were interviewed	Effective treatment of substance use disorder and other psychiatric conditions would significantly decrease suicidality, transforming the mental health-care system and training in suicide prevention for mental health-care providers help to prevent suicide
Naidoo *et al* [11], 2012	To determine the prevalence of severe mental disorders in a prison population in Durban, South Africa	This was a cross-sectional point prevalence study	193 prisoners were interviewed, and questionnaires were administered	There is a high prevalence of mental disorders among prisoners in the prison population in Durban, South Africa
Jack *et al* [15], 2014	To identify and review research from South Africa and sub-Saharan Africa on the direct and indirect costs of mental, neurological, and substance use disorders and the cost-effectiveness of treatment interventions	Narrative overview methodology		Reviewed studies indicate that integrating mental health-care into existing health systems may be the most effective and cost-efficient approach to increasing access to mental health services in South Africa
Khasakhala *et al*[17], 2011	To examine the relationship between lifetime mental disorders, subsequent suicide ideation, and suicide attempts in South Africa	A national survey of 4185 South African adults who were interviewed	4185 South African adults	There is a relationship between several mental disorders and suicidal behavior
Mokitimi *et al*[21], 2018	To examine the current state of child and adolescent mental health policy development and implementation in the nine provinces of South Africa and to perform a policy analysis of all CAMH-related policy documents	In order to identify all publicly-available policy documents related to CAMH, two search strategies were used	Health website searches	No South African province had a CAMH policy or identifiable implementation plans to support the national CAMH policy
Vawda *et al* [25], 2018	To establish what percentage of females admitted following a suicide attempt to a government tertiary hospital were pregnant and to establish associated clinical and sociodemographic factors	A retrospective review of medical and psychological charts of all female patients admitted to a tertiary hospital in Durban following a suicide attempt over one randomly chosen year (January 01, 2014 to December 31, 2014)		Participants diagnosed as having an MDD had also made previous suicide attempts while pregnant; no mental health help had been sought even when they showed a prior history of suicide attempts and depressive symptoms, which are risk factors for future suicide attempts
Petersen and Lund[32], 2011	To identify progress and challenges in mental health-care in South Africa and future mental health services research priorities	A systematic review of mental health services research. Literature searches were conducted in Medline, PsychInfo, and Sabinet databases	Of 215 articles retrieved, 92 were included	There is a paucity of intervention and economic evaluation studies. Common mental disorders remain primarily undetected and untreated in primary health-care
Steyn *et al* [33], 2013	To examine a possible link between PTSD and suicidal ideation and to examine whether any specific posttraumatic symptoms predict suicidal ideation	A cross-sectional survey design on South African police officers assessed utilizing the Posttraumatic Diagnostic Scale and a short version of the Adult Suicide Ideation Questionnaire	217 South African police officers	Hyperarousal was the primary predictor of suicidal ideation
Orri *et al* [34], 2022	To investigate childhood risk factors for suicidal ideation in adolescence and young adulthood	A longitudinal study used data from the largest and longest-running birth cohort in Africa, the Birth to Twenty Plus (Bt20+) study in South Africa Bt20+ cohort	Mothers and their singleton children born during 7 wk in 1990 in Soweto, South Africa	Prevalence rates peaked at age 17 and decreased continuously until age 28. Prevalence rates were higher among females than males; there are sex differences in the association of childhood individual, familial, and environmental factors with youth suicidal ideation
Bantjes *et al* [35], 2016	To investigate the 2-wk prevalence of suicidal ideations and their associations to symptoms of posttraumatic stress, depression, and anxiety among South African university students	Hierarchical regression analysis was used to investigate the relationship between suicidal ideation and symptoms of posttraumatic stress, depression, and anxiety	Data were collected from 1337 students between May and August 2013	Rates of suicidal ideation are higher among university students in South Africa than among the general population of the country and student populations in other parts of the world
Khuzwayo *et al*[36], 2018	To investigate key demographic factors and behaviors associated with planning and attempting suicide among high-school learners	A cross-sectional study in uMgungundlovu District, KwaZulu-Natal Province, South Africa	All Grade 10 learners (n = 1 759) at these schools completed a self-administered questionnaire	The suicide attempt prevalence rate is high in South Africa. The risk of planning suicide increases with age

Burgess *et al* [37], 2022	To pilot and evaluate the effectiveness of a complex intervention – Courage-Plus on symptoms of depression in Gauteng, South Africa	This pilot study used a non-randomized, repeated-measures design	47 depressed women	Courage-Plus was highly effective at reducing symptoms of depression across the spectrum of severities in this sample of women facing adversity in Gauteng, South Africa

CAMH: Child and Adolescent Mental Health; PWSUD: People with substance use disorder; PTSD: Posttraumatic stress disorder.

hindering mental health-care in South Africa, including too few state-run substance rehab services and staff shortages, and lack of budget from the federal and provincial governments, particularly for mental health services. As a result, mental health services are funded through general health budgets, which makes them inefficient[8].

To promote citizens' mental health, counseling is seen as an essential tool. Counseling is considered an acceptable form of intervention for perinatal depression. Additionally, up to 3–4 sessions of counseling interventions can improve depression and alcohol outcomes among patients in South Africa[40,41]. A study on mobile phone intervention for mental health in South Africa reported that using digital mental health interventions using social media platforms is one way to assist young people with mental health in South Africa through psychoeducation. Among the benefits of this program is that it improves mental health literacy and teaches individuals how to cope with mental illness[42]. In addition, Courage-plus, which is a 13-wk intervention, has been pilot-tested among women as an effective group intervention for depression in South Africa[37]. This counseling intervention incorporates collective narrative counseling with training and support in the treatment process. It is also worthwhile for the components of a suicide prevention program to include the provision of emotional and social support from family, members of the community, and friends [8].

It has been documented that mental illness may not often be best treated with medication, but interventions outside the biomedical model may be more appropriate and effective[43]. Researchers further note that task shifting is a feasible option, especially in rural South Africa, where there is a lack of appropriately trained medical staff. Many other studies support the task-shifting or sharing model. For instance, Kathree *et al*[44] reported that the training of primary healthcare workers in diagnosing, reporting, and treating depression within a collaborative task-shared model promoted the use of co-located or facility-based counselling by mental health workers who are not specialists in mental health. This helped facilitate the implementation of integrated, accessible mental health care services. Task sharing promotes mental health-care, especially where there is a lack of mental health experts and programs. Community health workers can be trained to perform the task of a professional mental health expert. This is the result of a study by Myers *et al*[45], which showed that patients who have mental challenges were willing to receive counseling from trained community health workers whose primary duty was not to counsel patients with mental challenges.

Furthermore, a study of caregivers revealed that a group cognitive–behavioral intervention was feasible, acceptable, and effective in reducing depression among this population in Latin America[46]. The study contributes to the increasing body of knowledge concerning the effectiveness of this form of treatment intervention among culturally and socioeconomically diverse population. In light of South Africa's culturally and socioeconomically diverse population, group cognitive-behavioral interventions with cultural components may be appropriate for South African men and women. This is crucial given that in South Africa, there are no adequate guidelines for suicide prevention within local contexts despite the existence of the national mental health policy document[47].

CONCLUSION

Many people, including South Africans, are exposed to violence, which predisposes them to experience serious mental health challenges. Mental health challenges are a grave issue that could lead to suicide if not properly addressed. South Africa has a significant burden of mental health issues, which contributes to the high suicide rate. Implementation of the country's mental health policy faces many challenges, such as a shortage of professionals and finances. As a result, the mental health gap still exists in South Africa, and this needs to be tackled using multi-level counseling interventions and task sharing. Adequate mental health-care provision and effective implementation of mental health policy could reduce the high suicide rate in South Africa.

FOOTNOTES

Author contributions: Edeh NC and Eseadi C conceived and designed the study, conducted the literature review, analysis, manuscript drafting, editing, final writing and gave their approval.

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OPINION REVIEW

Artificial intelligence in sleep medicine: Present and future

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Abstract

Artificial intelligence (AI) has impacted many areas of healthcare. AI in healthcare uses machine learning, deep learning, and natural language processing to analyze copious amounts of healthcare data and yield valuable outcomes. In the sleep medicine field, a large amount of physiological data is gathered compared to other branches of medicine. This field is primed for innovations with the help of AI. A good quality of sleep is crucial for optimal health. About one billion people are estimated to have obstructive sleep apnea worldwide, but it is difficult to diagnose and treat all the people with limited resources. Sleep apnea is one of the

major contributors to poor health. Most of the sleep apnea patients remain undiagnosed. Those diagnosed with sleep apnea have difficulty getting it optimally treated due to several factors, and AI can help in this situation. AI can also help in the diagnosis and management of other sleep disorders such as insomnia, hypersomnia, parasomnia, narcolepsy, shift work sleep disorders, periodic leg movement disorders, *etc.* In this manuscript, we aim to address three critical issues about the use of AI in sleep medicine: (1) How can AI help in diagnosing and treating sleep disorders? (2) How can AI fill the gap in the care of sleep disorders? and (3) What are the ethical and legal considerations of using AI in sleep medicine?

Key Words: Artificial intelligence; Machine learning; Deep learning; Ethical; Legal, and sleep disorders

Core Tip: Most of the sleep apnea patients remain undiagnosed worldwide. Artificial intelligence can help alert people to be evaluated and seek treatment on time to improve overall health. Treatment of sleep apnea may improve or delay certain chronic illnesses.

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INTRODUCTION

Approximately one billion people worldwide suffer from obstructive sleep apnea (OSA), a condition characterized by intermittent hypoxia due to upper airway blockage during sleep[1]. The condition is diagnosed with a sleep study test where a positive result shows an apnea and hypopnea index (AHI) of five or more events per hour. Out of those one billion people, about 435 million suffer from moderate to severe degrees of sleep apnea with AHI of 15 or more per hour in the age range of 30-69 years[1]. The prevalence could be even higher in the older population. About 82% of sleep apnea patients remain undiagnosed[2], where untreated intermittent hypoxia leads to significant end-organ damage and debility. Scientists working in different fields are coming to the conclusion that sleep apnea is associated with multiple health conditions. However, the treatment of sleep apnea with positive airway pressure (PAP) still has a lot of compliance issues. A study looked at 20 years of trends of CPAP adherence and found that the non-adherence rate was around 34% [3]. Other treatment options exist for sleep apnea, but individualized assessment and management are required. Artificial intelligence (AI) and machine learning (ML) bring the opportunity to understand and monitor sleep disorders with easy-to-use smart technologies and may lead to better treatment outcomes.

How artificial intelligence can help in diagnosing and treating sleep disorders?

The scoring of sleep studies is a very labor-intensive process that requires significant manual effort to analyze data sets. This can be done easily and efficiently by AI. At present, many automated scoring systems are used with fair accuracy. AI in sleep medicine is currently used for sleep staging, respiratory events scoring, insomnia characterization, prediction of circadian rhythm from gene expression, and phenotyping of OSA[4]. Multiple home sleep testing devices are available that integrate AI for automated scoring using ML. AI can help in scoring in-lab sleep studies using ML, making sleep lab staff and clinicians more efficient. The Food and Drug Administration (FDA) has cleared several auto-scoring software systems. So many wearable devices are directly available to consumers, such as the Fitbit Sense, Samsung Galaxy Watch, Garmin watch, and Apple Watch, which can alert users to seek medical help sooner rather than later. Abnormal sleep data obtained from a wearable device may give clues to its users to get further testing and seek treatment for sleep-disordered breathing.

Treatment of sleep apnea is complex in view of pathophysiology, risk factors, and comorbid health conditions that make the treatment challenging. The treatment non-adherence with PAP therapy is high (29%-83%) in sleep apnea patients[5]. AI can help understand the factors contributing to OSA, pathophysiology, treatment response, and choice of treatment options for individual patients. Thus, it can improve the overall success rate for sleep apnea treatment by choosing the most effective treatment for individual patients[6]. AI can help to predict adherence to PAP therapy in OSA patients and alert clinicians to take early interventions[7]. AI can also help insomnia patients by characterizing insomnia and providing longitudinal sleep-related data monitoring.

How AI can fill gap in the care of sleep disorders?

A snoring-based contactless AI system using two dimensions convolutional neural network and visibility graph method can recognize OSA-hypopnea syndrome (OSAHS) with an accuracy of 92.5%. With a predicted sensitivity of 93.9% and specificity of 91.2% of OSAHS, this system seems superior compared to polysomnography (PSG)[8]. This type of AI

technology can alert users to get tested and treated for sleep apnea and capture many previously undiagnosed patients. Recently, the FDA cleared Sunrise home sleep testing device that uses machine-based learning to analyze mandibular jaw movement to predict sleep apnea with comparable accuracy to in-home manually scored PSG[9]. This device also offers multi-night longitudinal home testing to minimize the effect of night-to-night variability in the current sleep testing environment.

Polymer sensor embedded, internet of Things (IoT) enabled t-shirts have many sensors to gather multiple cardio-pulmonary physiological data, and it can help diagnose and monitor sleep-disordered breathing, which can be further utilized in the future using ML and AI[10]. This can help clinicians monitor their patients remotely in a variety of settings. The fusion of IoT devices capable of interoperability can produce the IoT, which can help in the smart diagnosis and management of sleep apnea[11].

AI technology can also increase the scope of analysis beyond simple one on one interaction with patients. Using large-scale data obtained from sleep testing numerous patients, AI can help formulate algorithms that can advance the field of sleep medicine. Consumer sleep technologies, such as wearables and phone applications, generate millions of nights of sleep data, which can be analyzed in more meaningful ways with the help of standardized AI technologies. AI can fill this gap by evaluating the data in real-time to predict patterns that will help identify potential patients.

Similar to an alert generated for anticoagulation in atrial fibrillation while using the electronic health record (EHR) system, AI can also create an algorithm to alert clinicians if a certain patient is at high risk of sleep apnea. This algorithm could be generated using patients' health characteristics, STOP-BANG score, Epworth Sleepiness Scale score, laboratory profile, and imaging results. There is a certain pattern in the lipid profile, which is indicative of sleep apnea, as noted in a recent study[12]. Magnetic resonance imaging brain using diffusion tensor imaging with ML can diagnose sleep apnea with 73%-77% accuracy[13]. The Cleveland Clinic Foundation has developed a sleep app for general consumers to fill out a few questionnaires. It can alert users about their risks of sleep apnea, insomnia, shift work, and insufficient sleep[14]. Since most patients with sleep disorders are undiagnosed, this type of innovation will help them and clinicians manage sleep disorders to improve overall health outcomes.

Diagnosing narcolepsy is very challenging as it requires multiple sleep latency tests (MSLT), which have a lot of limitations with variability and depend upon several factors for their accuracy. The AI algorithm can help diagnose narcolepsy type 1 in a single night by using ML with reasonable accuracy[15]. A recent study found that if sleep parameters are added to routine sleep testing with the help of an interpretable machine-learning model, the Adaboost model, it can predict cardiovascular morbidity and all-cause mortality[16]. This integration and prediction model can help clinicians further intervene in potential future health problems.

Sleep disturbances boost the aging process. Researchers can predict age with fair accuracy from sleep studies analyzed using deep learning[17]. FDA recently cleared 'Dreem 3S', a wearable headband that uses AI and ML to provide equivalent data about sleep stages compared to PSG[18]. This type of device has a lot of potential in terms of diagnosis, treatment, research, and monitoring of various diseases caused by sleep disturbances. The Dreem 3S device can provide prolonged monitoring of sleep that is needed to diagnose idiopathic hypersomnia. It can also help monitor accurate sleep data and replace sleep logs and actigraphy prior to PSG and MSLT in the assessment of hypersomnia.

Generative pre-trained transformers such as ChatGPT are large language models that have recently been used in patient education. In healthcare, radiology has been at the forefront of AI adoption. However, ChatGPT has immense potential for patient education in the field of sleep medicine as well[19].

Clinicians spend a lot of time charting medical notes, which curbs direct time spent with the patients. As the AI starts capturing and helping more and more patients diagnosed with sleep disorders, time efficiency will be crucial for sleep medicine providers. The AI can help as a scribe for physicians to finish medical charts on time, as many physicians may need to improve at typing[20].

What are the ethical and legal considerations of using AI in sleep medicine?

As the use of AI is increasing, ethical and legal issues also arise. Multiple teams of scientists and researchers are working to develop several different technologies and algorithms, raising the need for governing international bodies for standardization. We need a lot of quality data for ML, but data gathering is difficult due to patients' privacy concerns, regulations, and organizational policies. The other challenge is using different data-gathering systems used by various organizations, creating roadblocks in interoperability and standardization. There is a potential for data breach while incorporating different organizations. To promote AI in the field of medicine, there should be some immunity for researchers from legal actions.

Furthermore, the baseline datasets should be diverse enough to avoid bias while developing AI algorithms. Most datasets do not include LGBTQ information, so there may be bias and limitations while using AI, especially for those patients[21]. The American Academy of Sleep Medicine has an AI committee that advocates for good practice guidelines in sleep medicine. The FDA also assesses these technologies from a safety point of view. The lack of extensive training data sets for AI and ML is a persistent challenge for more comprehensive clinical utilization of AI, and the regulatory landscape is rapidly evolving. Night-to-night and age-related variation in patients' sleep data limits the generalizability of this data[3,22]. The innovations in sleep medicine are happening quickly, and it is tough for governing bodies to keep pace with a fast-changing landscape. Collaboration between clinicians, researchers, health institutions with big data pools, and AI engineers will be crucial to advance the field of AI in sleep medicine (Figure 1).

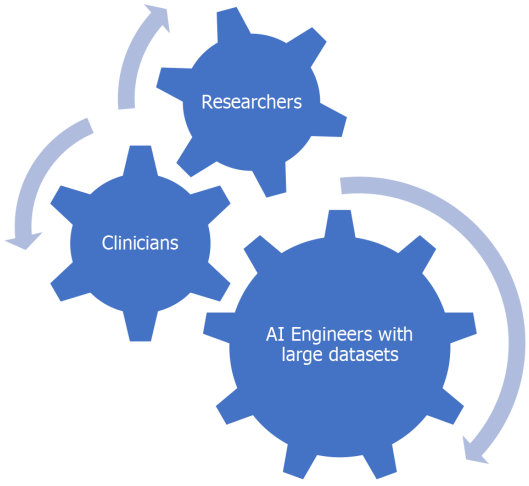

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Figure 1 Collaboration of researchers, clinicians, institutions with large datasets, and artificial intelligence engineers is needed for better use of artificial intelligence in medicine. AI: Artificial intelligence.

CONCLUSION

The development of AI technologies can aid in finding those patients who were previously undiagnosed with sleep apnea. It can also help choose the most effective treatment or combination of treatments for specific patients, leading to a higher success rate. Treatment failure signals can be identified earlier, which will alert clinicians to intervene on time. AI can also incorporate large data sets to provide clinical predictions, improving accuracy and long-term fidelity. If AI is integrated with EHR systems, it can alert the treating providers, using readily available objective data, that a specific patient is at risk of sleep-disordered breathing. Integrating AI into clinical workflows can improve efficiency and help sleep providers serve more patients effectively. In the future, AI will play a huge role in sleep disorders' screening, monitoring, prevention, prediction, diagnosis, and treatment.

FOOTNOTES

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REVIEW

Research progress on the relationship between Paneth cells-susceptibility genes, intestinal microecology and inflammatory bowel disease

Qi-Ming Zhou, Lie Zheng

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Abstract

Inflammatory bowel disease (IBD) is a disorder of the immune system and intestinal microecosystem caused by environmental factors in genetically susceptible people. Paneth cells (PCs) play a central role in IBD pathogenesis, especially in Crohn's disease development, and their morphology, number and function are regulated by susceptibility genes. In the intestine, PCs participate in the formation of the stem cell microenvironment by secreting antibacterial particles and play a role in helping maintain the intestinal microecology and intestinal mucosal homeostasis. Moreover, PC proliferation and maturation depend on symbiotic flora in the intestine. This paper describes the interactions among susceptibility genes, PCs and intestinal microecology and their effects on IBD occurrence and development.

Key Words: Susceptibility gene; Paneth cells; Intestinal microecology; Inflammatory bowel disease

Core Tip: Inflammatory bowel disease (IBD) is a disorder of the immune system and intestinal microecosystem caused by environmental factors in genetically susceptible people. Paneth cells (PCs) play a central role in IBD pathogenesis, especially in Crohn's disease development, and their morphology, number and function are regulated by susceptibility genes. In the intestine, PCs participate in the formation of the stem cell microenvironment by secreting antibacterial particles and play a role in helping maintain the intestinal microecology and intestinal mucosal homeostasis. Moreover, PC proliferation and maturation depend on symbiotic flora in the intestine. This paper describes the interactions among susceptibility genes, PCs and intestinal microecology and their effects on IBD occurrence and development.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a disorder of the immune system and intestinal microecosystem caused by environmental factors in genetically susceptible people. Paneth cells (PCs) play a central role in IBD pathogenesis, especially in Crohn's disease (CD) development, and their morphology, number and function are regulated by susceptibility genes. In the intestine, PCs participate in the formation of the stem cell microenvironment by secreting antibacterial particles and play a role in helping maintain the intestinal microecology and intestinal mucosal homeostasis. Moreover, PC proliferation and maturation depend on symbiotic flora in the intestine. This paper describes the interactions among susceptibility genes, PCs and intestinal microecology and their effects on IBD occurrence and development.

IBD is a group of chronic, nonspecific inflammatory diseases that include CD and ulcerative colitis (UC). PCs, derived from intestinal pluripotent stem cells, are gradually growing columnar epithelial cells located at the junction of villi and crypts[1]. During differentiation and maturation, PCs migrate to the base of crypts and spread throughout the small intestine. PCs are pyramidal, and the cytoplasm at the "top" of the pyramid is full of coarse and large eosinophilic secretory granules. The main components are α-defensin, lysozyme, phospholipase A2 and other antibacterial substances that can be released into the intestinal cavity and play an important role in the natural defense of the small intestinal mucosa[2]. Due to the high secretion capacity of PCs and their close relationship with intestinal microecology, PC abnormalities and flora disorders often occur in the intestinal inflammatory response[3]. In recent years, PCs have been found throughout the gastrointestinal tract, including the stomach and colon. However, the distribution of PCs throughout the gastrointestinal tract occurs mainly as a response to mucosal inflammation, and PC presence in abnormal areas is called metaplasia. Colorectal PCs are widely found in UC and inflammatory enteritis[4].

In the past 20 years, the results of whole-genome scanning have revealed that IBD susceptibility genes are distributed on chromosomes 1, 3, 4, 5, 6, 7, 10, 12, 14, 16, 19 and X, among which 9 susceptibility genes associated with IBD were named IBD1-9: IBD1 on chromosome 16q, IBD2 on 12p13.2-q24.1, IBD3 on 6p, IBD4 on 14q11-q12, IBD5 on 5q31, IBD6 on 19p13, IBD7 on 1p36, IBD8 on 16p and IBD9 on 3p26[5]. Studies have shown that more than 200 gene loci are associated with IBD susceptibility, including more than 150 that increase the risk of CD[6]. Studies have shown that IBD susceptibility genes can affect the important physiological processes of PC, leading to abnormal PCs and promoting the occurrence and development of intestinal mucosal inflammation[7].

Changes in the intestinal microecology are involved in IBD pathogenesis, which mainly manifests as a flora imbalance, including flora diversity, species and abundance changes. Studies have shown that the abundance of Firmicutes and Bacteroidetes, which dominate the intestinal flora of IBD patients, decreases, while the proportion of Proteobacteria and actinomycetes increases[8]. Therefore, based on the above knowledge, this paper reviews the relationship among PCs, susceptibility genes, intestinal microecology and IBD.

THE ORIGIN AND METAPLASIA OF PCS

In 1745, German anatomist Johann Nathanael Lieberkuhn first described intestinal glands, or crypts, present in the intestines. In 1872, Gustav Schwalbe observed PCs in the crypt of the small intestine. In 1888, the Austrian physician Joseph Paneth described PCs graphically as a group of specialized cylindrical cells in the crypts of the small intestine epithelium, whose cytoplasm is filled with granular matter. The cells have been named PCs in honor of Dr. Paneth. PCs are rare cells in the small intestine that provide the host with protection against microbial invasion. Their function is the secretion of antibacterial proteins.

When bacteria or bacterial antigens invade the body, PCs secrete antibacterial molecules such as defensins between the villi of the bowel to help maintain the gastrointestinal barrier[9]. PCs are characteristic cells of the small intestinal gland, located at the bottom of the gland, the cells are pyramidal, and the top cytoplasm is full of coarse and large eosinophilic secretory particles. Under the electron microscope, the cytoplasm contains a large number of rough endoplasmic reticulums and developed Golgi complexes, and the secretory particles contain defensin and lysozyme, which can kill intestinal microorganisms. Most of the substances secreted by PCs are antibacterial proteins, which are expelled from the

recess of the small intestine and dispersed into the mucosal layer to assist the mucosal immune barrier in its function. Later, PCs were found in the gastrointestinal tract, including the stomach, small intestineand colon[10]. However, PCs in the gastrointestinal tract are mainly found in response to mucous membrane inflammation, which is called metaplasia in abnormal colorectal regions. Paneth cell metaplasia is widespread in inflammatory enteritis.

PHYSIOLOGICAL FUNCTION OF PCS

Providing a niche for small intestinal stem cells in intestinal crypts

In adult mammalian tissues, the small intestine epithelium has a remarkable capacity for self-renewal. The renewal of the small intestinal epithelium depends on stem cells in the small intestinal crypt. Progenitor cells differentiated from small intestinal stem cells migrate from the bottom of the crypt to the small intestinal villi and continue to differentiate into goblet cells, plexus cells, neuroendocrine cells, intestinal epithelial cells and other cells[11]. After differentiation, these cells migrate from the crypt to the apex of the villi, where they gradually die and are replaced by new cells that migrate from the lower end. Intestinal epithelial cells have a life cycle of only four to five days, and this rapid self-renewal is thought to be essential for intestinal integrity. PCs are also derived from small intestine stem cells, but unlike other cells, PCs do not migrate upward after they are produced[12]. They always reside in the crypt, and the lifespan of this group of cells is more than 1 mo.

Intestinal stem cells are located at the base of the crypt, and recent research suggests that there may be two types of stem cells present. One type is crypt base columnar cells (CBC cells), which are spaced apart from PCs at the base of the crypt[13]. The target gene of Wnt, Lgr5, is the most representative marker of CBC cells and is expressed on the surface of CBC cells. The other type is static +4 cells, which are located above PCs, and the main markers include Bmi-1, Hopx, mTert and Lrig1. Little is known about +4 cells, but studies have shown that there is a close relationship between CBC cells and PCs[14].

The close spatial relationship between PCs and CBC cells has prompted speculation that PCs provide an important niche for stem cells[15]. However, one laboratory refuted this hypothesis. They created a transgenic mouse model in which PCs specifically expressed diphtheria toxin, causing most PCs to be knocked out, but this did not affect the proliferation of CBC cells in the crypt[16]. Later, with the identification of the Lgr5 marker and the establishment of a crypt system in vitro, the hypothesis that PCs provide a niche for stem cells was re-established. In vitro, isolated Lgr5^{hi} CBC cells hardly grew into crypt bodies[17]. However, when PCs and stem cells were cultured together, the stem cells could differentiate and develop into crypt bodies. Further studies in *in vivo* mouse models, including the Gordon model mentioned earlier, showed that knocking out PCs resulted in the loss of Lgr5 stem cells[18]. In terms of gene expression, PCs produce not only germicidal substances but also epidermal growth factor, Wnt3 and Notch ligand Dll4 in large quantities, providing necessary conditions for PCs to become a niche[19]. In conclusion, PCs provide the necessary niche signal for Lgr5^{hi} CBC stem cells (Figure 1).

Regulation of the intestinal flora

PCs contain a large number of endoplasmic reticulum and Golgi complexes, which have a major role in protein secretion. The main secretions of PCs are protein polypeptides with bactericidal ability, such as the cryptdin-related sequence peptide, lysozyme, IIA secretory phospholipase A2 (secretory group IIA phospholipase A2), regenerated insulin-derived proteins REG3β and REG3γ, angiogenin 4, and ANG4[20].

Antimicrobial peptides are important effectors in the innate immune response against pathogenic microbial infection. α-Defensins are one of the earliest recognized antimicrobial peptide families. They are the main components of secretory granules in phagocytes[21]. In addition to phagocytes, epithelial cells in various mucous membranes also secrete α-defensin. Mouse PCs secrete several subtypes of defensins, which can be divided into 6 subtypes from 1 to 6 by purification analysis in vitro. Immunohistochemical analysis showed that α-defensin was specifically expressed in PCs and was secreted into the intestinal cavity in a polar manner[22]. These α-defensins, which are secreted extracellularly, are thought to have important host defense functions.

Defensins are a class of small (15-20 residues) cationic proteins rich in cysteine. They are amphoteric molecules that can bind to bacterial cell membranes and form transmembrane ion channels, destroying the integrity of the membranes and causing cell contents to leak, thus killing bacteria[23]. At the same time, defensins can inactivate a variety of bacterial toxins by combining with them in order to denature them. However, how intestinal symbiotic bacteria coexist with the abundant bactericidal defensins in the gut has always been a perplexing problem. Recent studies have shown that intestinal symbiotic bacteria usually express dephosphatase (LpxF) to remove negative charges on the surface of bacteria to resist killing by cationic antibacterial peptides such as defensins[24].

Studies have shown that α-defensin secreted by PCs plays an important role in the response to pathogen infection. Gram-positive bacteria, gram-negative bacteria, lipopolysaccharide, muramic acid, muramyl dipeptides, and lipid A all stimulate defensin secretion by PCs in the small intestine[25]. Live fungi and protozoa do not stimulate PC degranulation. When PCs in the mouse small intestine encounter pathogens or pathogen antigens, they secrete granules rich in antimicrobial peptides within a few minutes to kill pathogenic microorganisms[26]. This secretion activity is dose-dependent for the pathogens or pathogen antigens. α-Defensins account for 70% of the total antimicrobial peptide killing activity[27].

It has been found that α-defensin derived from PCs plays an important role in establishing and maintaining the balance of intestinal microecology[28]. Mouse α-defensin is synthesized as a nonactivated precursor peptide and must be cleaved by matrix metalloproteinase 7 (MMP7) to be activated[29]. Two animal models, DEFA5 transgenic mice and MMP7-deficient mice, have been studied. DEFA5 transgenic mice express α-defensin 5 (also known as HD-5), which is an α-

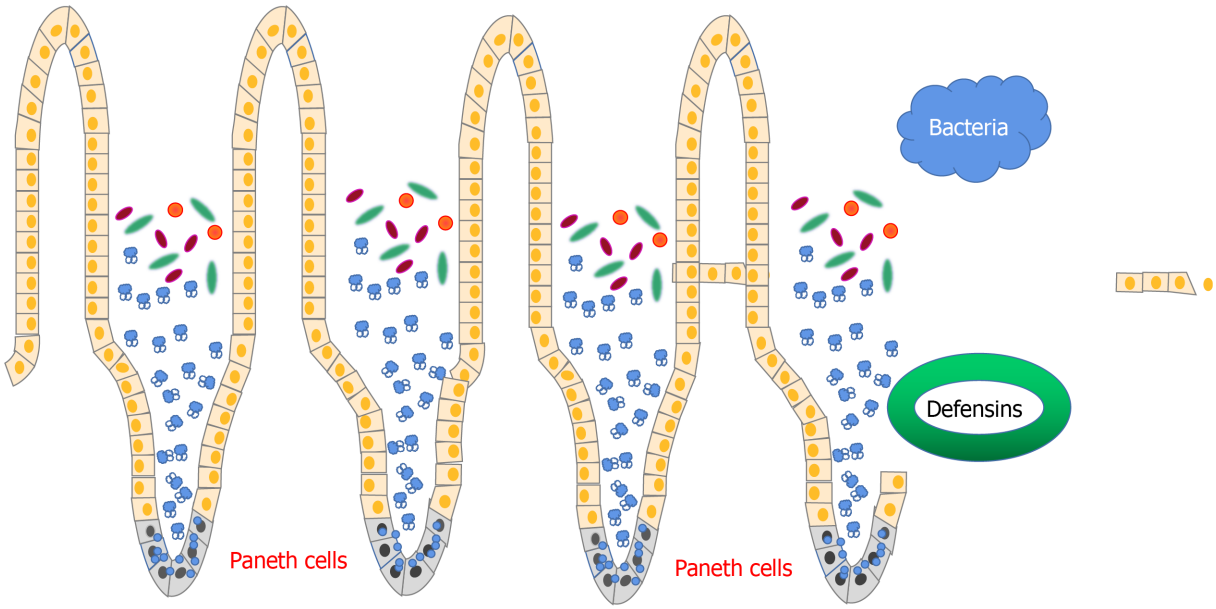

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Figure 1 Physiological function of Paneth cells.

defensin overexpression model[30]. MMP7-deficient mice do not produce active α-defensin and are a model of α-defensin deficiency in the small intestine. In both mouse models, the mRNA expression levels of PC effector factors, such as lysozyme, Defa1 and Defcr4 encoding α-defcr4, and the total number of intestinal bacteria did not change significantly, but the composition of intestinal bacteria did[31]. The proportion of Firmicutes in DEFA5 transgenic mice was significantly reduced, while the proportion of Bacteroides was significantly increased, but the opposite result was obtained in MMP7-deficient mice[32]. This suggests that changes in intestinal bacterial composition are dependent on α-defensin but α-defensin does not affect the total number of intestinal bacteria[33]. Moreover, segmented filamentous bacteria, important members of Firmicutes, were barely detected in DEFA5 transgenic mice, and the proportion and number of Th17 cells in the lamina proper were also affected. These results indicate that α-defensins derived from PCs affect the intestinal symbiotic bacterial composition and intestinal homeostasis[34].

PCs not only secrete antimicrobial peptides stored in vesicles under microbial stimulation but also regulate the production of some antimicrobial peptides upon sensing microorganisms[35]. It has been found that the presence of enterobacteria can greatly enhance REG3γ expression in PCs, the upregulation of REG3γ expression depends on the MyD88 signaling pathway of the downstream adaptor molecule of the Toll-like receptor (TLR), and the REG3γ expression is necessary to prevent microbial invasion into the host tissue. Using a model with MyD88 overexpression in PCs, researchers found that PCs directly sense microorganisms through the TLR-MyD88 pathway and activate the expression of MYD88-dependent antimicrobial peptides, such as Reg3γ[36]. These results demonstrated that MyD88 signaling pathway activation in PCs is sufficient to prevent microbial invasion of the host and does not require MyD88 signaling from other sources, such as bone marrow cells[37]. This study further employed a mouse model with a defensin promoter regulating the expression of diphtheria toxin (CR2-tox176) to deplete PCs and showed that mice with PC depletion did not effectively control intestinal symbiotic and pathogenic bacterial invasion into the spleen and mucosa-associated lymph nodes. Thus, the antibacterial substances derived from PCs are very important for controlling the invasion and diffusion of microorganisms in vivo[38].

SUSCEPTIBILITY GENES

The major susceptibility gene on chromosome 16

Nucleotide-binding oligomeric domain protein 2 (NOD2)/CARD15, the first discovered C and D susceptibility gene, is located around the centromeres of chromosome 16 (16q12) and is mainly expressed in macrophages and PCs specific to the small intestinal gland. It encodes 2 CARD domains and 6 LRR (1 eukaryotic repeat) proteins. CARD15 protein activates NF-κB by recognizing the muramyl dipeptide (MDP) of foreign bacteria and plays a role in the immune response to bacterial LPS[39]. In addition, CARD15 can induce the expression of human β-defensin-2 (HBD-2) in epithelial cells when encountering invading microorganisms, which constitutes the first line of rapid defense of epithelial cells against foreign microorganisms[40]. Therefore, mutation of the *CARD15* gene and subsequent alteration of the structure of the encoded protein is a risk factor for CD[41]. Most studies suggest that NOD2/CARD15 is closely related to genetic susceptibility to CD but not to UC. However, the presence of *TL4* or *CD14* gene mutations in conjunction with NOD2/CARD15 mutations increases UC susceptibility. The genes in IBD1 near D16s408 are also associated with the incidence of UC. For example, single allelic mutations increase the incidence of UC, while double allelic mutations can

lead to severe CD[42]. Therefore, although not as significantly as with C and D, the *NOD2* gene is also associated with UC.

The major susceptibility gene on chromosome 12

The human leucine-rich repetitive kinase 2 (LRRK2) gene consists of 51 exons located on chromosome 12q12 and encodes the LRRK2 protein, a multidomain protein composed of 2527 amino acids. LRRK2 is a multidomain protein kinase with a wide range of functions, including vesicle transport and entosis, protein synthesis, immune response regulation, and inflammation[43]. The LRRK2 protein consists of an ARM repeat, ankyrin repeat (ANK), leucine-rich repeat region (LRR), Ras protein complex (ROC), Ras protein C-terminal repeat (COR), kinase domain (MAPKKK) and tryptophan aspartic acid repeat region (WD40)[44]. Three scaffold domains, ANK, LRR and WD40, are involved in interactions with other proteins that can maintain the conformation and stability of those proteins. The ROC domain and MAPKKK domain are related to the GTPase activity and kinase activity of LRRK2, respectively, while the functions of the ARM repeat sequence and COR domain are not clear. Y1699C and R1628P mutations in the ROC domain have been found to be associated with Parkinson disease (PD) and leprosy, respectively[45]. Pathological and physiological studies of LRRK2 have indicated that the LRRK2 domain is significantly related to its various cellular functions, suggesting that LRRK2 is a pivotal protein with a wide range of functions. Gain-of-function mutations in the LRRK2 kinase domain lead to increased LRRK2 kinase activity and play an important role in disease pathogenesis[46].

TL1A gene

Most members of the tumor necrosis factor (TNF)/tumor necrosis factor receptor superfamily proteins (TNFR SFP) are expressed in immune cells and play a key role in the immune response[47]. Tumor necrosis factor ligand 1A (TL1A), a member of the TNFSF family, is the encoding product of the *TNFSF 15* gene, and its expression is increased in the intestinal inflammatory region of patients with IBD[48]. TL1A protein has been found to be expressed in mononuclear macrophages and CD4+/CD8+ lymphocytes in the intestinal lamina propria in patients with CD, and the expression level and the number of positive cells were positively correlated with the severity of intestinal lesions[49]. Furthermore, the number of DR3-positive T lymphocytes increased in the intestinal lamina propria of CD patients. The uniform upregulation of TL1A and DR3 expression indicates that downstream cytokines after TL1A and DR3 binding play an important role in CD[50]. In addition, TL1A helps balance promotion and inhibition of the inflammatory response in the intestinal mucosa in CD. At the initial stage of inflammation, when T cells are recruited to the inflammatory site of intestinal mucosa, TL1A interacts with DR3 to enhance inflammatory cytokine secretion, and these cytokines cause the recruitment and activation of macrophages and neutrophils, stimulating further inflammation[51].

ATG16L1 gene

The *Atg16L1* gene, which is involved in autophagy, is related to CD development and plays an important role in PCs, suggesting the importance of autophagy to the normal physiological function of PCs. CD patients with Atg16L1 mutations have an altered gut microbiota and abnormal PC granules[52]. A similar phenomenon was observed in mice with low expression of Atg16L1 protein. Notably, Zhang *et al*[53] found that autophagy of PCs was specifically activated in some CD patients, and this state was not related to mucosal inflammation and Atg16L1 mutation. This result suggested that in addition to Atg16L1, more autophagy-related genes might be involved in the pathological mechanism of CD[54]. Moreover, we do not currently know which genes are involved. Additionally, autophagy and endoplasmic reticulum stress have compensatory effects in PCs. When Atg16L1 and Xbp1 were knocked out simultaneously in the intestinal epithelium, mice developed more severe idiopathic enteritis than when either gene was knocked out alone[55].

PHYSIOLOGICAL FUNCTION OF INTESTINAL MICROECOLOGY

Changes in intestinal microecology are involved in IBD pathogenesis and development. Intestinal microecology includes intestinal microbes, intestinal epithelial cells and immune cells, among which intestinal microbes play the most important role in intestinal microecology[56]. Intestinal microorganisms are distributed on the surface of the intestinal cavity and are mainly composed of bacteria, viruses, fungi and parasites, among which the number of bacteria is approximately 10^{14}, approximately 10 times the number of human cells[57]. The total weight of intestinal bacteria is approximately 0.2 kg, accounting for 60% of the dry weight of stool. There are more than 50 bacterial groups and approximately 1100 species, most of which are Bacteroides and Firmicutes (90%), while a small portion are Actinobacteria and Proteus[58]. Many factors have been found to influence the composition of gut microbes. At birth, the environment can directly affect the intestinal microflora, including the birth canal, early diet, antibiotic use, pet contact, sex, and the mother's health, all of which are related to the intestinal microflora composition of infants in the early period[59]. The intestinal microbial diversity of infants under 1 year of age increases rapidly and tends to stabilize at 3 years of age, the intestinal microbial composition becomes more stable at 5 years of age, and Bacteroides dominates. Adult exposure to various environmental factors (such as smoking, air pollution, hygiene habits, stress, diet, drugs, *etc*.) can change the intestinal microbial composition[60].

Evidence suggests that the intestinal barrier plays an important role in intestinal microbial maintenance. The intestinal barrier is composed of intestinal symbiotic bacteria, the intestinal mucous layer, the intestinal epithelium and various lymphocytes in the lamina propria[61]. The intestinal mucus layer covers the intestinal epithelium, and its components are secreted by intestinal epithelial cells; this layer act as a physical barrier between the flora and the intestinal epithelium and provides nutrients and a living environment for the intestinal flora[62]. The mucus layer is rich in mucus secreted by

goblet cells, a variety of antibacterial substances secreted by PCs and ordinary epithelial cells, and IgA secreted by B cells, which are difficult obstacles for intestinal bacteria to cross, effectively preventing contact with and invasion of intestinal epithelium by intestinal bacteria and preventing inflammation[63]. Intestinal epithelial cells include goblet cells, PCs, M cells, neuroendocrine cells and absorptive intestinal epithelial cells, and intestinal epithelial cells are mainly connected by tight junctions, which can prevent the invasion of bacteria and their derivatives[64]. Moreover, there are a variety of gut-associated lymphoid tissues in the intestinal epithelium and lamina propria, such as Peyer's patches in the small intestine and lymphatic follicles and colonic patches in the large intestine[65]. Many immune cells, such as dendritic cells, T lymphocytes and B lymphocytes, exist in these enteric-associated lymphoid tissues. These lymphocytes cooperate with each other to promote immune tolerance and participate in host defense. Among them, M cells and dendritic cells directly sense intestinal contents and transmit information about the intestinal flora to other immune cells, inducing an immune response or tolerance[66].

INTERACTION OF PCS WITH INTESTINAL MICROECOLOGY

PCs regulate intestinal microecology and intestinal epithelial regeneration and differentiation

Normally, PC secretions are slowly released, and degranulation can be caused by feeding, microbial stimulation, and M receptor agonists[67]. There are many bacteria or foreign bacteria in the lumen. PCs can directly detect bacteria and express large quantities of particulate matter containing antibacterial factors through TLRs, which induces degranulation to increase the concentration of antibacterial factors in the intestinal cavity, inhibit the invasion of exogenous microorganisms, and control the microbial population in the small intestine[68]. This is an important reason why the microbial colonization density in the small intestine is lower than that in the large intestine. Therefore, PCs play important roles in controlling the passage of symbiotic bacteria and pathogenic bacteria through the intestinal barrier and in maintaining host and microbiological stability on the mucosal surface[69].

PCs and crypt basal columnar stem cells together constitute the stem cell microenvironment. The epithelial growth factors Wnt3 and Notch act on intestinal stem cells, which can promote self-renewal of intestinal stem cells and immune differentiation of different intestinal cell lines[70]. Therefore, PCs can regulate intestinal microecology and maintain intestinal mucosal homeostasis through mucosal defense and regulation of intestinal epithelial differentiation[71].

The distribution and maturation of PCs depend on intestinal microecology

Studies have shown that the distribution of intestinal bacteria in ordinary wild mice, laboratory mice and specific pathogen-free mice decreased successively, and the distribution of PCs in the same part of the small intestine of mice among these three populations also decreased successively, suggesting that the reduction in the number of bacteria in a certain part of the small intestine could lead to a decrease in the number of PCs in that part of the small intestine[72]. After consumption of amoxicillin for 3 d, the number of PCs in each segment of the small intestine decreased significantly, which may be because amoxicillin, as a broad-spectrum antibacterial, can kill a large number of gram-positive and gram-negative bacilli in the intestine, resulting in a decrease in the total number of bacteria in each segment of the small intestine and then the number of PCs in each segment of the small intestine[73]. However, after 1 d of amoxicillin consumption, the number of PCs in the jejunum and ileum increased significantly, which may be related to the sudden disturbance of intestinal microecology leading to a temporary increase in the number of PCs in a certain period of time, which improves the body's defense function[74].

In normal mice at 4 to 6 wk of age, there is a certain degree of particle abnormality in PCs, but with increasing age, the number of normal PCs gradually increases, while the number of abnormal PCs gradually decreases[75]. However, there is no obvious PC proliferation and maturation with age in germ-free mice. Compared with that in conditions without specific pathogens, the average number of PCs per crypt is lower under completely sterile conditions, and the proportion of the normal form of PCs was almost zero in young and old mice[76]. This finding suggests that the number, morphology, and maturation of normal PCs are dependent on the intestinal flora[77].

Changes in intestinal microecology have an obvious effect on the number of PCs in the small intestine of mice[78]. After *Escherichia coli* (*E. coli*) infection, the number of PCs in each segment of the small intestine of mice is significantly reduced, which may be related to intestinal damage caused by *E. coli* infection[79]. Studies have shown that the intestinal villi of mice infected with *E. coli* have varying degrees of damage, and the longer the infection extends, the more serious the intestinal villus damage, especially duodenum damage, which is the most serious, with thinning of some parts of the intestinal wall and intestinal inflammatory cell infiltration[80]. In addition, the decrease in the number of PCs after *E. coli* infection may be related to the large number of released particles participating in the intestinal inflammatory response [81]. A significant decrease in the number of PCs will lead to a decrease in the barrier defense function of the intestinal tract, resulting in further damage to the small intestine of mice by opportunistic pathogens or infecting *E. coli*[82]. Therefore, with the extension of infection time, the number of PCs is significantly reduced. Thus, the number of PCs is closely related to the intestinal microecological balance.

PANETH CELL ABNORMALITIES AND MICROECOLOGICAL DISORDERS IN IBD

PC abnormalities in IBD patients and mouse models

PCs are an important component of the intestinal epithelial barrier, so it is not surprising that functional abnormalities of

PCs play a role in CD development[83]. The first pathological analysis of small intestine samples from CD patients revealed the presence of intracellular vesicle abnormalities in PCs in these patients[84]. A better understanding of the role of PCs in CD development resulted from the discovery of CD susceptibility genes. A study showed that a CD susceptibility gene was highly expressed in PCs, which supported PCs as the origin of the disease[85]. Recently, it has been found that many CD susceptibility genes are involved in the important physiological activities of PCs, and research on the pathways regulated by these genes has revealed the significance of these pathways in regulating the physiological activities of PCs[86].

The abnormalities of PCs in IBD are mainly reflected in the abnormal quantity, morphology and function of PCs and their secretory granules[87]. Upon morphological examination of PCs from CD patients, abnormal PCs were found in 20%-50% of patients. Changes in susceptibility genes or risk-associated polymorphic sites can also cause PC abnormalities, and the more susceptibility genes CD patients carry, the higher the proportion of abnormal PCs[88]. For example, mutations in the CD susceptibility genes Atg16 L1 and Xbp1 resulted in abnormal particle morphology and a reduced number of PC particles in genetically deficient mice and in CD patients. Abnormal particle morphology and antimicrobial protein packaging in PCs were also observed in engineered CD-associated autophagy protein-deficient mice[89].

Microecological dysregulation in IBD patients and mouse models

Many studies have shown that microecological disorders exist in the intestinal tract of both IBD patients and mouse models[90]. Obvious PC defects can be seen in children with CD, and abnormal PCs can cause an increased abundance of inflammatory bacteria (*Corynebacterium*, *Erysipelotrichaceae*, *etc.*) and reduced abundance of barrier bacteria (*Faecalibacterium*, *Blautia*, *etc.*). *Prevotella* was found to be significantly enriched in IBD patients with susceptibility genes, which may lead to a loss of intestinal barrier function and in turn to increased epithelial cell penetration and chronic inflammation [91].

PC ABNORMALITIES MEDIATED BY SUSCEPTIBILITY GENES AND MICROECOLOGICAL DISORDERS PROMOTE THE DEVELOPMENT OF INTESTINAL INFLAMMATION

Effects of the NOD2 gene on PCs and intestinal inflammation

Nod2 is the most significant CD susceptibility gene. In macrophages, NOD2 recognizes bacterial-derived muramyl dipeptides and activates the immune response[92]. Three major Nod2 mutants (R702W, G908R and L1007insC) have been found to be associated with the development of CD, resulting in the inability of NOD2 to effectively activate the downstream immune response[93]. In NOD2-deficient mice, α-defensin expression in PCs is decreased, terminal ileal symbiosis was increased, and pathogenic bacteria were enriched. In particular, granulomatous inflammation characterized by increased expression of Th1-related genes and inflammatory cytokines was observed in the ileum of NOD2-deficient mice inoculated with *Helicobacter* hepatis[94]. However, the overexpression of α-defensin in mouse PCs *via* transgenic technology resulted in decreased Th1 inflammation. Therefore, NOD2 can effectively inhibit the development of Th1-induced ileal granulomatous inflammation in mice. It is currently believed that lysozyme sorting in PCs is carried out through a NOD2-LRRK2-RIP2-Rab2A pathway dependent on intestinal symbiotic bacterial stimulation[95]. The absence of any one of NOD2, LRRK2, RIP2, Rab2A or symbiotic bacteria will cause lysozyme in PCs to be degraded by lysosomes, resulting in the breakdown of the balance between the organism and symbiotic bacteria, thus promoting the occurrence of CD[96].

However, the specific role of Nod2 mutations in the development of inflammatory enteritis is still under investigation. Because all three Nod2 mutations reduce the ability of Nod2 to activate the immune response, Nod2$^{-/-}$mice are widely used to study the role of NOD2 in inflammatory enteritis[97]. Nod2 is mainly expressed in PCs and bone marrow-derived lymphocytes in the small intestine. The downregulation of α-defensin expression in Nod2$^{-/-}$mouse PCs was reported to result in a decreased immune response to listeria[98]. It has been found that α-defensin expression in PCs is significantly reduced in patients with ileum CD compared with that in healthy individuals or patients with other types of IBD[99]. The decrease in α-defensin levels in PCs is not affected by intestinal inflammation, suggesting that the decrease in α-defensin levels is not caused by inflammation but is probably an inherent phenomenon that occurs early[100]. There was also a decrease in α-defensin levels in CD patients with 1007fs (SNP13) NOD2 mutations. However, some studies have not been able to identify defects in α-defensin production in Nod2$^{-/-}$ mice, which may be related to the genetic background of the mice[101]. Additional studies have shown that Nod2 functions by regulating the intestinal flora, as Nod2$^{-/-}$ mice have an altered intestinal flora, and Nod2$^{-/-}$ mice have granulomatous lesions in the ileum after infection with *Helicobacter pylori*, consistent with the pathological state of CD[102]. This granulomatous damage is relieved when PCs of Nod2$^{-/-}$ mice are transferred to α-defensin HD5 gene knockout mice.

Effects of LRRK2 gene deficiency on PCs and intestinal inflammation

TLRs in PCs can activate and promote the formation and secretion of antibacterial particles such as lysozyme after directly sensing intestinal bacteria and their metabolites. NOD2 secreted by PCs senses the presence of symbiotic bacteria by detecting the cell wall acyl dipeptides of symbiotic bacteria, and symbiotic microbiota-derived signals trigger NOD2 binding to receptor interaction protein 2 (RIP2)[103]. LRRK2 and Rab2a are recruited into dense core vesicles (DCVs) containing lysozyme to regulate the sorting of lysozyme in DCVs[104]. In this process, on the one hand, LRRK2 can affect the composition of intestinal microorganisms by regulating lysozyme sorting. On the other hand, symbiotic flora constituents can not only guide lysozyme sorting in PCs but also promote symbiosis between the symbiotic flora and host

through the NOD2-LRRK2-Rab2a axis[105].

Cellular life activities depend on the precise transfer and directional transport and secretion of intracellular substance transport systems. If the regulation of the vesicle transport system is abnormal, the normal life activities of cells will be affected[106]. Abnormal PC vesicle transport, characterized by a reduced number of DCVs containing lysozyme, occurs in CD patients[107]. A similar phenomenon was also observed in LRRK2$^{-/-}$ mice. Although the expression level of lysozyme mRNA in the PCs of LRRK2$^{-/-}$ mice was normal, lysozyme deficiency was also found in the intestinal cavity because lysozyme was degraded by intracellular lysosomes[108]. However, other antibacterial substances, such as defensin and islet RegIIIγ, in PCs were not affected by LRRK2 knockout, suggesting that LRRK2 can specifically regulate lysozyme transport and secretion in PCs[109].

CD patients often exhibit significant dysregulation of innate immunity in the intestine. In CD pathogenesis, cytokines such as interferon-γ (IFN-γ), IFN-β, TNF-α and IL-6 can induce and upregulate LRRK2 expression[109]. Additional studies have shown that LRRK2 is involved in inflammatory cytokine production and macrophage chemotaxis in the innate immune response. LRRK2 mutation may regulate the innate immune response in CD14+ monocytes[110]. Therefore, abnormal LRRK2 expression may aggravate the innate immune disorder and further damage the tissue.

The NOD(1/2)/RIP2 signaling pathway is an important signaling pathway for the innate immune response to bacterial infection and endoplasmic reticulum stress[111]. LRRK2 enhances the activity of RIP2 by promoting the phosphorylation of RIP2 at Ser176, thus enhancing NOD(1/2)/RIP2 signaling and promoting the production of inflammatory cytokines [112]. Because LRRK2 overexpression activates NF-κB and promotes inflammatory cytokine secretion in lamina propria dendritic cells in mice, an LRRK2 overexpression group exhibited more severe colitis symptoms in DSS-induced colitis mice than a control group (wild-type mice)[113]. LRRK2 inhibitors can reduce LP-induced TNF receptor-related factor 6 (TRAF6) interaction with LRRK2 and inhibit MAPK and NF-κB suppressor protein α (Ik Bα) phosphorylation by inhibiting LLP-induced kinase activity of the LRRK2 protein[114]. Thus, the production of the inflammatory cytokine TNF-α in the dendritic cells of CD patients is reduced, which exerts an anti-inflammatory activity and ameliorates the symptoms of DSS-induced colitis[115]. In addition, a similar phenomenon has been found in macrophages, where LRRK2 defects significantly inhibit the secretion of inflammatory cytokines by macrophages when NOD2 is activated by muramyl dipeptide and NOD1 is activated by γ-D-glutamine-racemo-disaminophenic acid (I-e-DAP) or endoplasmic reticulum stress. In conclusion, LRRK2 can positively regulate the secretion of inflammatory cytokines[116].

However, other studies have shown that LRRK2 has the opposite regulatory effect. Activated T nuclear factor (NFAT) is an important mediator in the immune response, while LRRK2 is a major component of the NRON complex, an inhibitor of NFAT[117]. Normally, LRRK2 can trap NFAT by forming NRON complexes in the cytoplasm, thus sequestering NFAT in the cytoplasm[118]. However, in LRRK2$^{-/-}$ mice, LRRK2 deficiency leads to the failure of NFAT sequestration in the cytoplasm, thus causing NFAT translocation to the nucleus and inducing the transcription of inflammatory cytokines, increasing the level of inflammatory cytokines, increasing susceptibility to DSS-induced colitis and aggravating colitis symptoms[119]. This finding suggests that LRRK2 may also negatively regulate the secretion of inflammatory mediators and cytokines by sequestering NFAT in the cytoplasm.

When LRRK2 is defective or mutated, NFAT regulation is altered, which activates the expression of inflammatory genes in macrophages, exacerbating intestinal inflammation in colitis mouse models and leading to the development of CD[120]. It has also been found that the lysozyme mRNA expression level in the PCs of LRRK2$^{-/-}$ mice was normal, but lysozyme is readily degraded by intracellular lysosomes, while other antibacterial substances in PCs are not affected by LRRK2 deletion, suggesting that LRRK2 regulates lysozyme transport and secretion in PCs[121].

Effects of XBP1 gene deficiency on PCs and intestinal inflammation

Another remarkable genetic factor of the CD unfolded protein response (UPR) is the transcription factor X-box binding protein-1 (XBP-1), which is a key transcription factor in the endoplasmic reticulum stress response and is involved in UPR regulation, endoplasmic reticulum amplification, and the development of hypersecretory cells (such as PCs)[122]. XBP-1 can regulate the number of PCs by preventing apoptosis and mediating cell renewal. Furthermore, mucosal defense function and susceptibility to IBD are affected[123]. The specific clearance of XBP1 from IECs induces endoplasmic reticulum stress, PC loss, reduced lysozyme and defensin expression, increased IEC death and idiopathic enteritis. Similarly, PC-specific clearance of XBP1 can produce similar symptoms of spontaneous ileitis, suggesting that the PC-specific UPR plays an important role in maintaining ileal mucosal homeostasis in mice[124]. Xbp1 knockout in the mouse epithelium resulted in spontaneous enteritis in mice[125]. Pathological analysis showed that the deletion of Xbp1 resulted in endoplasmic reticulum stress and a lack of lysozyme and α-defensin expression in PCs[125]. Therefore, XBP1 may play a partially compensatory role in inhibiting proinflammatory signals, maintaining mucosal homeostasis and assisting PC function in mice, thus supporting the function of PCs[126].

Effects of TL1A overexpression on PCs and intestinal inflammation

TL1A/DR3 (TL1A functional receptor) signal transduction can not only promote the proliferation of T-effector cell subsets but also promote the production of cytokines and accelerate the progression of inflammatory diseases[127]. Different levels of TL1A expression in mice have different effects on PCs and intestinal inflammation. With increasing age, the number of PCs in wild-type mice gradually increased, lysozyme particles gradually matured, and there was no spontaneous ileitis[128]. Although the number of PCs in TL1A$^{-/-}$ mice was reduced, normal lysozyme particle morphology was maintained, so spontaneous ileitis did not occur in older TL1A$^{-/-}$ mice[129]. However, in the TL1A-overexpressing mouse model, the number of PCs increased significantly, and the granules did not mature with age, accompanied by spontaneous ileitis and long-distance intestinal stenosis[130]. However, an anti-TL1A antibody could block TL1A function, reverse colonic fibrosis, and reduce existing colonic inflammation. Therefore, overexpression of TL1A can aggravate proximal intestinal inflammation and fibrous stenosis and promote disease progression[131].

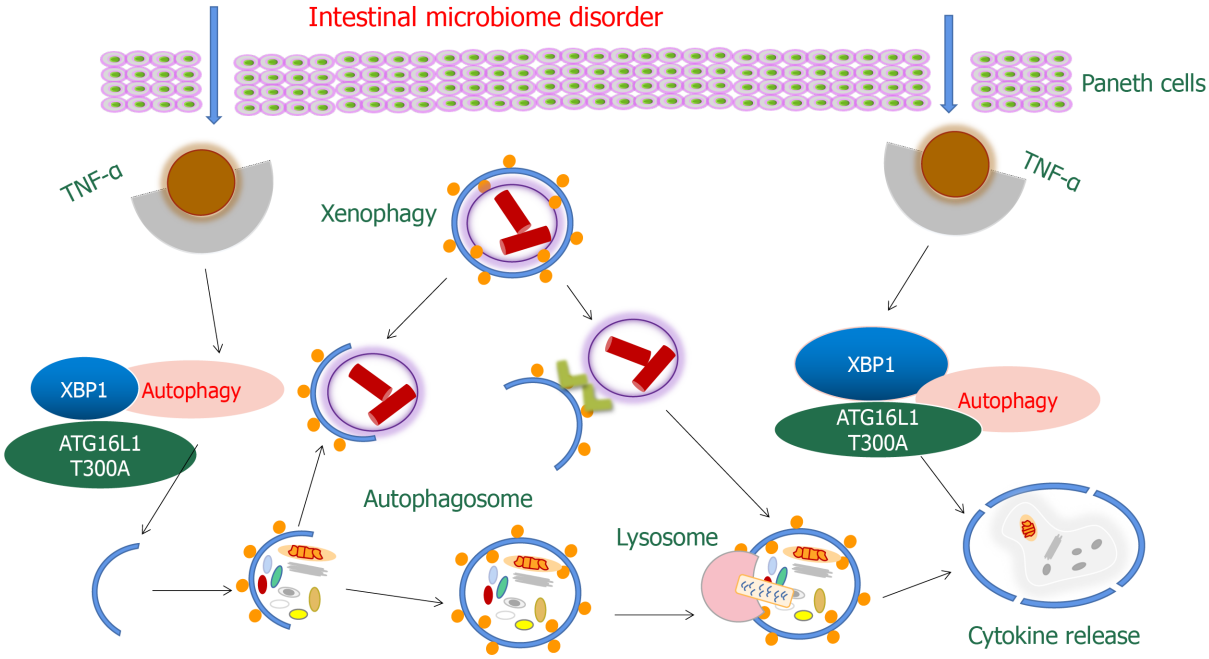

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Figure 2 Paneth cells and intestinal inflammation. TNF: Tumor necrosis factor.

Effects of the ATG16L1 gene on PCs and intestinal inflammation

ATG16L1 is an autophagy-related protein that protects against PC necrosis by participating in autophagosome formation, maintaining autophagy and mitochondrial homeostasis, and preventing PC necrotic apoptosis mediated by TNF-α[132]. In addition, ATG16L1 can also play an important role in the pathogenesis of CD by affecting the extracellular secretion of PC particles in patients or activating the transcription factor XBP1 in the endoplasmic reticulum stress response[133]. In IEC-specific ATG16L1 knockout mice, loss of autophagy resulted in increased IEC sensitivity to TNF-induced cell death. Moreover, since defensins and antimicrobial peptides are mainly secreted by PCs, changes in the abundance distribution of protein components in PCs caused by ATG16L1 defects may also trigger CD[134].

ATG16L1 T300A is the most important risk-associated polymorphic site of ATG16L1. Abnormal particle morphology and antibacterial protein packaging in PCs can be seen in mice injected with ATG16L1 T300A or in CD patients carrying ATG16L1 T300A[133]. Lysozyme in PCs is packaged and secreted in secretory autophagy during bacterial infection, and secretory autophagy was inhibited in mice carrying ATG16L1 T300A in PCs[133]. In addition, ATG16L1 T300A can also reduce selective autophagy, shorten the remission interval, increase cytokine release and reduce intracellular bacterial clearance, leading to abnormal PCs, early immune infiltration and intestinal ecological disorders[134] (Figure 2).

CONCLUSION

IBD pathogenesis is influenced by genetics, the environment, the intestinal flora and immunity, among which abnormal PCs play a central role. Both susceptibility genes and their risk-associated polymorphic loci can cause the development of abnormal PCs, and the more susceptibility genes a patient carries, the higher the proportion of abnormal PCs. The interaction between abnormal PCs and intestinal microecology is reflected in two aspects. On the one hand, the stability of the intestinal microecology needs to be maintained by the physiological function of PCs, and abnormal PCs can also cause an imbalance in intestinal microecology. On the other hand, the proliferation and maturation of PCs depend on intestinal microecology, and environmental conditions can also aggravate the influence of susceptibility genes on PCs by changing the intestinal microecology. Intestinal microecology and susceptibility genes interact with each other. On the one hand, intestinal microecology can enhance the effect of susceptibility gene expression products and promote the occurrence of IBD. If there is no intestinal flora, abnormal susceptibility genes cannot cause idiopathic enteritis. On the other hand, when IBD-related genes are abnormal, the abundance of specific bacteria in the gut is altered, which can disrupt the intestinal barrier and promote chronic inflammation. In conclusion, susceptibility genes may cause PC abnormalities and intestinal microecological disorders, and the interaction among the three can lead to potential diseases or aggravate existing diseases when they reach a specific functional threshold. In the future, more clinical and disease mechanism studies are needed to identify other genes associated with PC abnormalities and explore the cellular and molecular mechanisms of PC abnormalities caused by susceptibility genes. In addition, exploring ways to restore intestinal homeostasis by regulating the intestinal microecosystem, improving diseases by utilizing the mutual benefit between the host and intestinal flora, and identifying peripheral markers related to CD development and PC activity changes can also provide new methods for the diagnosis, treatment and prognosis of CD.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Case-control analysis of venous thromboembolism risk in non-alcoholic steatohepatitis diagnosed by transient elastography

Mithil Gowda Suresh, Maya Gogtay, Yuvaraj Singh, Lekha Yadukumar, Ajay Kumar Mishra, George M Abraham

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Abstract

BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide. Studies have shown a strong association between non-alcoholic steatohepatitis (NASH) cirrhosis and portal vein thrombosis. Specifically, there is paucity of data on the association of NASH and venous thromboembolism (VTE), with one such study predicting a 2.5-fold increased risk for VTE compared to other liver diseases in hospitalized patients. The mechanism is believed to be a hepatocellular injury, which causes a chronic inflammatory state leading to the unregulated activation of procoagulant factors. There has been no prior analysis of the degree of steatosis and fibrosis (measured using transient elastography, commonly known as FibroScan) in NASH and its association with VTE.

AIM

To examine the association between the degree of hepatic steatosis and fibrosis, quantified by transient elastography, and the incidence of VTE in patients with NASH.

METHODS

In our case-control study, we included patients with a documented diagnosis of NASH. We excluded patients with inherited thrombophilia, hemoglobinopathy, malignancy, alcohol use disorder, autoimmune hepatitis, and primary biliary cirrhosis. The collected data included age, demographics, tobacco use, recreational drug use, medical history, and vibration controlled transient elastography scores. VTE-specific data included the location, type of anticoagulant, need for hospital stay, and history of VTE recurrence. Steatosis was categorized as S0-S1 (mild) and S2-S3 (moderate to severe) based on the controlled attenuation parameter score. Fibrosis was classified based on the kilopascal score and graded as F0-F1 (Metavir stage), F2, F3, and F4 (cirrhosis). $\chi 2$ and Mann-Whitney *U* tests were used for the qualitative and quantitative variable analyses, respectively. Furthermore, we performed a logistic regression using VTE as the dependent variable.

RESULTS

A total of 415 patients were analyzed, and 386 met the inclusion criteria. 51 and 335 patients were included in the VTE and non-VTE groups, respectively. Patients with VTE had a mean age of 60.63 years compared to 55.22 years in the non-VTE group ($P < 0.014$). Patients with VTE had a higher body mass index (31.14 kg/m² *vs* 29.30 kg/m²) and a higher prevalence of diabetes mellitus (29.4% *vs* 13.1%). The history of NASH was significantly higher in the VTE group (45.1% *vs* 30.4%, $P < 0.037$). Furthermore, moderate-to-severe steatosis was significantly higher in the VTE group (66.7% *vs* 47.2%, $P < 0.009$). Similarly, the F2-F4 fibrosis grade had a prevalence of 58.8% in the VTE group compared to 38.5% in the non-VTE group ($P < 0.006$). On logistic regression, using VTE as a dependent variable, diabetes mellitus had an odds ratio (OR) =1.702 ($P < 0.015$), and F2-F4 fibrosis grade had an OR = 1.5 ($P < 0.033$).

CONCLUSION

Our analysis shows that NASH is an independent risk factor for VTE, especially deep vein thrombosis. There was a statistically significant association between the incidence of VTE, moderate-to-severe steatosis, and fibrosis. All hospitalized patients should be considered for medical thromboprophylaxis, particularly those with NASH.

Key Words: Nonalcoholic fatty liver disease; Venous thromboembolism; Non-alcoholic steatohepatitis; Diabetes mellitus; Liver fibrosis; Steatosis; Deep vein thrombosis; Anticoagulation management

Core Tip: Our study delineates the intricate relationship between nonalcoholic fatty liver disease (NAFLD) and venous thromboembolism (VTE), highlighting the increased risk and prevalence of VTE in patients with NAFLD-related conditions. Notably, it demonstrates a significant correlation between advanced steatosis and fibrosis grades and the occurrence of VTE, suggesting that patients with more severe NAFLD characteristics require vigilant monitoring for potential thrombotic complications. These insights delineate the necessity for tailored clinical approaches in managing NAFLD patients to mitigate the risk of VTE, marking a substantial step forward in understanding NAFLD's systemic impacts.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has emerged as a global health concern, presenting as a prevalent cause of chronic liver disease worldwide. The geographical distribution of NAFLD exhibits substantial variation, with the highest reported rates in South America (31%) and the Middle East (32%), followed by Asia (27%), the United States (24%), and Europe (23%). Notably, Africa reports a lower incidence, with NAFLD affecting 14% of the population in this continent [1]. This distribution pattern calls for a tailored understanding of NAFLD across populations and unveils the rising epidemic in regions with changing lifestyle patterns. NAFLD encompasses a spectrum of liver conditions, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), progressive fibrosis, cirrhosis, and even hepatocellular carcinoma[2].

Steatosis, an early manifestation of NAFLD, has several well-established risk factors, including obesity, diabetes, and hypertriglyceridemia. Beyond metabolic factors, NAFLD can also be influenced by a myriad of factors such as toxins,

medications (*e.g.*, amiodarone, diltiazem, highly active antiretroviral therapy, steroids, and tamoxifen), and inborn errors of metabolism, encompassing disorders of lipid metabolism and total parenteral nutrition[3,4].

NASH represents a severe, more advanced form of NAFLD characterized by the accumulation of fat in the liver, accompanied by inflammation and progressive fibrosis[5]. The pathogenesis of NASH is intricate and multifaceted, involving a complex interplay of cellular interactions between liver parenchymal and nonparenchymal cells[6]. This intricate crosstalk extends to diverse immune cell populations within the liver microenvironment[7]. Among the prevailing theories, insulin resistance emerges as a central mechanism, with lipotoxicity taking a pivotal role in driving hepatocellular injury through processes such as oxidative stress and endoplasmic reticulum stress[8].

The clinical presentation of NASH varies widely, ranging from asymptomatic cases to vague complaints of fatigue, malaise, and vague right upper abdominal discomfort[9]. Notably, hepatomegaly is a common physical finding in NASH patients[10]. While elevated levels of liver enzymes such as aspartate aminotransferase and alanine aminotransferase are often observed in patients with NAFLD, it's essential to recognize that normal aminotransferase levels do not rule out the presence of NAFLD[11]. NASH not only affects the liver but also has systemic complications, putting patients at risk of severe complications such as venous thromboembolism (VTE). Our research aims to fill the gap in medical literature by investigating the link between NASH and VTE.

The diagnosis and assessment of NAFLD severity have evolved to incorporate noninvasive testing methods. These encompass various imaging techniques such as liver ultrasound, computerized tomography (CT), magnetic resonance imaging (MRI), and vibration controlled transient elastography (VCTE)[12-14]. VCTE, commonly referred to as FibroScan®, utilizes shear wave imaging to estimate liver stiffness[15]. This technique involves the application of mechanical vibrations to liver tissue, with the resulting shear waves measured by an ultrasound detector. Through this method, at least ten valid measurements are obtained during the imaging examination. VCTE offers precise diagnostic capabilities, effectively identifying cirrhosis [fibrosis stage 4 (F4)] and distinguishing advanced fibrosis (F2 or higher) from minimal or no fibrosis (F1 or F0)[4]. Notably, as liver fat content affects ultrasound wave propagation, the controlled attenuation parameter (CAP), which is integrated with VCTE, provides a numerical value reflective of the histological severity of liver steatosis[16].

While recent research efforts have increasingly focused on the diagnosis and management of NAFLD, the connection between NASH and VTE remains an underexplored area in the scientific landscape. A noteworthy study in this regard suggested a 2.5-fold heightened risk of VTE in patients with NASH in comparison to individuals with other liver diseases, particularly among those hospitalized[8]. Additionally, multiple epidemiological and case-control investigations have shed light on an association between NAFLD and elevated vascular thrombotic risk, which appears to be independent of conventional cardiometabolic risk factors[17]. These findings emphasize the existence of a graded relationship between the severity of NAFLD and heightened vascular risk[18]. The prevailing hypothesis attributes this phenomenon to hepatocellular injury, which triggers a chronic inflammatory state, leading to the unregulated activation of procoagulant factors[19].

Surprisingly, there exists a significant knowledge gap regarding the degree of steatosis and fibrosis, as assessed using VCTE, in NASH and its potential connection to VTE. This connection between chronic liver inflammation and systemic vascular events remains a pathophysiological puzzle. By methodically assessing steatosis and fibrosis grades to VTE risk, our study breaks new ground in the quest to understand NASH not just as a hepatic problem but as a systemic one, particularly with its propensity to foreshadow VTE, a potentially life-threatening condition. The findings of our study have significant implications for clinical practice, particularly in relation to the use of medical thromboprophylaxis in patients with advanced NASH. This recommendation is not currently included in existing guidelines, but our research suggests that it could be an effective strategy for reducing the risk of VTE. This investigation not only fills a crucial gap in the literature but also highlights the need for heightened surveillance. This study also spotlights the intersection of hepatology and hematology, needing a multidisciplinary approach to managing the rising epidemic.

MATERIALS AND METHODS

Protocol and registration

The comprehensive investigation into the potential link between NASH and VTE was conducted in adherence to a well-defined protocol. This protocol was developed, reviewed, and sanctioned by the joint institutional review board at MetroWest Medical Center under Approval No. 2020-035. The ethical requirement for individual informed consent was appropriately waived by the institutional review board due to the retrospective nature of this case-control study.

Eligibility criteria

In this case-control study, rigorous eligibility criteria were applied to ensure the accuracy, relevance, and validity of the research findings. Patients who met the following criteria were considered eligible for inclusion in the study: (1) Age criteria: Patients were eligible if they were over 18 years of age, indicating that the study focused on adult populations; (2) Diagnosis of NASH: Patients were required to have a well-documented diagnosis of NASH, ensuring that the studied population had the specific medical condition of interest; (3) VCTE scores: Inclusion necessitated the presence of at least one FibroScan® report, confirming the use of VCTE parameters. This included CAP and kilopascal (KPA) scores, which were key indicators in evaluating hepatic steatosis and fibrosis; and (4) Primary care clinic visits: Eligible patients had a history of at least two or more visits to our primary care clinic, ensuring an adequate medical record history for analysis.

To maintain research integrity and accuracy, several exclusion criteria were also applied, including: (1) Thrombophilia or hemoglobinopathy: Patients with a documented history of inherited thrombophilia or hemoglobinopathy were excluded to minimize confounding factors in the analysis of VTE; (2) Active malignancy: Individuals with an active malignancy were excluded, as malignancies can increase the risk of thromboembolism; (3) Alcohol use disorder: Exclusion of patients with alcohol use disorder ensured that the study focused on non-alcoholic factors related to NASH; (4) Hepatitis B or C infection: Patients with concurrent hepatitis B or C infection were excluded ensuring that the study focused on non-alcoholic factors related to NASH; (5) Autoimmune hepatitis and primary biliary cirrhosis: To maintain homogeneity within the study cohort, patients with autoimmune hepatitis or primary biliary cirrhosis were excluded; (6) Age restriction: To adhere to the adult focus of the study, individuals under the age of 18 years were excluded from the analysis; and (7) Incomplete outpatient records: Patients with incomplete outpatient medical records were excluded to maintain data accuracy and completeness.

Information sources

The data employed in this case-control study were drawn from a dedicated source - patients seen at a single-centered community hospital outpatient clinic. This inclusive dataset covered a substantial time frame, spanning from January 1, 2001, to December 31, 2019. The primary information source for the study consisted of medical records, including crucial imaging reports that confirmed the presence of VTE diagnoses.

Search

The study was inherently retrospective, primarily reliant on the availability of patient data from the designated time frame.

Patient selection

The procedure for selecting patients and categorizing them into the VTE and non-VTE groups was executed with the utmost diligence to eliminate bias. Initial screening for eligibility resulted in the identification of 386 patients who met the above-specified inclusion criteria. From this initial pool, 51 patients were identified as having VTE, constituting the VTE group, while the remaining 335 patients were categorized as the non-VTE group. This clear distinction allowed for precise group comparison, contributing to the robustness of the study findings (Figure 1).

Data collection process

The authors methodically extracted data from a broad array of medical records. The data collection process incorporated a diverse range of variables, each meticulously documented for analysis. Key data elements collected from each patient encompassed demographic information, including age, sex, and race, essential for the contextualization of the findings. Body mass index (BMI), a crucial indicator of patient health, was noted. The presence or absence of diabetes mellitus, human immunodeficiency virus (HIV) status, and substance use - specifically alcohol and tobacco consumption - were accurately documented, allowing for the examination of the potential influence of these factors on VTE in patients with NASH.

Furthermore, the data collection process included the recording of VCTE scores, a pivotal element of the study. The CAP and KPA scores, reflective of hepatic steatosis and fibrosis, were systematically collected, enriching the dataset with specific markers of NASH severity. The scope of this case-control study necessitated the acquisition of VTE-specific data, allowing for a comprehensive analysis of the condition. Variables related to VTE, including the location of VTE events, the type of anticoagulant administered, the duration of treatment, instances of treatment failure, the need for hospitalization, and any history of VTE recurrence, were diligently recorded.

Data items

A wide array of data items was meticulously cataloged and incorporated into the dataset. These variables encompassed: (1) Demographic information: Parameters including age, sex, and race were logged to provide an understanding of the patient population's diversity; (2) Medical history: Crucial medical history elements were documented, such as the presence of diabetes mellitus, HIV status, and substance use (alcohol and tobacco), shedding light on factors that could impact VTE risk in NASH patients; (3) VCTE scores: The CAP and KPA scores were pivotal data points, serving as objective measures of hepatic steatosis and fibrosis, respectively; and (4) VTE specifics: Data on the occurrence of VTE, including location, anticoagulant therapy, treatment duration, instances of treatment failure, need for hospitalization, and VTE recurrence history, provided a comprehensive picture of the VTE aspect of the study. The careful selection and documentation of these data items ensured the robustness and reliability of the dataset.

Risk of bias

Unlike prospective studies, where selection and attrition bias can be assessed, this retrospective design leveraged existing patient data and medical records, minimizing the potential for inherent bias in data collection. The primary focus of the study was on the accurate extraction and analysis of data, ensuring that the risk of bias was kept to a minimum.

Summary measures

Within this multifaceted study, a diverse array of summary measures and variables were considered. The primary outcome, which was the presence of VTE, formed the cornerstone of the analysis. In addition to this primary endpoint, a host of secondary variables were included, encompassing demographics, hepatic steatosis (as assessed through the CAP score), and hepatic fibrosis (evaluated using the KPA score). The inclusion of these additional variables allowed for a

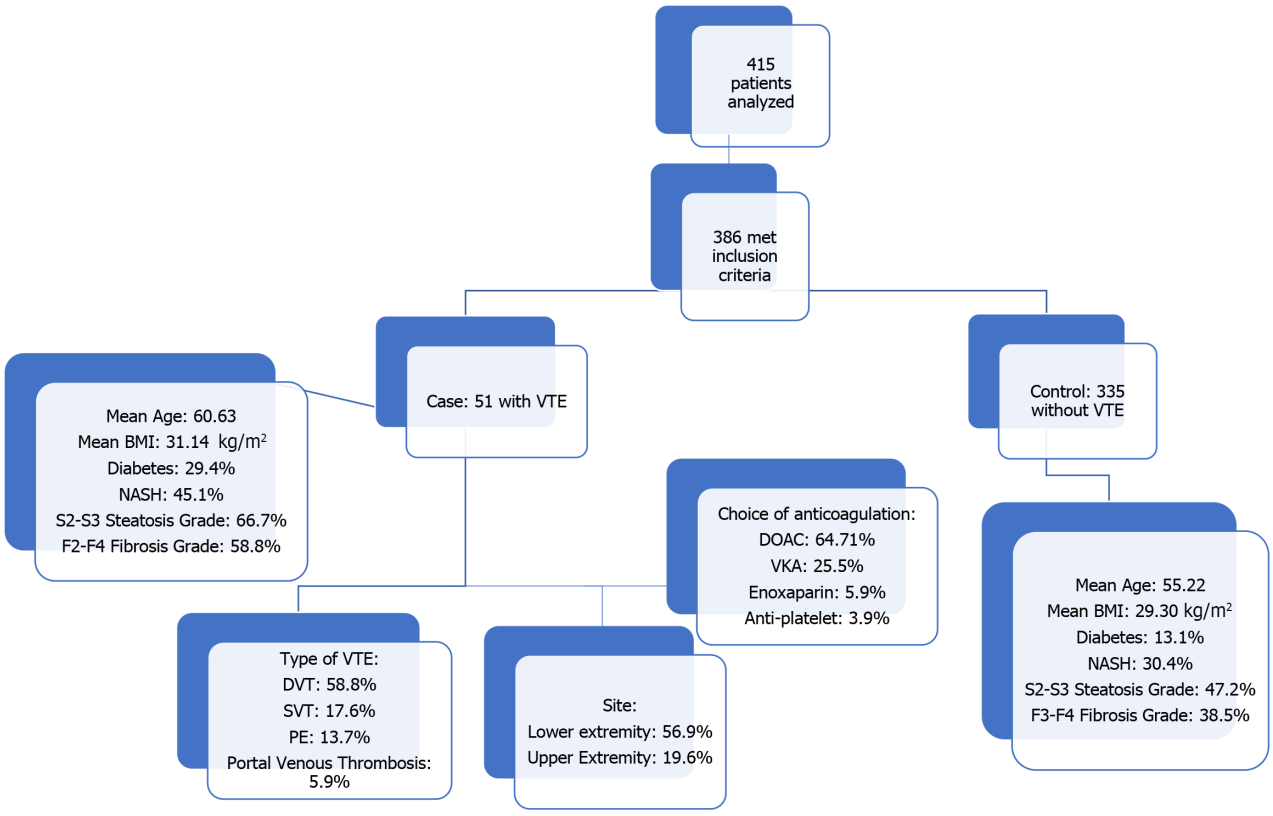

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Figure 1 Study design. VTE: Venous thromboembolism; DVT: Deep vein thrombosis; SVT: Superficial venous thrombosis; DOAC: Direct oral anticoagulant; VKA: Vitamin K antagonist; NASH: Non-alcoholic steatohepatitis; BMI: Body mass index; PE: Pulmonary embolism.

comprehensive examination of the factors influencing the association between NASH and VTE, ensuring a nuanced and holistic approach to the study's objectives.

Synthesis of results

A range of statistical methods were instrumental in the assessment of associations and relationships between variables. These methods included the Mann-Whitney *U* test, χ^2 analysis, and logistic regression, which were chosen to suit the nature of the data and the research questions. The Mann-Whitney *U* test was employed to compare continuous variables between groups, allowing for the evaluation of differences in patient characteristics, including age, BMI, and VCTE scores. This non-parametric test was selected due to its suitability for this data that might not follow a normal distribution.

χ^2 analysis was particularly valuable for assessing associations between categorical variables, such as the presence of diabetes mellitus, HIV status, and substance use, within the study groups. This statistical tool enabled the identification of statistically significant relationships, allowing for a comprehensive understanding of the patient population and their characteristics.

Logistic regression, a more complex statistical technique, was applied to analyze the primary outcome variable, the presence of VTE. This method allowed for the assessment of the influence of NASH, as indicated by hepatic steatosis (CAP score) and hepatic fibrosis (KPA score), on the likelihood of VTE. The results were presented in a clear and informative manner, using tables and figures to succinctly communicate significant findings, associations, and potential risk factors.

The inclusion of these diverse statistical techniques offered a comprehensive approach to data analysis, enabling a nuanced understanding of the complex relationships within the dataset. The resulting findings, supported by statistical evidence, allowed for the vigorous testing of the study's hypotheses.

RESULTS

Patient characteristics

A comprehensive analysis involving 415 patients revealed that 386 of these individuals met the inclusion criteria set for this study. Among the study participants, 51 patients were classified into the VTE group, whereas the remaining 335 formed the non-VTE group. The demographic profile of these two groups showcased notable differences. Firstly, patients in the VTE group exhibited a slightly higher mean age, with an average of 60.63 years, in contrast to the non-VTE group,

which had a mean age of 55.22 years ($P < 0.014$). Gender distribution, racial background, tobacco use, and HIV status showed comparable distribution across both groups. However, key disparities came to light regarding specific health parameters. Patients in the VTE group presented with a higher average BMI (31.14 kg/m^2), notably exceeding the 29.30 kg/m^2 seen in the non-VTE group ($P < 0.041$). Additionally, the prevalence of diabetes mellitus was significantly more pronounced among patients with VTE, accounting for 29.4%, in stark contrast to the non-VTE group's prevalence of 13.1% ($P < 0.002$) (Tables 1 and 2).

Primary outcome: NASH and associated factors

Of particular interest in the primary outcome was the history of NASH, a condition intricately linked to NAFLD. Here, a notable distinction arose between the VTE group and the non-VTE group. In the VTE group, the history of NASH was significantly more prevalent, with 45.1% of patients carrying this diagnosis, while the non-VTE group reported a history of NASH in 30.4% of cases ($P < 0.037$). Moreover, steatosis, a critical parameter characterizing liver fat accumulation, exhibited distinct variations between the two groups. The VTE group displayed a notably higher steatosis score, averaging 279.04, in comparison to the non-VTE group, which had an average score of 249.54 ($P < 0.005$). An even more compelling contrast emerged concerning the fibrosis grade, an essential measure of liver health. In this regard, the VTE group showcased a considerably higher fibrosis grade, quantifying at 15.29, whereas the non-VTE group exhibited a lower average of 12.67 ($P < 0.001$). An in-depth exploration of the data revealed that moderate to severe steatosis (classified as S2-S3) was strikingly more frequent in the VTE group, constituting 66.7% of this patient cohort, compared to 47.2% in the non-VTE group ($P < 0.009$). A similar trend emerged regarding the fibrosis grade. Within the VTE group, fibrosis grades F2-F4 were notably more prevalent, accounting for 58.8% of patients, whereas in the non-VTE group, this grade represented 38.5% of cases ($P < 0.006$). Utilizing logistic regression as an analytical tool, considering VTE as the dependent variable, two critical predictors emerged. Patients diagnosed with diabetes mellitus exhibited an odds ratio (OR) of 1.702 ($P < 0.015$), highlighting a significant association between diabetes and the presence of VTE. Furthermore, a robust association was noted between the F2-F4 fibrosis grade and VTE, with an OR of 1.5 ($P < 0.033$) (Table 3).

VTE analysis

Within the VTE group, a comprehensive analysis of the distribution of VTE types was conducted. Results indicated that 58.8% of these patients presented with deep vein thrombosis (DVT), 17.6% with superficial vein thrombosis, 13.7% with pulmonary embolism, 5.9% with portal vein thrombosis, and 3.9% with embolic stroke (Table 4).

Lower extremity emerged as the most common location for VTE, observed in 56.9% of cases, followed by the upper extremity at 19.6%. In terms of laterality, right-sided VTE prevailed, accounting for 66.7% of cases. Regarding the severity of VTE cases, a significant majority of patients, precisely 74.5%, necessitated hospital admission, with 2% of this cohort requiring admission to the intensive care unit (Table 5).

The management of VTE involved the administration of anticoagulants, and the distribution of anticoagulant types revealed that 64.71% of patients were on direct oral anticoagulants (DOAC), while 25.5% were on warfarin (Table 6). The persistence of indefinite anticoagulation therapy was observed in 84.3% of patients. Furthermore, an impressive 96.1% required the full therapeutic dose of anticoagulation. However, 5.9% of these individuals experienced treatment failure, reflecting the complexity and variability in managing VTE in patients with NAFLD. These findings underscore the multifaceted nature of VTE in the context of NAFLD and the importance of precise diagnosis and tailored therapeutic strategies to address this medical challenge effectively.

DISCUSSION

NAFLD is the most prevalent cause of chronic liver disease in the United States and globally[20]. Within the context of NAFLD, a spectrum of liver conditions can be observed, ranging from healthy liver function to the perilous extremes of cirrhosis and primary liver cancer. This characterization underscores the importance of closely monitoring liver health and taking proactive steps to mitigate risk factors associated with NAFLD[21]. NAFLD has been intricately tied with metabolic syndromes like insulin resistance and obesity, but it also affects lean individuals, particularly those with lipodystrophy[22,23]. African Americans appear to have the lowest prevalence, Hispanics the highest, and Caucasians occupying the middle ground[24]. The risk of developing cirrhosis is very low in individuals with isolated steatosis (NAFLD), but the risk increases as steatosis becomes complicated by liver-cell injury and death and the accumulation of inflammatory cells (NASH)[25]. NASH is also a heterogeneous condition that can improve to steatosis or normal histology, remain relatively stable for years, or cause progressive accumulation of fibrous scar that eventuates in cirrhosis (F4). NAFLD-related cirrhosis is the primary predictor of eventual liver-related morbidity and mortality. Once cirrhosis develops, the annual incidence of primary liver cancer can be as high as per year[26]. Heritable factors play a significant role in the development of NAFLD, NASH, liver fibrosis, and liver cancer. Genetic variants on or near *TM6SF2*, *MBOAT7*, and *PNPLA3* genes increase the risk of NAFLD and its severity. Recent studies have shown that PNPLA3 has a strong influence on hepatic fat accumulation, NASH severity, and liver fibrosis. Epigenetic factors may also play a role in NAFLD pathogenesis and progression[27]. The mechanisms underlying the pathogenesis and progression of NAFLD are not fully understood. Hepatic steatosis occurs when the mechanisms for triglyceride synthesis is altered, leading to the accumulation of fat within hepatocytes. Obesity and insulin resistance also stimulate hepatocyte triglyceride accumulation. Triglyceride precursors and metabolic by-products may damage hepatocytes, leading to lipotoxicity. The liver parenchymal cells then respond with an aim to replace lost hepatocytes, involving the expansion of other cell types and recruitment of immune cells. NASH is the morphologic manifestation of lipotoxicity and resultant wound healing

Table 1 Patient characteristics

Variables	Thromboembolism	Total (*N*)	mean ± SD	Median	IQR	*P* value[1]
Age	No	335	55.22 ± 14.377	58.00	20	0.014[a]
	Yes	51	60.63 ± 11.421	61.00	17	
BMI	No	335	29.30 ± 5.950	28	8	0.041[a]
	Yes	51	31.14 ± 6.340	31	10	

[1]χ^2 test.
[a]$P < 0.05$.
IQR: Interquartile range; BMI: Body mass index.

responses. Cirrhosis and liver cancer are potential outcomes of futile repair, *i.e.*, progressive accumulation of wound healing cells, fibrous matrix, and abnormal vasculature (scarring), rather than efficient reconstruction/regeneration of healthy hepatic parenchyma[28-30]. NAFLD diagnosis requires the detection of steatosis in the absence of alternate causes. The determination of NAFLD-related liver injury severity and scarring is crucial for treatment recommendations. Noninvasive and invasive staging approaches are available, with liver biopsy being the gold standard for establishing liver injury and fibrosis severity. Noninvasive approaches, such as long-fiber thermoplastic and imaging (CT, MRI, ultrasonography and FibroScan), are being developed to stage NAFLD and monitor fibrosis progression and regression. Combining these tests enhances their predictive power, and they are being used serially or in combination to monitor fibrosis progression and regression in NAFLD patients[31-33]. Most individuals with NAFLD do not exhibit any symptoms. Typically, the diagnosis is made when a patient undergoes an evaluation for other reasons and abnormal liver aminotransferases or features of fatty liver are detected. In some cases, NAFLD may be diagnosed when a patient experiences vague right upper quadrant abdominal pain, hepatomegaly, or an abnormal-appearing liver during abdominal surgery[9]. Some patients may show subtle symptoms of chronic liver disease, such as spider angiomata, palmer erythema, or splenomegaly. In rare cases, individuals with advanced NAFLD may experience complications of end-stage liver disease, such as jaundice, features of portal hypertension (ascites or variceal hemorrhage)[34]. Currently, there are no United States Food and Drug Administration-approved therapies for the treatment of NAFLD. Hence, the current approach to NAFLD management focuses on treating risk factors for NASH, such as obesity, insulin resistance, metabolic syndrome, and dyslipidemia. Lifestyle changes and dietary modifications that result in weight loss and/or improve insulin sensitivity are the primary treatments for NAFLD. Studies show that loss of body weight improves steatosis, and greater weight loss improves steatohepatitis and hepatic fibrosis[35]. Modifying dietary macronutrient contents, such as low-carbohydrate low-fat diets or saturated unsaturated fat diets, is mainly beneficial since they reduce energy intake and improve obesity[36]. A Mediterranean-type diet has been reported to improve NASH and liver fibrosis independently of weight loss[37]. Excluding foods and beverages high in added fructose and increasing coffee consumption are also recommended[38]. High-fructose diets exacerbate hepatic steatosis, steatohepatitis, and fibrosis, while consuming two or more cups of coffee per day is associated with reduced risk of liver fibrosis[39]. Modifying lifestyle to increase physical activity complements dietary caloric restriction and expedites weight loss. Exercise also improves muscle insulin sensitivity, which improves the metabolic syndrome independent of weight loss. Several large clinical trials designed to identify effective and safe treatments for these conditions are in progress. Statins are an important class of agents to treat dyslipidemia and decrease cardiovascular risk. Although interest in bariatric surgery as a treatment for NAFLD exists, there is a lack of randomized clinical trials or adequate clinical studies to assess the benefits and harms of bariatric surgery as a treatment for NASH[40]. Most studies of bariatric surgery have shown that it is generally safe in individuals with well-compensated chronic liver disease and improves hepatic steatosis and necroinflammation[41]. However, the effects on hepatic fibrosis have been variable. NAFLD-related cirrhosis and, particularly, those with portal hypertension should be excluded as candidates for bariatric surgery[42]. Patients with NAFLD in whom end-stage liver disease develops should be evaluated for liver transplantation. The outcomes of liver transplantation in well-selected patients with NAFLD are generally good, but comorbid medical conditions associated with NAFLD, such as diabetes mellitus, obesity, and cardiovascular disease, often limit transplant candidacy. Our analysis sheds light on NASH as an independent risk factor for VTE, particularly DVT. Furthermore, it underscores a positive association between the degree of steatosis/fibrosis and an increased incidence of VTE. While this finding is significant, the underlying mechanisms connecting NASH and the heightened risk of VTE remain enigmatic. It's well-documented that NASH contributes to a pro-inflammatory state, evident through elevated levels of biomarkers like high-sensitivity C-reactive protein, plasminogen activator inhibitor-1, and fibrinogen concentrations[43]. Recent studies suggest that NASH patients exhibit elevated factor VIII, a potent pro-coagulant, as well as reduced protein C and anticoagulant levels, which creates a procoagulant imbalance and heightens the risk of cardiovascular events[11]. This imbalance might also explain the increased incidence of VTE. Additionally, increased levels of von Willebrand factor, mean platelet volume, and decreased antithrombin III levels have been suggested as potential contributors to the pro-coagulative state in NASH[4]. The intrahepatic thrombi generated by these changes can induce tissue ischemia, exacerbate the disease by activating stellate cells and fibrogenesis, and further aggravate hemostatic alterations favoring pro-coagulation. This theory provides a plausible explanation for the observed linear association between the degree of steatosis/fibrosis and the increased incidence of VTE[8]. The retrospective design used in our study has certain limitations that can affect the

Table 2 Patient characteristics and percent of patients with thromboembolism

Variables		Thromboembolism		Total	*P* value[1]
		No	Yes		
Gender	Male	194	33	227	0.358
		57.9%	64.7%	58.8%	
NASH	Yes	102	23	125	0.037
		30.4%	45.1%	32.4%	
Smoking	No	228	26	254	
		68.1%	51.0%	65.8%	
	Yes	76	17	93	
		22.7%	33.3%	24.1%	
	Former	31	8	39	
		9.3%	15.7%	10.1%	
Alcohol consumption	Yes	55	6	61	0.396
		16.4%	11.8%	15.8%	
Ethnicity	Caucasian	268	39	307	NA
		80.0%	76.5%	79.5%	
	Hispanic	39	10	49	
		11.6%	19.6%	12.7%	
	Asian	11	1	12	
		3.3%	2.0%	3.1%	
	African American	15	1	16	
		4.5%	2.0%	4.1%	
	Others	2	0	2	
		0.6%	0.0%	0.5%	
Diabetic status	Non DM	281	32	313	0.002[a]
		83.9%	62.7%	81.1%	
	Type 1 DM	10	4	14	
		3.0%	7.8%	3.6%	
	Type 2 DM	44	15	59	
		13.1%	29.4%	15.3%	
HIV status	Reactive	9	1	10	0.761
		2.7%	2.0%	2.6%	
CAP (steatosis) grade	S0	145	14	159	0.031[a]
		43.3%	27.5%	41.2%	
	S1	32	3	35	
		9.6%	5.9%	9.1%	
	S2	34	4	38	
		10.1%	7.8%	9.8%	
	S3	124	30	154	
		37.0%	58.8%	39.9%	
KPA (fibrosis) grade	F0	87	6	93	0.03[a]
		26.0%	11.8%	24.1%	

	F0-F1	116	14	130
		34.6%	27.5%	33.7%
	F1	3	1	4
		0.9%	2.0%	1.0%
	F2	32	2	34
		9.6%	3.9%	8.8%
	F3	25	7	32
		7.5%	13.7%	8.3%
	F4	72	21	93
		21.5%	41.2%	24.1%

[1]χ^2 test.
[a]$P < 0.05$.
NASH: Non-alcoholic steatohepatitis; CAP: Controlled attenuation parameter; KPA: Kilopascal; DM: Diabetes millitus; HIV: Human immunodeficiency virus; NA: Not available.

Table 3 Primary outcome: Non-alcoholic steatohepatitis and associated factors

Variable	Venous thromboembolism	Venous thromboembolism	*P* value
	Yes	No	
NASH	45.1%	30.4%	0.037[a]
CAP (steatosis) grade			
S0	27.5%	43.3%	0.031[a]
S1	5.9%	9.6%	
S2	7.8%	10.1%	
S3	58.8%	37.0%	
KPA (fibrosis) grade			
F0	11.8%	26%	0.030[a]
F1	29.5%	35.5%	
F2	3.9%	9.6%	
F3	13.7%	7.5%	
F4	41.2%	21.5%	
Diabetes mellitus			0.002[a]
Type I	7.8%	3%	
Type II	29.4%	13.1%	

[a]$P < 0.05$.
NASH: Non-alcoholic steatohepatitis; CAP: Controlled attenuation parameter; KPA: Kilopascal.

accuracy of our results. Errors in data collection can occur despite our efforts to carefully review the patient records. There is a possibility that some important factors have not been documented. Our study was conducted at a single center, that may affect the generalizability of our findings to the broader population. Socioeconomic differences, healthcare practices, and location can impact the prevalence of NASH and related complications such as VTE. To get a more comprehensive understanding of this issue, studies from various locations and patient groups are needed. The sample size of our study, particularly those with VTE, was relatively small. A larger study with more participants would provide more reliable results and could reveal more detailed connections between NASH, steatosis, fibrosis, and VTE risk. Incomplete data is another limitation that can lead to less precise results, which could influence the strength of our conclusions. Our study found links between VTE and factors such as age, BMI, and diabetes mellitus. However, these factors can independently increase the risk of VTE, which could complicate our analysis. Further research is needed to better understand how these factors relate to VTE in people with NASH. Finally, while our study highlighted a strong

Table 4 Distribution of type of thrombosis in study population

Type of thromboembolism	Number	Percentage
Deep vein thrombosis	30	58.8%
Superficial venous thrombosis	9	17.6%
Pulmonary embolism	7	13.7%
Portal vein	3	5.9%
Stroke (embolic)	2	3.9%
Total	51	100.0%

Table 5 Distribution of thromboembolism in study population by location

Location	Frequency	Percentage
Lower limb	29	56.9%
Upper limb	10	19.6%
Upper lobe	3	5.9%
Middle lobe	2	3.9%
Lower lobe	2	3.9%
Others	5	9.8%
Total	51	100.0%

Table 6 Distribution of choice of anticoagulation in study population

Type of anticoagulant used	Frequency	Percentage
Direct oral anticoagulants	33	64.7%
Vitamin K antagonists	13	25.5%
Enoxaparin sodium	3	5.9%
Antiplatelet	2	3.9%
Total	51	100.0%

connection between NASH and VTE, it does not prove that one causes the other. More research, particularly prospective studies, is necessary to uncover the exact mechanisms underlying this relationship.

CONCLUSION

In summary, our study reveals that NASH is an independent risk factor for VTE, thereby providing further evidence that NASH is associated with a hypercoagulable state. This risk is particularly pronounced in NASH patients with moderate-to-severe steatosis and F2-F4 fibrosis, with DVT being the predominant manifestation. While our study found a positive association between VTE and age, higher BMI, and diabetes mellitus, this could potentially be attributed to confounding factors. As such, more extensive studies are necessary to validate these findings. The role of VTE prophylaxis for primary prevention in this specific population remains unclear. In our study, we observed that 64.71% of patients were on DOAC, 25.5% were on warfarin, 5.9% were on low molecular weight heparin, and 3.9% were on antiplatelet agents. However, we noted treatment failure in 5.9% of patients during follow-up, indicating that recurrence is a possibility despite treatment. Our study underscores the crucial importance of promptly recognizing and managing individuals at risk of NASH to prevent devastating complications, especially the increased risk of VTE. Further research is warranted to better understand the underlying mechanisms, prevention strategies, and management options for this vulnerable patient population.

ARTICLE HIGHLIGHTS

Research background

To investigate the relationship between nonalcoholic fatty liver disease (NAFLD) and the risk of venous thromboembolism (VTE). The study underscores the need for greater awareness of the risk factors contributing to VTE in the context of NAFLD.

Research motivation

The motivation behind this research is to identify the connection between NAFLD, particularly non-alcoholic steatohepatitis (NASH), and the development of VTE. There is a knowledge gap and a compelling need to understand this association to enhance clinical outcomes and tailor management strategies for patients with NAFLD.

Research objectives

The primary objective was to evaluate the incidence and characteristics of VTE in patients with NAFLD and identify associated risk factors. Achieving this goal is significant for improving the prognosis and management of NAFLD patients by enabling the early detection and treatment of VTE.

Research methods

The case-control study employed comprehensive patient data analysis, logistic regression, and comparative assessments between patient groups with and without VTE. These methods facilitated a detailed examination of the clinical parameters and outcomes, highlighting the robustness and replicability of the study.

Research results

Key findings include the higher prevalence of diabetes mellitus and more severe liver pathology (steatosis and fibrosis) in the VTE group. The study revealed that these patients often required hospitalization and intensive management, including anticoagulation therapy. The results contribute significantly to the current understanding of the relationship between NASH and VTE, emphasizing the importance of monitoring at-risk patients.

Research conclusions

The study proposes that NAFLD, particularly with advanced liver pathology from NAFLD, is a significant factor in the development of VTE.

Research perspectives

Future research should focus on longitudinal studies to further define the causal relationships and investigate the underlying mechanisms that link advanced NAFLD with VTE. Additionally, there is a need for clinical trials to test targeted interventions aimed at reducing the risk of thrombosis in this patient population.

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FOOTNOTES

Author contributions: Suresh MG conceived the idea for the study, designed and undertook the literature review, performed the statistical analysis, figures, and appendix and analyzed and interpreted the data; Suresh MG, Singh Y, and Gogtay M collected data; Suresh MG, Singh Y, Gogtay M, Gogtay M, and Yadukumar L wrote the first draft of the manuscript; Suresh MG, Gogtay M, Singh Y, Yadukumar L, Mishra AK, and Abraham GM revised the subsequent manuscript drafts; and all authors reviewed and agreed on the final draft of the manuscript.

Institutional review board statement: The comprehensive investigation into the potential link between non-alcoholic steatohepatitis and venous thromboembolism was conducted in adherence to a well-defined protocol. This protocol was developed, reviewed, and sanctioned by the joint institutional review board at MetroWest Medical Center under Approval No. 2020-035.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of tenofovir alafenamide in patients with chronic hepatitis B exhibiting suboptimal response to entecavir

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Abstract

BACKGROUND

Entecavir (ETV) is a potent and safe antiviral agent for patients with chronic hepatitis B (CHB); however, some patients may exhibit suboptimal response or resistance to ETV. Tenofovir alafenamide (TAF) is a novel tenofovir prodrug with improved pharmacokinetics and reduced renal and bone toxicity compared with tenofovir disoproxil fumarate.

AIM

To evaluate the efficacy and safety of switching from ETV to TAF in patients with CHB exhibiting suboptimal response to ETV.

METHODS

A total of 60 patients with CHB who had been treated with ETV for at least 12 mo and had persistent or recurrent viremia [Hepatitis B virus (HBV) DNA ≥ 20 IU/mL] or partial virologic response (HBV DNA < 20 IU/mL, but detectable) were enrolled in the study. The patients were randomly assigned to either continue ETV (0.5 mg) daily or switch to TAF (25 mg) daily for 48 wk. The primary endpoint was the proportion of patients who achieved a virologic response (HBV DNA level < 20 IU/mL) at week 48. Secondary endpoints included changes in serum alanine aminotransferase (ALT), hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and anti-HBe levels, and renal and bone safety parameters.

RESULTS

At week 48, the proportion of patients who achieved a virologic response was significantly higher in the TAF group than in the ETV group (93.3% *vs* 66.7%, P = 0.012). The mean reduction in HBV DNA from baseline was also significantly greater in the TAF group than in the ETV group (-3.8 *vs* -2.4 Log10 IU/mL, P < 0.001). The rates of ALT normalization, HBeAg loss, HBeAg seroconversion, and

HBsAg loss were not found to significantly differ between the two groups. None of the patients developed genotypic resistance to ETV or TAF. Both drugs were well tolerated, with no serious adverse events or discontinuations caused by adverse events. No significant changes were observed in the estimated glomerular filtration rate, serum creatinine level, or urine protein-to-creatinine ratio in either group. The TAF group had a significantly lower decrease in bone mineral density at the lumbar spine and hip than the ETV group (-0.8% *vs* -2.1%, $P = 0.004$; -0.6% *vs* -1.8%, $P = 0.007$, respectively).

CONCLUSION

Switching from ETV to TAF is effective and safe for patients with CHB exhibiting a suboptimal response to ETV and may prevent further viral resistance and reduce renal and bone toxicity.

Key Words: Entecavir; Tenofovir alafenamide; Chronic hepatitis B; Virologic response; Renal and bone toxicity; Suboptimal response

Core Tip: Switching from Entecavir (ETV) to Tenofovir alafenamide (TAF) is an effective and safe strategy for patients with chronic hepatitis B (CHB) who exhibit a suboptimal response to ETV. This switch improves virologic response rates and reduces the risk of viral resistance. TAF also demonstrates reduced renal and bone toxicity compared to Tenofovir disoproxil fumarate. This finding highlights the potential benefits of switching to TAF in managing CHB patients with suboptimal response to ETV, providing improved treatment outcomes and minimizing long-term safety concerns.

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INTRODUCTION

Chronic hepatitis B (CHB) is a major global health problem, affecting approximately 257 million people worldwide and causing approximately 880000 deaths annually due to liver cirrhosis and hepatocellular carcinoma (HCC)[1]. Nucleos(t)ide analogs (NUCs) are the mainstay treatment for CHB as they can suppress Hepatitis B virus (HBV) replication, reduce liver inflammation and fibrosis, and prevent disease progression[2]. Among the available NUCs, entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are currently recommended as first-line agents by international guidelines owing to their high potency and low resistance[3-5].

ETV is a deoxyguanosine analog that inhibits HBV polymerase by competing with the natural substrate, deoxyguanosine triphosphate. ETV has been demonstrated to result in high rates of virological response (> 90%) and histological improvement (> 70%) in both hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients with CHB after long-term treatment[6-7]. However, some patients exhibit suboptimal response or resistance to ETV, which is associated with an increased risk of disease progression and HCC. A suboptimal response is defined as persistent or recurrent viremia (HBV DNA ≥ 20 IU/mL) after at least 12 mo of treatment, whereas resistance is defined as virologic breakthrough (increase in HBV DNA by > 1 Log10 IU/mL from nadir) with confirmed genotypic mutations. The cumulative incidence of suboptimal response to ETV has been reported to range from 9% to 30% at 5 years, whereas the incidence of resistance is relatively low (< 1.2%)[8-9].

TAF is a novel prodrug of tenofovir that delivers the active metabolite, tenofovir diphosphate, to hepatocytes more efficiently than TDF, resulting in higher intracellular and lower plasma concentrations. TAF has been found to exhibit an antiviral efficacy similar to TDF in patients with CHB, with comparable rates of virologic response (> 90%) and biochemical and serological improvement. TAF has also been demonstrated to improve renal and bone safety compared to TDF, with a lower decline in estimated glomerular filtration rate (eGFR) and bone mineral density (BMD)[10-12]. TAF is effective and safe for patients with CHB and renal impairment or osteoporosis.

The optimal management strategy for patients with CHB exhibiting a suboptimal response or resistance to ETV remains controversial. According to some studies, switching from ETV to TDF, or adding TDF to ETV, can lead to higher rates of virological response and prevent further resistance[13-14]. However, these strategies may increase the risk of renal and bone toxicities, particularly in elderly patients and those with comorbidities. Therefore, switching from ETV to TAF may be an alternative option that can provide both efficacy and safety benefits. However, data on the efficacy and safety of switching from ETV to TAF in patients with CHB exhibiting a suboptimal response to ETV are limited. This study aimed to compare the efficacy and safety of switching from ETV to TAF *vs* continuing ETV in patients with CHB exhibiting a suboptimal response to ETV.

MATERIALS AND METHODS

Study design and population

This randomized, open-label, parallel-group, single-center study was conducted at a hospital in China. The study protocol was approved by the hospital's ethics committee and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines[15-16]. All patients provided written informed consent prior to enrollment.

A total of 60 patients with CHB who met the following inclusion criteria were enrolled: (1) Aged 18 to 65 years; (2) Diagnosed with CHB according to the Chinese guidelines; (3) Treated with ETV (0.5 mg daily) for at least 12 mo; and (4) Had suboptimal response to ETV, defined as persistent or recurrent viremia (HBV DNA ≥ 20 IU/mL) or partial virologic response (HBV DNA < 20 IU/mL but detectable) at two consecutive visits within 6 mo before enrollment. The exclusion criteria were: (1) Co-infection with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus; (2) History of liver decompensation, liver transplantation, or HCC; (3) History of renal impairment (eGFR < 60 mL/min/1.73 m^2), osteoporosis, or bone fracture; (4) History of hypersensitivity or resistance to ETV, TDF, or TAF; (5) Use of other antiviral agents, immunomodulators, or hepatoprotective agents within 3 mo before enrollment; (6) Pregnancy or lactation; and (7) Other serious medical conditions that could interfere with the study.

Randomization and intervention

Eligible patients were randomly assigned to either continue ETV (0.5 mg daily) or switch to TAF (25 mg daily) in a 1:1 ratio using a computer-generated random number table. Randomization was performed based on the HBeAg status and baseline HBV DNA level (< or ≥ 2000 IU/mL). The allocation was concealed from the investigators and patients until the end of the study period. The patients received their assigned treatment for 48 wk and were followed-up every 12 wk. Treatment adherence was assessed based on pill counts and patient self-reports.

Outcomes and assessments

The primary endpoint was the proportion of patients who achieved a virologic response, defined as an HBV DNA level < 20 IU/mL at week 48. Secondary endpoints included changes in serum alanine aminotransferase (ALT), HBsAg, HBeAg, and anti-HBe levels from baseline to week 48; rates of ALT normalization (< 40 U/L for males and < 30 U/L for females), HBeAg loss (< 0.1 S/CO), HBeAg seroconversion (HBeAg loss and anti-HBe positive), and HBsAg loss (< 0.05 IU/mL) at week 48; incidence of genotypic resistance to ETV or TAF at week 48; changes in renal and bone safety parameters from baseline to week 48, including eGFR, serum creatinine, urine protein-to-creatinine ratio (UPCR), BMD at the lumbar spine and hip, serum calcium, phosphate, alkaline phosphatase, and parathyroid hormone levels.

Serum HBV DNA levels were measured using a real-time polymerase chain reaction, with a lower limit of detection of 10 IU/mL. Serum ALT, creatinine, calcium, phosphate, alkaline phosphatase, and parathyroid hormone levels were measured using standard laboratory methods. The serum HBsAg, HBeAg, and anti-HBe levels were measured using an electrochemiluminescence immunoassay. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. UPCR was calculated by dividing the urine protein concentration by the urine creatinine concentration. BMD was measured using dual-energy X-ray absorptiometry. Genotypic resistance to ETV or TAF was determined *via* direct sequencing of the HBV polymerase gene.

Statistical analysis

The sample size was calculated based on the assumption that the proportion of patients who achieved virologic response at week 48 would be 90% in the TAF group and 70% in the ETV group, with a significance level of 0.05 and a power of 80%. Considering a dropout rate of 10%, we estimated that 30 patients would be required per group.

Data were analyzed using SPSS software version 22.0. Baseline characteristics were compared between the two groups using the *t*-test for continuous variables and the chi-square test for categorical variables. An intention-to-treat analysis was conducted for the primary endpoint, which included all randomized patients who received at least one dose of the study drug. A per-protocol analysis was performed for the secondary endpoints, which included only patients who completed the study without major protocol violations. Between-group differences in the primary and secondary endpoints were assessed using the chi-square test or Fisher's exact test. Within-group and between-group differences in continuous variables were assessed using paired *t*-tests or independent *t*-tests, respectively. A *P* value of < 0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics

Sixty patients with CHB exhibiting suboptimal response to ETV were enrolled and randomized to either continue ETV (n = 30) or switch to TAF (n = 30) therapy. The baseline characteristics of the two groups are presented in Table 1. Age, sex, body mass index, HBeAg status, baseline HBV DNA levels, baseline ALT levels, or duration of ETV treatment did not significantly differ between the two groups. The mean age of patients was 45.7 years, and 65% were males. The mean baseline HBV DNA level was 3.6 Log 10 IU/mL, and 40% of patients were HBeAg-positive.

Table 1 Baseline characteristics of the study population

Variable	ETV group (*n* = 30)	TAF group (*n* = 30)	*P* value
Age (yr)	46.2 ± 9.8	45.3 ± 10.2	0.69
Sex (male/female)	20/10	19/11	0.77
Body mass index (kg/m^2)	24.5 ± 3.2	24.7 ± 3.4	0.82
HBeAg status (positive/negative)	12/18	12/18	> 0.99
Baseline HBV DNA (log 10 IU/mL)	3.7 ± 1.2	3.5 ± 1.1	0.48
Baseline ALT (U/L)	51.3 ± 28.6	49.7 ± 26.4	0.82
Duration of ETV treatment (months)	18.4 ± 6.2	18.7 ± 5.9	0.84

Data are presented as mean ± SD or number. ETV: Entecavir; TAF: Tenofovir alafenamide; HBV: Hepatitis B virus; ALT: Alanine aminotransferase.

Virologic response

The primary endpoint of virologic response at week 48 was achieved by significantly more patients in the TAF group than in the ETV group (93.3% *vs* 66.7%, $P = 0.012$). The mean reduction in HBV DNA from baseline to week 48 was also significantly greater in the TAF group than in the ETV group (-3.8 *vs* -2.4 Log10 IU/mL, $P < 0.001$). The virological response rates and changes in HBV DNA levels at each time point are shown in Table 2.

Biochemical and serologic response

Changes in serum ALT, HBsAg, HBeAg, and anti-HBe levels from baseline to week 48 are shown in Table 3. The mean reductions in ALT, HBsAg, and HBeAg levels did not significantly differ between the two groups. The mean increase in anti-HBe level was significantly higher in the TAF group than in the ETV group (0.8 *vs* 0.2 S/CO, $P = 0.03$). The rates of ALT normalization, HBeAg loss, HBeAg seroconversion, and HBsAg loss after 48 wk are shown in Table 4. The rates of ALT normalization, HBeAg loss, and HBsAg loss did not significantly differ between the two groups. The rate of HBeAg seroconversion was significantly higher in the TAF group than in the ETV group (33.3% *vs* 8.3%, $P = 0.04$).

Renal and bone safety

Changes in the renal and bone safety parameters from baseline to week 48 are shown in Table 5. The mean changes in eGFR, serum creatinine level, or UPCR were not found to significantly differ between the two groups. The mean decrease in BMD at the lumbar spine and hip was significantly lower in the TAF group than in the ETV group (-0.8% *vs* -2.1%, $P = 0.004$; -0.6% *vs* -1.8%, $P = 0.007$, respectively). The mean changes in serum calcium, phosphate, alkaline phosphatase, and parathyroid hormone levels did not significantly differ between the two groups.

Adverse events and resistance

Both drugs were well tolerated, with no serious adverse events or discontinuation due to adverse events reported in either group during the study period. The most common adverse events were headache, nausea, diarrhea, and fatigue, which were mild and transient, and did not require dose adjustment or interruption. The incidence or severity of adverse events did not significantly differ between the two groups. None of the patients developed genotypic resistance to ETV or TAF at week 48 based on direct sequencing of the HBV polymerase gene.

DISCUSSION

Based on the findings of this study, switching from ETV to TAF is effective and safe for patients with CHB exhibiting a suboptimal response to ETV and may provide additional benefits in terms of virologic response, HBeAg seroconversion, and bone safety over continuing ETV[17].

Switching from ETV to TAF resulted in patients exhibiting a significantly higher virologic response at week 48 than those continuing ETV (93% *vs* 67%, $P = 0.012$), which is the primary finding of this study. This finding is consistent with that of previous studies, in which switching from ETV to TDF or adding TDF to ETV improved the virological response in patients with CHB exhibiting a suboptimal response or resistance to ETV[18-20]. The possible mechanisms for this improvement may include the higher potency and lower resistance of tenofovir than ETV, the synergistic effect of tenofovir and ETV on HBV replication, and enhanced intracellular delivery of tenofovir by TAF. Moreover, switching from ETV to TAF did not result in any genotypic resistance to either drug at week 48, suggesting that TAF is a safe and effective rescue therapy for patients with CHB exhibiting suboptimal response to ETV.

Notably, switching from ETV to TAF resulted in a significantly higher rate of HBeAg seroconversion than continuing ETV at 48 wk (33% *vs* 8%, $P = 0.04$). HBeAg seroconversion is a desirable outcome for patients with HBeAg-positive CHB, as it indicates a reduction in viral replication and infectivity, and is associated with improved prognosis and reduced risk of HCC. The higher rate of HBeAg seroconversion in the TAF group than in the ETV group may be related to the greater

Table 2 Virologic response rates and changes in hepatitis B virus DNA levels

Time point	Virologic response rate in the ETV group (%)	Virologic response rate in the TAF group (%)	Change in HBV DNA level in the ETV group (log 10 IU/mL)	Change in HBV DNA level in the TAF group (log 10 IU/mL)
Baseline	0	0	0	0
Week 12	33.3	53.3	-1.8	-2.6
Week 24	50	76.7	-2.2	-3.2
Week 36	60	86.7	-2.4	-3.6
Week 48	66.7	93.3	-2.4	-3.8

ETV: Entecavir; TAF: Tenofovir alafenamide; HBV: Hepatitis B virus.

Table 3 Changes in serum ALT, HBsAg, HBeAg, and anti-HBe levels from baseline to week 48

Variable	ETV group (*n* = 30)	TAF group (*n* = 30)	*P* value
ALT (U/L)	-16.7 ± 21.4	-18.3 ± 19.6	0.72
HBsAg (log 10 IU/mL)	-0.1 ± 0.3	-0.2 ± 0.4	0.31
HBeAg (S/CO)	-1.2 ± 2.4	-1.4 ± 2.6	0.69
Anti-HBe (S/CO)	0.2 ± 0.5	0.8 ± 1.1	0.03

Data are presented as mean ± SD. ETV: Entecavir; TAF: Tenofovir alafenamide; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen.

Table 4 Rates of alanine aminotransferase normalization, hepatitis B e antigen loss, hepatitis B e antigen seroconversion, and hepatitis B surface antigen loss at week 48

Outcome	ETV group (*n* = 30)	TAF group (*n* = 30)	*P* value
ALT normalization (%)	76.7	80.0	0.72
HBeAg loss (%)	25.0	33.3	0.51
HBeAg seroconversion (%)	8.3	33.3	0.04
HBsAg loss (%)	0.0	0.0	> 0.99

ETV: Entecavir; TAF: Tenofovir alafenamide; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen.

reduction in HBV DNA and the greater increase in anti-HBe levels owing to TAF. According to previous studies, low HBV DNA and high anti-HBe levels are predictive factors for HBeAg seroconversion[21-22]. However, the rate of HBsAg loss did not significantly differ between the two groups, which may be due to the short duration of the study and low baseline HBsAg levels in patients.

Switching from ETV to TAF resulted in a significantly lower decrease in BMD at the lumbar spine and hip than continuing ETV at week 48 (-0.8% *vs* -2.1%, $P = 0.004$; -0.6% *vs* -1.8%, $P = 0.007$, respectively). This finding aligns with that of previous studies, in which TAF had a lower impact on BMD than TDF in patients with CHB[23-25]. The lower decrease in BMD induced by TAF may be attributed to the lower plasma concentration and higher intracellular concentration of tenofovir achieved by TAF than by TDF, which may reduce the systemic exposure and toxicity of tenofovir to bone cells. Moreover, switching from ETV to TAF did not result in any significant changes in renal function or mineral metabolism, indicating that TAF is a safe and well-tolerated drug for patients with CHB exhibiting suboptimal response to ETV.

This study had some limitations. First, the sample size was relatively small, and the study duration was relatively short, which may limit the generalizability and reliability of the results. Second, the study was open-label and non-blinded, which may have introduced biases and confounding factors. Third, this study did not include a control group of patients who switched from ETV to TDF, enabling a direct comparison of the efficacy and safety of TAF and TDF in this population. Fourth, this study did not assess the quality of life or cost-effectiveness of switching from ETV to TAF, which are important factors in clinical decision-making.

Table 5 Changes in the renal and bone safety parameters from baseline to week 48

Variable	ETV group (*n* = 30)	TAF group (*n* = 30)	*P* value
eGFR (mL/min/1.73 m^2)	-1.3 ± 3.2	-1.5 ± 2.9	0.76
Serum creatinine (μmol/L)	1.7 ± 5.6	2.1 ± 4.8	0.67
UPCR (mg/mmol)	-0.2 ± 0.6	-0.1 ± 0.5	0.58
BMD at lumbar spine (%)	-2.1 ± 1.4	-0.8 ± 1.2	0.004
BMD at hip (%)	-1.8 ± 1.3	-0.6 ± 1.1	0.007
Serum calcium (mmol/L)	-0.01 ± 0.05	-0.02 ± 0.04	0.42
Serum phosphate (mmol/L)	-0.03 ± 0.12	-0.04 ± 0.11	0.69
Serum alkaline phosphatase (U/L)	-3.7 ± 12.4	-4.3 ± 11.6	0.79
Serum parathyroid hormone (pg/mL)	-2.4 ± 8.7	-3.1 ± 9.2	0.68

Data are presented as mean ± standard deviation. ETV: Entecavir; TAF: Tenofovir alafenamide; BMD: Bone mineral density; eGFR: Estimated glomerular filtration rate; UPCR: Urine protein-to-creatinine ratio.

CONCLUSION

Overall, switching from ETV to TAF was identified to be effective and safe in patients with CHB exhibiting suboptimal response to ETV and may offer additional advantages over continuing ETV in terms of virologic response, HBeAg seroconversion, and bone safety. Further studies with larger sample sizes, longer durations, and more comprehensive outcomes are warranted to confirm and extend these findings.

ARTICLE HIGHLIGHTS

Research background

Entecavir (ETV) is an effective antiviral treatment for chronic hepatitis B (CHB) patients. However, some patients may not respond optimally or develop resistance to ETV. Tenofovir alafenamide (TAF) is a new prodrug of tenofovir with improved pharmacokinetics and reduced renal and bone toxicity compared to tenofovir disoproxil fumarate. This study aims to evaluate the efficacy and safety of switching from ETV to TAF in CHB patients who exhibit suboptimal response to ETV.

Research motivation

The main topic of this study is evaluating the efficacy and safety of switching from ETV to TAF in CHB patients with suboptimal response to ETV. The key problem to be solved is addressing the suboptimal response or resistance to ETV treatment in CHB patients. By investigating the effectiveness of TAF as an alternative treatment, this study aims to provide a potential solution for patients who do not respond well to ETV. Solving these problems is significant for future research in this field as it can enhance treatment outcomes, prevent viral resistance, and minimize renal and bone toxicity in CHB patients.

Research objectives

The main objective of this study was to evaluate the efficacy and safety of switching from ETV to TAF in CHB patients with suboptimal response to ETV. The specific objectives included assessing the virologic response, changes in liver function markers [alanine aminotransferase (ALT)], Hepatitis B virus (HBV)-related antigens [hepatitis B surface antigen, hepatitis B e antigen (HBeAg)], and renal and bone safety parameters.

Research methods

Method include its prospective design, randomization to minimize bias, and objective measurement of virologic and biochemical parameters. The novelty of this research method lies in assessing the efficacy and safety of switching from ETV to TAF specifically in CHB patients with suboptimal response to ETV. This approach provides valuable insights into alternative treatment options for this specific patient population and addresses the need for optimized therapeutic strategies in CHB management.

Research results

Switching from ETV to TAF improved virologic response and reduced renal and bone toxicity in CHB patients. TAF showed higher response rates and greater HBV DNA reduction compared to ETV. Both drugs were well-tolerated without resistance development or serious adverse events. TAF had a favorable safety profile regarding renal and bone

parameters, with lower bone mineral density decline. These findings support TAF as an effective and safe alternative for CHB patients with suboptimal ETV response. Further research is needed to explore long-term effects, optimal switching timing, treatment response factors, cost-effectiveness, and accessibility. Addressing these gaps will enhance CHB management and patient care.

Research conclusions

Switching from ETV to TAF is an effective and safe approach for patients with CHB who have a suboptimal response to ETV. The study demonstrated that the TAF group had a significantly higher virologic response rate and greater reduction in HBV DNA levels compared to the ETV group. There were no significant differences in other endpoints such as ALT normalization, HBeAg loss, seroconversion, or adverse events between the two groups. TAF also exhibited favorable renal and bone safety profiles. These findings support the use of TAF as an alternative treatment option, reducing viral resistance and minimizing renal and bone complications associated with CHB treatment.

Research perspectives

Further research perspectives include investigating the long-term effects of switching from ETV to TAF, exploring optimal timing for the therapeutic switch, identifying factors that influence treatment response, assessing cost-effectiveness, and improving accessibility of TAF. Additionally, studying the impact of this switch on different patient populations and evaluating its efficacy in real-world clinical settings would provide valuable insights into the broader applicability and outcomes of this treatment approach for CHB patients with suboptimal ETV response.

FOOTNOTES

Author contributions: Yuan GC, Chen AZ, and Qiu ZH jointly proposed the concept of this study; Wang WX and Yi XL contributed to data collection; Tu L and Peng F contributed to formal analysis; Yuan GC, Qiu ZH, and Chen AZ participated in the research; Qiu ZH and Yuan GC have contributed to these methods; Chen AZ guided research; Yuan GC and Qiu ZH validated this study; Tu L and Peng F contributed to the visualization of this study; Chen AZ and Yuan GC drafted the first draft; All authors jointly reviewed and edited the manuscript.

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ORIGINAL ARTICLE

Prospective Study

Arthroscopic findings after manipulation under anesthesia in idiopathic capsulitis of the shoulder: A prospective study

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Abstract

BACKGROUND

Manipulation under anesthesia (MUA) of the shoulder joint is a commonly used method for the treatment of adhesive capsulitis. Though it has been known to be associated with a variety of complications, there is a paucity of studies describing the arthroscopic findings after MUA.

AIM

To describe the arthroscopic findings in patients with idiopathic adhesive capsulitis of the shoulder after MUA.

METHODS

We recruited 28 patients with idiopathic adhesive capsulitis who underwent arthroscopic capsular release. Manipulation of the shoulder was performed under anesthesia in all of these patients before capsular release. Intra-articular findings were recorded during arthroscopic capsular release in these patients.

RESULTS

All patients showed the presence of synovitis. Twenty-seven patients showed tears in the capsule on the anterior aspect. One patient had an avulsion of the anterior rim of the glenoid and labrum following the manipulation. Four patients had partial rotator cuff tears, and one patient showed a superior labrum anterior posterior lesion, which was not diagnosed preoperatively on magnetic resonance imaging.

CONCLUSION

MUA leads to rupture of the capsule, which is the desired outcome. However, the site of rupture of the capsule is dependent on the maneuvers of MUA. In addition,

partial tears of the rotator cuff and osteochondral fractures of the glenoid can also occur.

Key Words: Frozen shoulder; Arthroscopy; Manipulation under anesthesia; Prospective study

Core Tip: Manipulation under anesthesia for a frozen shoulder can lead to damage to other intra-articular structures besides the rupture of the capsule, which is the main aim of this procedure. In most cases, it leads to rupture of the anterior capsule. This is the same area where arthroscopic releases are most often performed. Rupture of the posterior and inferior capsule can also occur depending on the rotational and adduction manipulation of the shoulder.

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INTRODUCTION

Adhesive capsulitis, popularly known as 'frozen shoulder', is a common cause of shoulder pain and stiffness of the glenohumeral joint. It is thought to afflict between 2% and 5% of the population[1]. The condition has been described by some as self-limiting, lasting on average for a period of 2-3 years[2-4]. However, some studies have shown that between 20% and 50% of the patients still experience discomfort and stiffness beyond 3 years[5,6]. Although it is a self-limiting condition, patients find it impractical and challenging to wait for such a long period as it interferes with everyday life tasks. Most of the studies have reported manipulation under anesthesia (MUA) to be efficacious[7,8] and at least equivocal compared to other methods such as steroid injection and hydrodilatation[9,10].

Iatrogenic injuries to the upper limb including humeral fractures, glenohumeral dislocations, rotator cuff tears, glenoid fractures, brachial plexus injuries, labral tears, and hematomas pose the biggest risk and challenge during MUA[11]. Even though MUA is a very commonly practiced modality of treatment of adhesive capsulitis of the shoulder, there is not enough literature that documents the intra-articular changes after MUA. We could find only three published reports that described the arthroscopic findings post MUA[12-14], and only two publications have described the imaging of the shoulder after MUA[15,16]. Our study documented the arthroscopic findings after MUA of the shoulder in patients with idiopathic adhesive capsulitis of the shoulder.

MATERIALS AND METHODS

The study was performed after obtaining institutional ethical committee clearance. Twenty-eight patients were included in this study for arthroscopic capsular release for idiopathic adhesive capsulitis of the shoulder. All patients included in the study had idiopathic stiffness of the shoulder with global restriction of shoulder movements for the prior 6 mo. Patients with a prior history of trauma or surgery to the shoulder were excluded. Any patient who received any form of treatment other than physiotherapy was also excluded. There were 20 females and 8 males. The ages ranged from 42 years to 62 years with an average age of 49.7 years. All patients had complaints of spontaneous onset of pain and stiffness of the shoulder. The opposite shoulder was normal.

All the patients had preoperative X-rays and magnetic resonance imaging (MRI) scans completed to rule out any secondary cause of adhesive capsulitis of the shoulder. The MRI was performed with the patient in a supine position and arms by the side. The images were obtained in axial, coronal oblique, and sagittal oblique planes. The protocols used were T1-weighted and T2-weighted with fat saturation and inversion recovery sequences.

The patients did not show improvement in their symptoms with physiotherapy and analgesics for at least 6 mo. After the administration of general anesthesia, manipulation of the shoulder was performed in a supine position. Manipulation was first done in flexion. Following this, the limb was manipulated in abduction. During the MUA, the proximal humerus was held with one hand close to the axilla and the other hand stabilized the scapula. Gentle pressure was used to manipulate. An increase in flexion and abduction was associated with a crackling sound, palpable crepitus, and a feeling of sudden giving way. Manipulation was not performed in external rotation, adduction, or internal rotation to avoid any iatrogenic fracture of the humerus.

The patient was then placed in a semi-lateral position and the arm was abducted using a traction tower for arthroscopic global capsular release. Intra-articular findings were recorded before proceeding with capsular release. Entering the shoulder joint with sheath and trocar through the posterior portal was difficult compared to a non–stiff shoulder. The presence of blood and blood clots in the joint was the first arthroscopic finding. This required repeated joint lavage to clear all the blood and blood clots. When all the clots and blood were removed from the joint, the intra-articular struc-

tures could be visualized.

To make the anterior portal, the rotator interval was identified. The rotator interval had shrunken in size and had the presence of synovitis. A needle was passed from the outside to locate the site of the anterior portal within the rotator interval. The two portals were used alternately to pass the instruments and arthroscope to evaluate all the corners of the shoulder joint and perform a global capsular release. After surgery, patients were provided adequate analgesia and began active and passive range of motion exercises of the shoulder. The patients were followed at monthly intervals up to 5 mo, and all patients had significant relief in pain and improvement in range of motion.

RESULTS

Out of the twenty-eight patients, 27 had global synovitis, and 1 patient had synovitis localized to the rotator interval. Twenty-seven patients had thickening of the middle glenohumeral ligament, while one patient had normal ligaments. There were tears in the anterior capsule in 27 patients, whereas 1 patient had an anterior glenoid rim avulsion. The avulsed fragment was not repaired, and the patient had no complaints during follow-up. There were no instances of humeral head fracture or posterior capsular tear. Four patients experienced partial rotator cuff tears, which were not evident in the preoperative MRI. Since the tear involved less than 50% of cuff thickness, it was only debrided. There was also an instance of superior labrum anterior posterior tear that was not evident in preoperative MRI in 1 patient. It was not repaired, and the patient had an uneventful follow-up (Table 1).

DISCUSSION

Manipulation under general anesthesia is a widely practiced method of treatment of a frozen shoulder. In this technique, the shoulder joint capsule is gently stretched by moving the humerus after stabilizing the scapula into flexion and abduction, and finally (optionally) moving the adducted humerus into external rotation. It is an effective method for the treatment of adhesive capsulitis of the shoulder but with a potential for significant intra-articular and rotator cuff injuries.

Atoun *et al*[16] evaluated the rotator cuff by ultrasound before and after MUA. They did not find any rotator cuff lesions on ultrasound examination after shoulder manipulation. We found four partial articular-sided rotator cuff tears in our study during arthroscopy after manipulation. None of these tears were evident on preoperative MRI. Loew *et al*[14] also found 4 cases with partial subscapularis tears. This difference could be due to the difficulty in the detection of partial thickness cuff tears on ultrasound.

Sasanuma *et al*[15] performed MRI examination before and after MUA. They found tears in the inferior capsule either in the mid-substance or near the humeral insertion of the inferior capsule. They reported anterior and posterior tears of the inferior capsule but did not report any tears in the anterior capsule. This was quite different from the results of our study where we found only anterior tears. This could be due to the difference in the method of manipulation of the shoulder. Unlike these authors, we did not aim to achieve a range of motion equal to the opposite side. We applied gentle force and stopped short of forceful manipulations. In addition, we did not perform any rotational movements of the shoulder during MUA.

Gerber *et al*[17] described a correlation between the limb position and tension in the articular capsule. They reported tension in the posterior capsule in the position of internal rotation and adduction. These movements were not performed in the manipulation in our study, and this may explain the lack of posterior capsular tears in our patients. A combination of abduction/external rotation and forward flexion tightened the anterior inferior capsule. The presence of anterior injuries in our study can be explained by the flexion and abduction manipulation of the joint. Sasanuma *et al*[15] also reported four labrum tears occurring in patients with mid-substance tears of the inferior capsule and the absence of any new rotator cuff tears. However, Loew *et al*[14] described MUA quite similar to that performed by Sasanuma *et al*[15], and they found capsular ruptures all around the shoulder.

Wiley *et al*[12] in their landmark paper presented the arthroscopy findings of frozen shoulder. They described the arthroscopy findings in 37 patients, and most of the patients had patchy synovitis, which was in contrast to the findings of our paper. They also noticed a subset of patients having tears in the labrum and partial tears in the cuff. The paper also discussed tears in the subscapularis and attributed them to the manipulation maneuver for regaining external rotation as observed by Depalma. In our technique, we have not used manipulation in rotations.

Uitvlugt *et al*[13] presented arthroscopy findings of frozen shoulder patients. They described 21 patients before manipulation and post-manipulation in 10 patients. In all the patients the entry into the shoulder was difficult due to the reduced volume before manipulation, and there was synovitis in all of the patients. The synovitis was anterior in most patients followed by in the axillary pouch and near the rotator cuff. Post manipulation the entry into the shoulder was easier, and there were capsular tears in the anterior and inferior walls in most of the patients[13].

Loew *et al*[14] documented arthroscopic findings after manipulation in 30 patients. They found anterior capsule ruptures in 24 patients, posterior ruptures in 16 patients, and superior capsule ruptures in 11 patients. They showed anterior labral detachment in 4 patients, superior labrum anterior posterior lesions in 3 patients, partial ruptures of the subscapularis in 2 patients, an osteochondral defect in 1 patient, and a tear of the medial glenohumeral ligament in 2 patients. They performed MUA to gain internal and external rotations, flexion, and abduction. However, they did not aim to achieve range of motion equal to the normal side.

Table 1 Arthroscopic findings after manipulation under anesthesia, *n* = 28

Sample number	Arthroscopic finding	Patients, *n*
1	Global synovitis	27
2	Synovitis limited to rotator interval	1
3	Anterior capsular tears	27
4	Anterior glenoid rim avulsion	1
5	Thickened middle glenohumeral ligament	27
6	Normal middle glenohumeral ligament	1
7	Superior labrum anterior posterior tears	1
8	Rotator cuff tears	4

We have noticed anterior capsular tears post-manipulation in our patients. As the MUA for a frozen shoulder has a risk of iatrogenic fractures, we have not attempted rotational manipulation. Hence, we performed arthroscopic global capsular release in all of our patients post-manipulation.

Our strict inclusion and exclusion criteria during the patient recruitment is a strength of our study, and a low sample size is our limitation. Arthroscopic findings of the shoulder both before and after the MUA can provide better insight and should be considered as a potential area for future research.

CONCLUSION

MUA leads to rupture of the capsule, which is the desired outcome. The site of rupture of the capsule depends on the maneuver of manipulation. In most cases, it leads to rupture of the anterior capsule. This is the same area where arthroscopic releases are most often performed. Rupture of the posterior and inferior capsule can also occur depending on the rotational and adduction manipulation of the shoulder. In addition, partial tears of the rotator cuff and osteochondral frac-tures of the glenoid can occur.

ARTICLE HIGHLIGHTS

Research background

Manipulation under anesthesia (MUA) of the shoulder joint is a commonly used method for the treatment of adhesive capsulitis. Though it has been known to be associated with a variety of complications, there is a paucity of studies describing arthroscopic findings after MUA.

Research motivation

Even though MUA is a very commonly practiced modality of treatment of adhesive capsulitis of the shoulder, there is not enough literature that documents the intraarticular changes after MUA.

Research objectives

The object of this study was to document the arthroscopic findings after MUA of the shoulder in patients with idiopathic adhesive capsulitis of the shoulder.

Research methods

This was a prospective study to describe the arthroscopic findings in patients with idiopathic adhesive capsulitis of the shoulder after MUA.

Research results

All patients showed the presence of synovitis. Most patients had global synovitis, while 1 patient had synovitis limited to the rotator interval. A majority of patients post manipulation showed tears in anterior capsule, whereas only 1 patient had avulsion of the anterior labrum post manipulation.

Research conclusions

MUA leads to the rupture of the capsule, which is the desired outcome. However, the site of rupture of the capsule is dependent on the maneuvers of MUA. In addition, partial tears of the rotator cuff and osteochondral fractures of the glenoid can occur.

Research perspectives

MUA for a frozen shoulder can lead to damage to other intra-articular structures besides the rupture of the capsule, which is the main aim of this procedure. In most cases, it leads to rupture of the anterior capsule.

FOOTNOTES

Author contributions: Mlv SK and Chauhan N contributed to the data acquisition, initial manuscript drafting, and incorporating revisions of this manuscript; Mittal R participated in the conception, supervision, and critical analysis and was the primary surgeon of this study.

Institutional review board statement: The study was approved by the institutional ethical committee (IESC/T-300/02.08.2013).

Clinical trial registration statement: We have not done any intervention or any randomization as a part of our study. We have only documented the findings observed during the procedure. The same was documented in the consort statement.

Informed consent statement: Informed consent was obtained from all the patients.

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CASE REPORT

Intra-arterial lipo-prostaglandin E1 infusion for arterial spasm in liver transplantation: A case report

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Abstract

BACKGROUND

Hepatic artery obstruction is a critical consideration in graft outcomes after living donor liver transplantation. We report a case of diffuse arterial vasospasm that developed immediately after anastomosis and was managed with an intra-arterial infusion of lipo-prostaglandin E1 (PGE1).

CASE SUMMARY

A 57-year-old male with hepatitis B virus-related liver cirrhosis and hepatocellular carcinoma underwent ABO-incompatible living donor liver transplant. The grafted hepatic artery was first anastomosed to the recipient's right hepatic artery stump. However, the arterial pulse immediately weakened. Although a new anastomosis was performed using the right gastroepiploic artery, the patient's arterial pulse rate remained poor. We attempted angiographic intervention immediately after the operation; it showed diffuse arterial vasospasms like 'beads on a string'. We attempted continuous infusion of lipo-PGE1 overnight *via* an intra-arterial catheter. The next day, arterial flow improved without any spasms or strictures. The patient had no additional arterial complications or related sequelae at the time of writing, 1-year post-liver transplantation.

CONCLUSION

Angiographic evaluation is helpful in cases of repetitive arterial obstruction, and intra-arterial infusion of lipo-PGE1 may be effective in treating diffuse arterial spasms.

Key Words: Liver transplantation; Hepatic artery; Vasospasm; Prostaglandin E1; Intervention; Case report

Core Tip: Diffuse arterial spasms are difficult to correct surgically, and there are no clear standard management protocols. This short report shows that angiography is helpful for evaluating the hepatic artery after liver transplantation and that intra-arterial infusion of lipo-prostaglandin E1 might be an effective non-surgical treatment option for diffuse arterial spasms.

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INTRODUCTION

Liver transplantation (LT) is a favorable treatment option for advanced liver cirrhosis, hepatocellular carcinoma (HCC), and other life-threatening diseases. However, LT can be complicated depending on the recipient's condition, immunological issues, and technical difficulties. Problems with LT include primary non-function, rejection, and biliary or vascular complications. Hepatic artery complications, such as thrombosis or stenosis, are among the most critical complications of LT[1,2]. They are more frequent in living donor LTs (LDLT) and can lead to anastomotic rupture, sepsis, diffuse intrahepatic biliary stricture, and graft failure[3-5]. Thus, arterial flow is usually evaluated using a duplex Doppler ultrasound scan before the operation is completed and again during the early postoperative period. Although hepatic artery complications are usually managed with thrombectomy and re-anastomosis, they can often be controlled with radiological intervention and medical management. Recently, we encountered a case of LT with diffuse arterial spasm that was not surgically corrected but was successfully managed with intra-arterial lipo-prostaglandin E1 (PGE1).

CASE PRESENTATION

Chief complaints

A 57-year-old male patient presented with hepatitis B virus-related liver disease and multiple HCCs.

History of present illness

Eventually, the patient underwent ABO-incompatible LDLT from his 29-year-old daughter despite having good liver function (Child-Pugh score, 5; Model for end-stage liver disease score, 8).

History of past illness

Although he underwent radiofrequency ablation for HCC, followed by four rounds of transarterial chemoembolization for two years, subsequent imaging studies still showed multiple dysplastic nodules or possible HCCs.

Personal and family history

He presented with hepatitis B virus-related liver disease and multiple HCCs.

Laboratory examinations

The patient's blood type was B+, whereas the donor's was AB+. The patient was treated with rituximab and plasmapheresis before transplantation. Rituximab was administered at a single dose of 300 mg/m^2 body surface area. Plasmapheresis was performed in triplicate. The final anti-A isoagglutinin titer was 1:8 before LT.

Operation process

The right liver graft was retrieved laparoscopically, and the hepatic vein branch from segment 5 was reconstructed using a polytetrafluoroethylene artificial graft. No events occurred during the donor or bench surgeries. The graft weight was 654 g, and the graft-to-recipient weight ratio was 0.99. Anastomoses of the hepatic and portal veins were performed, and reperfusion was uneventful. The first and second warm ischemia times were 12 and 55 min, respectively, whereas the cold ischemia time was 58 min.

The graft hepatic artery was first anastomosed end-to-end to the recipient's right hepatic artery stump using interrupted 8-0 nylon. The first pulse of the hepatic artery was good after the anastomosis. However, the arterial pulse was much weaker when rechecked after the bile duct anastomosis. We were unable to detect arterial flow in the graft using intraoperative Doppler imaging; thus, we removed the anastomosis and attempted re-anastomosis. No definitive

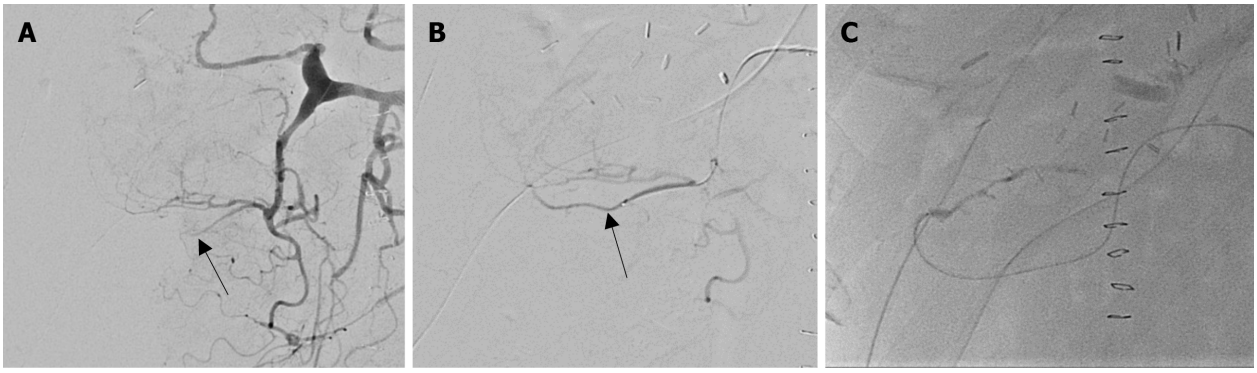

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Figure 1 Angiography immediately following liver transplantation. A: The hepatic artery and right gastroepiploic artery (RGEA) were not initially delineated (black arrow); B: RGEA (black arrow) was gradually visualized using thrombolysis; C: Anastomotic site between the RGEA and the graft artery.

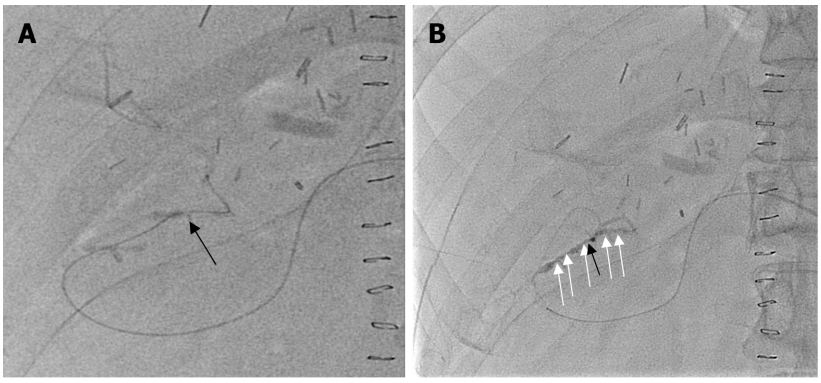

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Figure 2 Diffuse arterial spasm on angiography. A: Guidewire passed through the anastomotic site (black arrow); B: Diffuse arterial spasm (white arrows) in the right gastroepiploic artery and graft artery.

arterial thrombosis was observed. After heparin injection into both arteries, re-anastomosis was performed in the same manner; however, the arterial pulse weakened. We decided to change the artery on the recipient's side because of the poor quality of the recipient's hepatic artery from the previous chemoembolization. We carefully dissected the right gastroepiploic artery (RGEA) from the lower body of the gastric greater curvature and created a new anastomosis in the same manner. However, the pulse rate of the hepatic artery was poor. We decided to perform an angiographic intervention immediately after the operation.

MULTIDISCIPLINARY EXPERT CONSULTATION

The RGEA was not well-delineated on the first angiography (Figure 1). Thrombolysis was induced by injecting heparin and a tissue plasminogen activator into the gastroduodenal artery just once. After thrombolysis, the RGEA and hepatic artery anastomosis sites were delineated.

FINAL DIAGNOSIS

Although there was no mechanical stricture at the anastomosis site, multiple irregular constrictions were found in the RGEA and graft hepatic artery, which looked like 'beads on a string' (Figure 2).

TREATMENT

We attempted infusion of lipo-PGE1 *via* an arterial catheter for diffuse arterial spasm. We observed improvement in the spasm 10-20 min later. Thus, we decided to maintain the intra-arterial infusion of lipo-PGE1 overnight at 6 μg/h, in addition to an intravenous infusion of 20 μg/h, based on the routine protocol. Since there was no study of complications

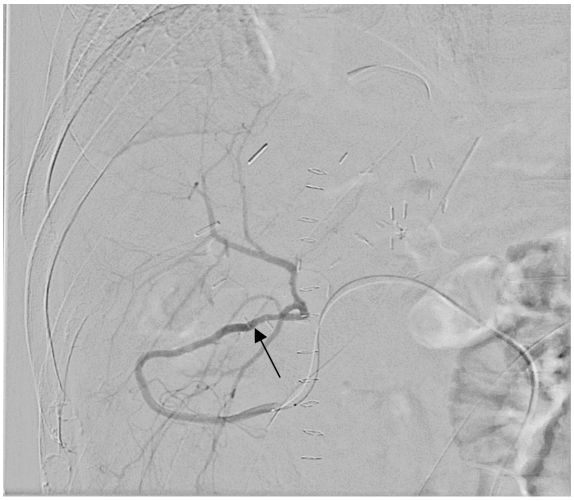

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Figure 3 Angiography after overnight intra-arterial infusion of lipo-prostaglandin E1. Good arterial flow with no spasms or anastomotic strictures (black arrow).

after such a liver transplant, there was no exact criterion for doses, so I started with a 1/3 dose of the Systemic Dose and then used a method of gradually increasing the spasm when F/U Angiography done on the following day revealed excellent arterial flow without spasms or strictures (Figure 3). Diffuse arterial spasms completely disappeared. We stopped the continuous infusion of intra-arterial PGE1 and removed the arterial catheter on the second postoperative day (POD).

OUTCOME AND FOLLOW-UP

Vascular flow was repeatedly evaluated using Doppler ultrasound every day until the third POD with dynamic computed tomography (CT) on the sixth POD. The arterial flow was good in all examinations, and no additional intervention was required. Intravenous lipo-PGE1 was administered until sixth postoperative POD. The patient was discharged on the thirteenth POD. A recent CT scan performed 10 mo post-LT also showed good arterial flow. Eventually, the patient had no additional arterial complications or related sequelae at the time of writing, 1-year post-LT.

DISCUSSION

Many studies have been published on hepatic artery complications after LT. The treatment of choice for these complications is revascularization by surgery or radiological intervention. However, because the anastomosis is very narrow and the arterial course may be tortuous in LDLT, an interventional approach may be difficult. If both surgery and intervention fail to correct these complications, the only way forward may be observation with or without medical treatment, and retransplantation may be needed in many situations[6].

Diffuse vasospasm of the hepatic artery is rare in LT, and its standard management remains unclear. Delayed cerebral ischemia due to cerebral vasospasm is known to be one of the most fatal complications after subarachnoid hemorrhage [7]. Treatment options for cerebral vasospasm include intravenous volume expansion, radiological interventions, such as balloon angioplasty, and intra-arterial injection of a vasodilator[7,8]. Diffuse arterial spasms are difficult to treat surgically. Although the spasm may be transient and leave no sequelae, it still needs to be thoroughly evaluated and managed because arterial flow disturbances in the early postoperative period can lead to diffuse intrahepatic cholangiopathy and graft failure.

As a vasodilator, PGE1 acts directly on the vascular smooth muscles and decreases the response to vasoconstriction[9]. PGE1 is commonly used in LT because of its effects on graft protection, including an increase in hepatic blood flow, enhanced recovery of mitochondrial respiration function after reperfusion, and stabilization of membrane microviscosity [10]. According to our LT protocol, we infuse lipo-PGE1 intravenously immediately after reperfusion, and continuous infusion of 20 μg/h is maintained through the sixth POD. In this case, we added lipo-PGE1 at 6 μg/h *via* an intra-arterial catheter. Diffuse spasms completely blocked arterial flow despite the administration of intravenous lipo-PGE1. Fortunately, intra-arterial infusion led to a quick improvement in the spasm, which resolved the next day.

The cause of the diffuse arterial spasm was not clarified in this case. Such an event is rare, and the present case represents our first experience. Hepatic artery vasospasms can resolve without treatment. Hepatic artery flow, however, is critical to the viability of the bile duct, and its insufficiency can cause fatal outcomes in LT.

CONCLUSION

Our experience shows that angiography is helpful for evaluating the hepatic artery after LT and that intra-arterial infusion of lipo-PGE1 may be effective in treating diffuse arterial spasms. Therefore, we suggest that early angiographic evaluation can be attempted in suspected post-LT arterial insufficiency cases, and intra-arterial PGE1 can be considered in patients with severe arterial spasms.

FOOTNOTES

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CASE REPORT

Pulmonary fungal infection in a neonate with methylmalonic acidemia: A case report

Chun-Fang Gao, Dan Wang, Ling-Kong Zeng, Xu-Wei Tao

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Abstract

BACKGROUND

Methylmalonic acidemia (MMA) is characterized by non-specific symptoms such as vomiting, and feeding difficulties, along with delayed mental and physical development. However, no case of MMA combined with pulmonary fungal infection has been reported yet.

CASE SUMMARY

We report the case of a neonate who presented pulmonary fungal infection along with the non-specific features of MMA. Exome sequencing revealed a c.331C>T variant in exon 3 of *MMACHC* from the father, and a c.658-c.660delAAG variant in exon 4 from the mother, which confirmed the diagnosis of cblC type MMA combined with hyperhomocysteinemia.

CONCLUSION

Invasive fungal infection might occur in some infants with MMA. Therefore, early diagnosis is recommended for unexplained pulmonary infection.

Key Words: *MMACHC*; Fungal infection; Genotype; Clinical approach; Case report

Core Tip: We have retrospectively reported the case of a neonate with pulmonary Aspergillus infection as the main clinical manifestation, which was later confirmed as methylmalonic acidemia (MMA) by full exon sequencing and blood amino acid/urine organic acid analysis. Our findings provide a novel clinical diagnostic approach for neonatal MMA.

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INTRODUCTION

Methylmalonic acidemia (MMA) is an autosomal/X-linked recessive disorder of organic acid metabolism that occurs due to mutations in methylmalonyl-CoAmutase or its coenzyme vitamin B12 (cobalamin)[1]. It is characterized by the accumulation of metabolites such as methylmalonic acid, 3-hydroxypropionic acid, and methylcitrate. Aberrant cobalamin metabolism can be classified into defects in adenosylcobalamin synthesis, including mitochondrial cobalamin deficiency (cblA) and mitochondrial cobalamin adenosyltransferase deficiency (cblB), and defects in adenosylcobalamin and methylcobalamin synthesis due to abnormal cytoplasmic and lysosomal cobalamin metabolism (cblC, cblD, and cblF). The coding genes for these types are *MMAA*, *MMAB*, *MMACHC*, *MMADHC*, and *LMBRD1*, respectively. The cblC type predominantly occurs in neonates and typically presents with non-specific symptoms. We report a case of a neonate admitted to the Department of Neonatology, Wuhan Children's Hospital, with pulmonary Aspergillus infection as the main clinical manifestation, which was later confirmed as MMA through full exon sequencing and blood amino acid/urine organic acid analysis. Our findings provide a novel clinical diagnostic approach for neonatal MMA.

CASE PRESENTATION

Chief complaints

The baby developed shortness of breath for one day.

History of present illness

The patient was a 25-day-old girl, G2P1, G36W, cesarean delivered, with Apgar score 9 after 1 min and 10 after 5 min of birth. The birth weight was 2.06 kg (P10, -1.2SD), head circumference was 32 cm (P50, 0SD), and body length was 46 cm (P50, 0SD). The baby developed shortness of breath without any notable history and was subsequently admitted to our hospital.

History of past illness

No previous history.

Personal and family history

No personal and family history.

Physical examination

On admission, the body temperature was 37.6 °C, heart rate was 162 beats/min, blood pressure was 70/37 mmHg, weight was 2.88 kg (P20), head circumference was 33 cm (P10), and body length was 46 cm (P3). The only abnormal finding on examination was coarse respiratory sounds in both lungs. Evaluation of other systems did not reveal any irregularities.

Laboratory examinations

Routine blood count, biochemical parameters, Torch-immunoglobulin M test, blood cultures, 1,3-D glucan test (G test), and galactomannan polysaccharide antigen detection (GM test) showed no obvious abnormalities. Respiratory exudates tested negative for influenza virus, respiratory syncytial virus, and other respiratory viruses. Electrocardiography, electrocorticography, and echocardiography results were normal. The hypersensitive protein level upon admission was relatively high at 21.7 mg/L (< 3 mg/L) but returned to normal after 3 d.

Imaging examinations

Lung ultrasound and X-ray examination revealed multiple round-like high-density shadows in both lungs, while computed tomography (CT)-scan showed infectious lesions in both lungs with air-containing cavities (Figure 1).

FINAL DIAGNOSIS

cblC type MMA combined with homocysteinemia.

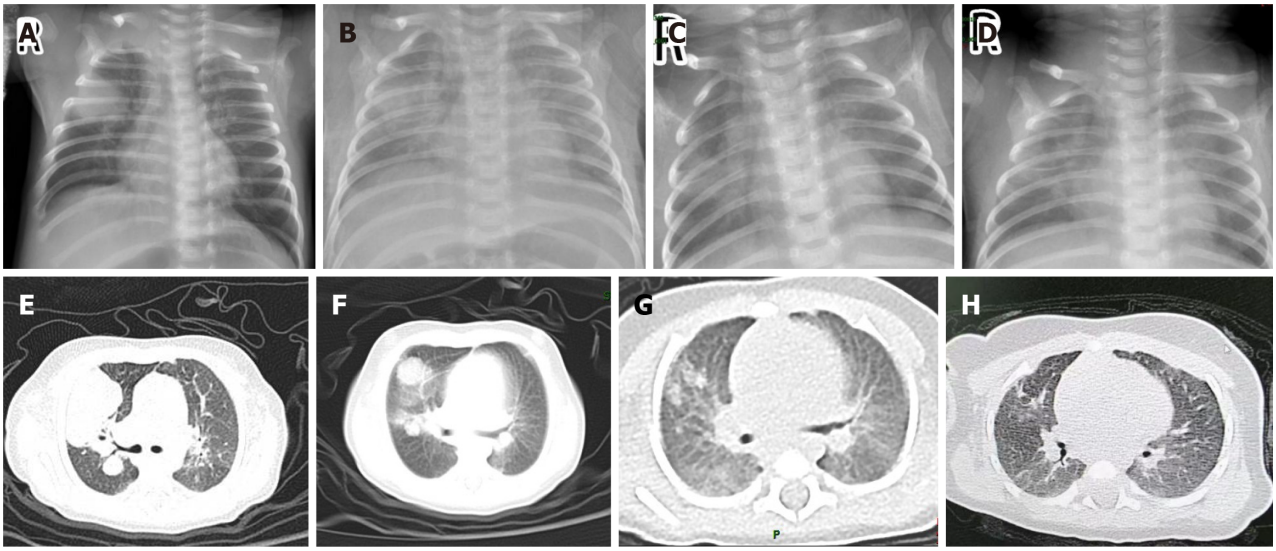

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Figure 1 The result of chest x-ray and pulmonary computed tomography. A: On the day of admission; B: 1 wk after admission; C: 2 wk after admission; D: 3 wk after admission; E: On the day of admission; F: 2 wk after adjust treatment; G: 15 d after discharge; H: 2 mo after discharge.

TREATMENT

The infant experienced intermittent fever for 8 d after hospitalization and vomited after formula feeding. The main clinical symptom was shortness of breath with a respiratory rate of 60-70 breaths/min in a calm state. Empirically, ceftazidime combined with vancomycin was administered, but no improvement was observed after one week. Fiberoptic bronchoscopy showed caseous material and pseudomembranous structures in the subbranch lumen of the anterior bronchial. Metagenomics next-generation sequencing of alveolar lavage fluid confirmed Aspergillus infection, leading to a switch in treatment to Voriconazole.

OUTCOME AND FOLLOW-UP

Regular outpatient follow-ups were conducted after discharge. Lung CT-scan was performed after 15 d and in the 2nd mo of follow-up, revealing improvements (Figure 1). Considering the unexplained fungal infection, full exon sequencing was performed to investigate the possibility of an immunodeficiency disease. The results confirmed a compound heterozygous variant in the *MMACHC* gene, with c.331C>T in exon 3 inherited from the father and c.658-c.660delAAG in exon 4 inherited from the mother, indicating cblC type MMA combined with homocysteinemia (Figure 2). Elevated blood malonylcarnitine, malonylcarnitine/acetylcarnitine ratio, urinary methylmalonic acid, urinary methylcitrate, and urinary homocysteine levels further confirmed the diagnosis. The patient received levocarnitine, betaine, calcium folinic acid, and hydroxocobalamin. At the 6-mo follow-up, the metabolic indicators showed improvement, and the infant exhibited normal physical and neurological development thereafter.

DISCUSSION

MMA is the most commonly diagnosed organic aciduria in China, and presents a diverse and complex clinical phenotype and genotype. The accumulation of methylmalonic acid and its metabolites can cause damage to the central nervous system, as well as the cardiovascular, renal, pulmonary vascular and hematological tissues, resulting in high mortality and disability rates[2]. The cblC type is the most common form of MMA combined with homocysteinemia (combined MMA). It is caused by mutations in the *MMACHC* gene[3], which is located on chromosome 1p34 and consists of 4 coding exons and 1 non-coding exon. The cblC protein is composed of 282 amino acids and is primarily found in the cytoplasm. Its main functions include catalyzing the reductive decyanation of cyanocobalamin and the synthesis of adenosine drillamin and methylcobalamin[4]. To date, nearly 80 different MMACHC gene mutations have been identified [5]. In China, the most common early-onset mutations are c.609G>A (48.1%-67.8%) and c.658_660delAAG (7.1%-13.9%). These mutations lead to sequence changes in the C-terminal region of cb1C and may impact the proton pump energy conversion required for cobalamin transport. Surviving children typically have compound heterozygous mutations, and carriers of these mutations often exhibit microcephaly, epilepsy, and severe developmental delay. More than 90% of MMA patients experience delayed intellectual and motor development, convulsions, abnormal psychiatric behavior, and, in some cases, feeding difficulties, vomiting, and malnutrition[6]. Only one published report exists of a neonatal MMA case combined with oral Candida infection after hospitalization[7]. Our neonate patient, on the other hand, presented

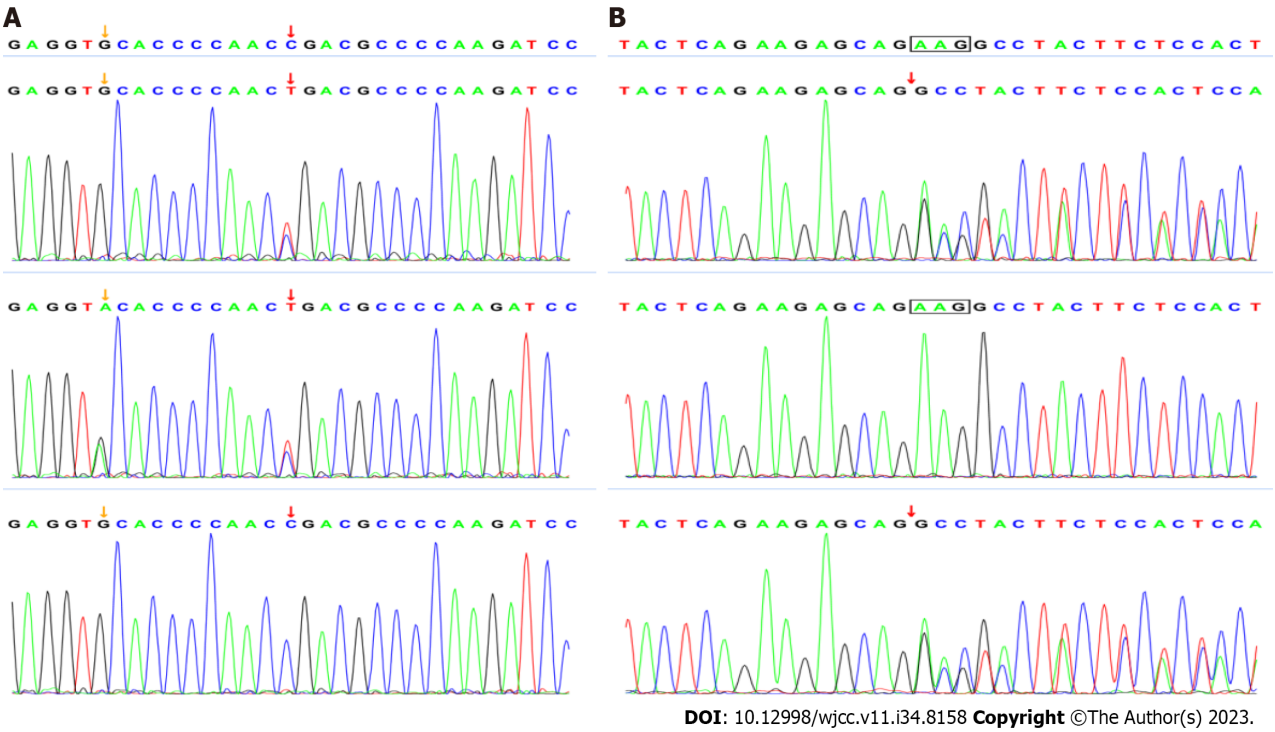

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Figure 2 Gene mutation map of the children and their parents. A: The child and his father: c. 331(exon3) c>T; B: the child and his mother: c. 658(exon4)-c. 660(exon4) delAAG.

with pulmonary fungal infection and exhibited atypical symptoms such as fever, lagging physical development, and vomiting during hospitalization. No neurological abnormalities were observed. Neutrophil deficiency is a known risk factor for invasive Aspergillus infection; however, in our case, no significant changes were observed in the neutrophil count or ratio, even during periods of intermittent fever. While we cannot rule out the possibility of neutrophil dysfunction, it is likely that the observed findings are due to decreased endothelial function resulting from the MMACHC mutation. Totoskovic *et al*[8] proposed a potential relationship between neutrophil morphometric indices and impaired cobalamin status. Vitamin B12 deficiency is known to cause hypersegmentation of the neutrophil nucleus and an increase in cell volume[9,10]. Based on these observations, the authors hypothesized that these changes may impact neutrophil Cell Population Data (CPD). CPD refers to the mean values and standard deviations of volume, conductivity, and light scatter for different leukocyte subpopulations. The study found a strong correlation between hypersegmented neutrophils and vitamin B12 deficiency. However, it remains unclear to what extent neutrophil scatter distribution width could be utilized to assess cobalamin status in patients with inflammatory or infectious conditions, requiring further investigation. This report presents the first documented case of neonatal methylmalonate acidemia combined with pulmonary Aspergillus infection, highlighting the need for future research into potential impairments in neutrophil function caused by methylmalonic acid and vitamin B12 deficiency. In a study involving six children with MMA combined with diffuse pulmonary disease as the primary presentation, four of them were identified as heterozygous or homozygous for the c.80A>G mutation, which has been previously reported in Chinese patients with pulmonary hypertension[11]. The accumulation of methylmalonic acid and homocysteine is often associated with nonspecific symptoms like anemia and poor feeding, while reduced methionine serves as a phenotype of *MMACHC* mutation[12-14]. Homocysteine, a sulfhydryl amino acid, can accumulate and lead to vascular endothelial damage and hematologic abnormalities, including thrombocytopenia, hemolytic-uremic syndrome, and bone marrow suppression[15]. Consequently, aberrant hematocrit levels can be observed. Anemia is commonly manifested due to factors such as bone marrow suppression, the accumulation of metabolic intermediates that harm the vascular endothelium and erythrocytes, impaired vitamin B12 utilization, and iron deficiency resulting from inadequate feeding[16,17].

CONCLUSION

It is worth mentioning that although the infant was being effectively treated, the non-specific symptoms such as vomiting and delayed development were considered as possible infection-related and ignored, which delayed the diagnosis. Therefore, a multipronged clinical approach is recommended for neonates with unexplained fungal infection.

FOOTNOTES

Co-first authors: Chun-Fang Gao and Dan Wang.

Author contributions: All authors contributed to the study conception and design. Gao CF, Wang D, Zeng LK, and Tao XW contributed to the material preparation, data collection and analysis; Gao CF and Wang D wrote the first draft of the manuscript; and all authors commented on previous versions of the manuscript; and all authors read and approved the final manuscript.

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CASE REPORT

Adult localized Langerhans cell histiocytosis: A case report

Pan-Pan Yang, Su-Ye Hu, Xu-Ya Chai, Xiao-Meng Shi, Li-Xia Liu, Ling-E Li

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Abstract

BACKGROUND

Langerhans cell histiocytosis (LCH) is a rare clonal proliferative disease of Langerhans cells with unknown pathogenesis. An increasing number of clinicians recognize that LCH has a wide clinical spectrum and a highly varied course. Adults rarely develop LCH. Here, we report a case of adult localized LCH.

CASE SUMMARY

A 32-year-old woman presented with plaques and ulcers on the vulva and crissum, accompanied by pain that persisted for more than one year. Physical examination revealed a red-infiltrating plaque with ulcerations and exudates in the vulva and crissum. Pathological examination revealed a diffuse infiltration of lymphocytes, eosinophilic granulocytes, and histiocytoid cells in the superficial dermis. Proliferative histiocytoid cells showed mild atypia, partly with kidney-shaped nuclei. Immunohistochemical examination showed that the histiocytoid cells were positive for S100 protein and CD1 and weakly positive for CD68 (20% +), with a Ki-67 index of 30%. Laboratory tests did not reveal any other systemic damage. The patient was diagnosed with adult localized LCH and was prescribed oral prednisone (20 mg) once daily. The skin lesions gradually improved and are still being followed-up.

CONCLUSION

Adult localized LCH is rare and must be differentiated from other common conditions.

Key Words: Langerhans cell histiocytosis; Adult; Vulva; Crissum; S100; Case report

Core Tip: Langerhans cell histiocytosis (LCH) is a rare clonal proliferative disease of Langerhans cells that express an immunophenotype positive for S100 protein, CD1 (CD1a), and Langerin (CD207) and contain cytoplasmic Birbeck granules. Adult localized LCH presenting with plaques and ulcers on the vulva and crissum is rare and must be differentiated from other common conditions.

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is a disease characterized by the proliferation of Langerhans cells that express an immunophenotype positive for S100 protein, CD1 (CD1a), and Langerin (CD207) and contain cytoplasmic Birbeck granules[1]. Several organs are involved in this process. The childhood and adult forms of LCH should be considered separately. Two-thirds or more children under one year of age and those aging 1–4 years have multi-system diseases, including those of the liver, lungs, or bone marrow. In adults, the peak age of presentation is between 20 years and 35 years, with multi-system diseases occurring in one-third to two-thirds of adults with LCH. The bones are the most commonly involved organs. Skin and mucosal involvement are the second most common manifestations in adults[2]. Here, we report a case of adult LCH that presented solely with skin involvement, without systemic damage.

CASE PRESENTATION

Chief complaints

A 32-year-old woman presented with plaques and ulcers on the vulva and crissum, accompanied by pain and exudates on the surface of the ulcers.

History of present illness

The patient reported a rash on the vulva as the first manifestation, which gradually enlarged and extended to the perianal area. She did not complain of diarrhea, constipation, melena, hematochezia, diabetes insipidus, changes in appetite, or weight loss.

History of past illness

The patient denied any previous chronic diseases, hepatitis, tuberculosis, and any history of infectious disease and close contact with infected people. She also denied drug and food allergies. Her vaccination history was unknown.

Personal and family history

The patient had no family history of cancer.

Physical examination

Physical examination revealed red erosive plaques and ulcers on the vulva and perianal areas, which were covered with exudates (Figure 1). No skull defects were observed.

Laboratory examinations

A punch biopsy was performed at the intersection between the normal skin and vulvar rash during the initial visit. The tissue section was fixed in 10% neutral formalin, paraffin-embedded, sectioned, stained with hematoxylin and eosin, and subjected to direct immunohistochemistry before observation under light microscopy. Each immunohistochemistry test group included a negative self-control. All primary and secondary antibodies were purchased from ZSGB-BIO, Beijing, China. The primary antibody incubation lasted 50 min at 37 °C and 20 min at 37 °C for the secondary antibody. Visualization was performed using DAB (3,3'-diaminobiphenyl), and results were assessed by capturing images with a light microscope.

Pathology revealed histiocytoid cells in the superficial and middle dermal layers with mild nuclear atypia and a population of occasional eosinophils. The atypical histiocytoid cells were positive for S100 protein and CD1a, and weakly positive for CD68 (20% +), with a Ki-67 index of 30%. These cells were negative for creatine kinase (Figures 2 and 3).

Imaging examinations

Computed tomography of the sacroiliac joint showed that the cortical bone of the sacral surface of the right sacroiliac joint was discontinuous.

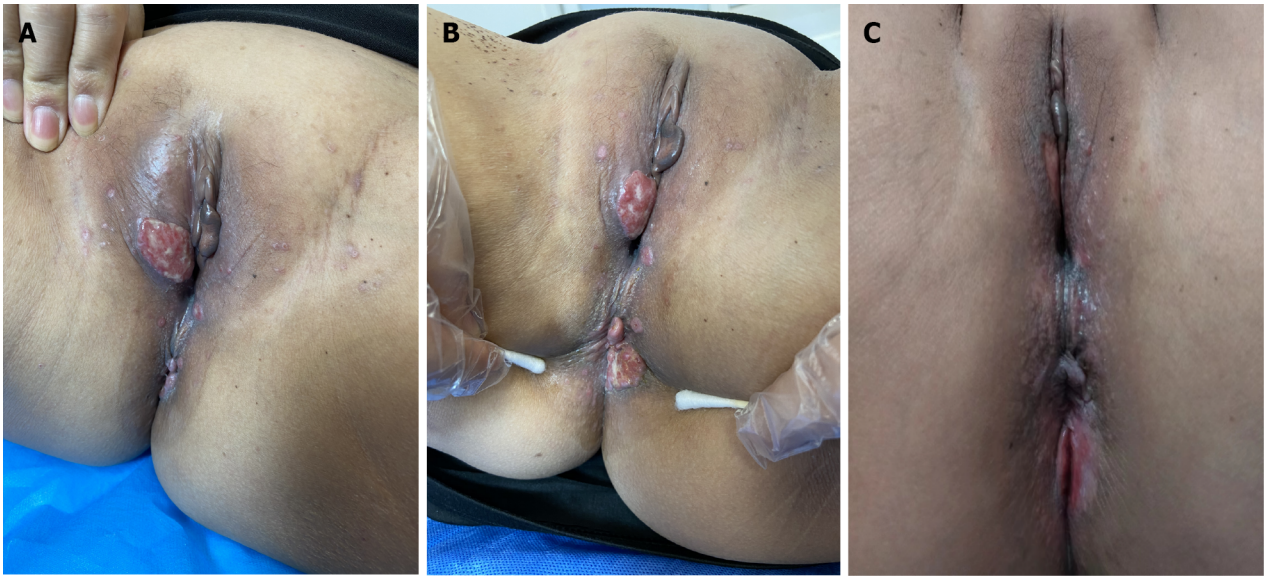

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Figure 1 Clinical feature. A: Red erosive plaques and ulcers on the vulva; B: Red erosive plaques and ulcers on the perianal area; C: Lesions after 6 mo of oral prednisone 20 mg orally.

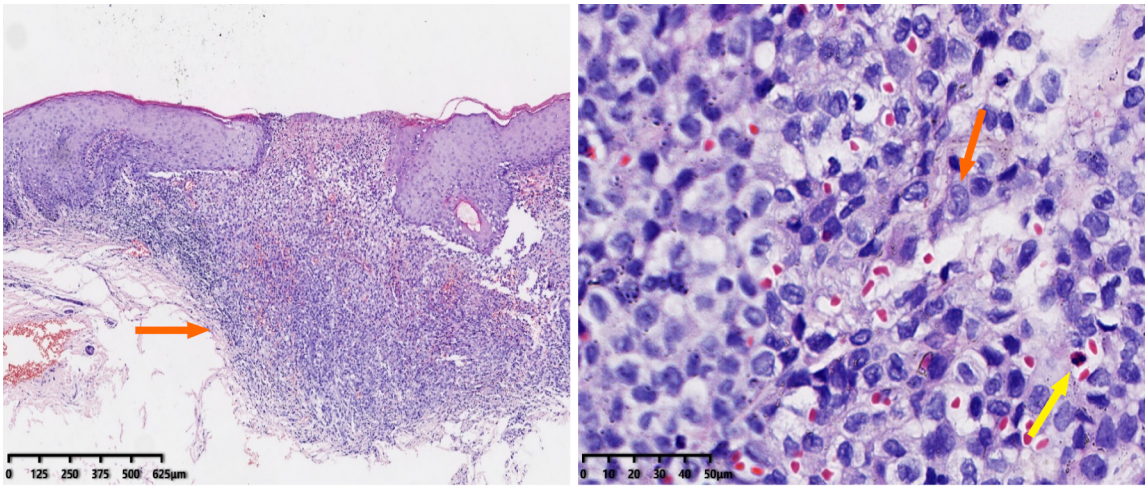

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Figure 2 Hematoxylin and eosin staining. A: The histiocytoid cells in the superficial and middle dermis layer with mild nuclear atypia, with occasional eosinophils; B: The histiocytoid cells in the superficial and middle dermis layer with mild nuclear atypia (orange arrow), with occasional eosinophils (yellow arrow).

FINAL DIAGNOSIS

Based on these results, the patient was diagnosed with adult localized LCH.

TREATMENT

The patient was prescribed thalidomide 0.1 g orally twice daily and methotrexate 7.5 mg once weekly.

OUTCOME AND FOLLOW-UP

Three months later, the patient reported a poor response and was prescribed prednisone 20 mg orally once daily; the lesions gradually improved and the patient is still being followed up (Figure 1).

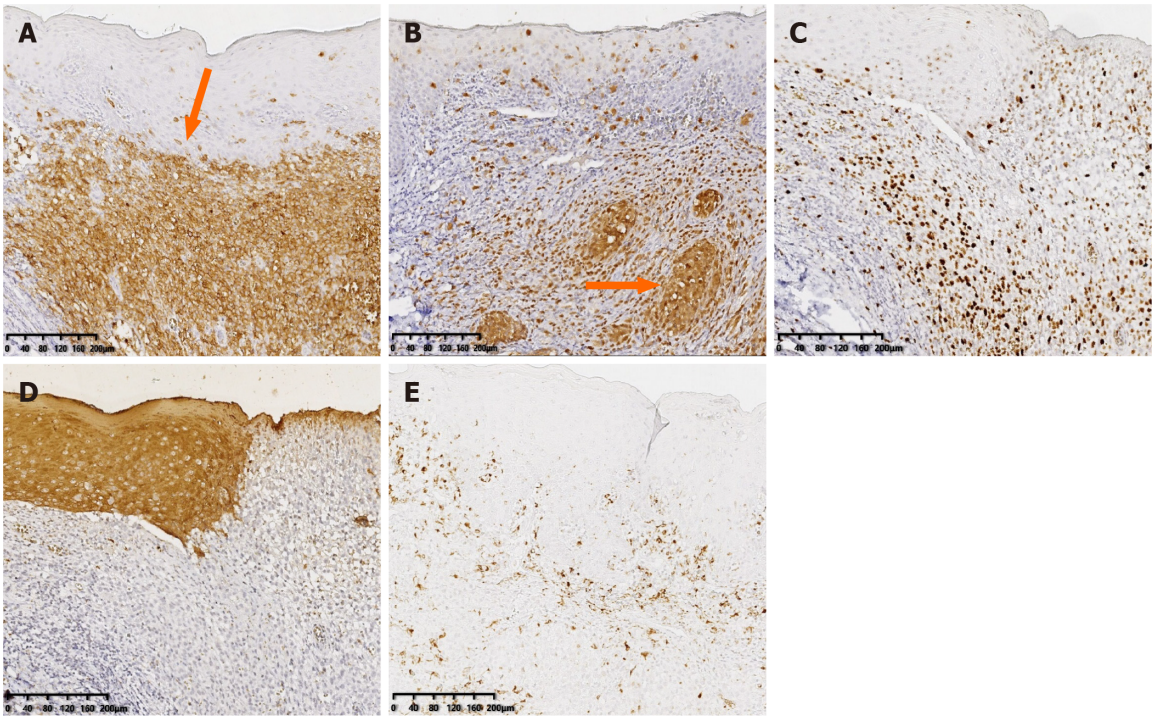

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Figure 3 Immunohistochemistry. A: CD1 (+++); B: S100 (+++); C: Ki-67 (30%); D: CK (-); E: CD68 (20%+).

DISCUSSION

LCH is a rare group of disorders in which mononuclear macrophages and dendritic cell systems proliferate, often affecting the skin and bones. It can also lead to multi-system diseases of the liver, spleen, lung, central nervous system, lymph nodes, thymus, gastrointestinal tract, and bone marrow[1-5]. Liver and spleen involvement causes abnormal liver function, hepatomegaly, and hypersplenism[6]. Involvement of the lungs may cause chest pain and dyspnea[7]. The pituitary gland may also be affected by LCH causing diabetes insipidus[8-10]. The bones of the skull are the most common sites affected by LCH, but other bones, such as the femur, scapula, rib, mandible, and vertebrae, can also be affected[11-13].

Depending on the number of systems involved in the patient, LCH is divided into single-system-LCH (SS-LCH) and multi-system-LCH (MS-LCH)[14]. SS-LCH is divided into SS-S (a single site involving the bone, skin, or lymph nodes) and SS-M (involving multiple parts of the bone or lymph nodes). Patients with SS-LCH have a good prognosis, whereas those with MS-LCH, especially those with liver and hematopoietic system involvement, have a poor prognosis and higher mortality rate[6,15]. Generally, patients with LCH in whom only the skin is affected have a good prognosis and about 50% of the patients can be in remission within a few months; however, disease progression and persistence are more common, and long-term follow-up is recommended[16].

The most common areas of skin involvement in LCH are the scalp, trunk, skin folds, and mucosa. Skin lesions vary and present as papules, blisters, pustules, purpura, plaques, or ulcers[2]. The most characteristic presentations of adult LCH are groin, perianal, and vulvar involvements. Chen *et al*[17] reported a case of adult LCH with an eczematoid lesion in the vulva as the initial manifestation, whereas Wu *et al*[18]reported a case of LCH with perianal skin lesions as the first presentation. In the present case, the skin lesions were located on both the vulvar and perianal regions. Computed tomography of the sacroiliac joint revealed discontinuity in the cortical bone of the right sacroiliac joint. Changes in the sacroiliac joint necessitated further follow-up and progressed slowly with no apparent systemic involvement. In conclusion, adult LCH is a rare disease that must be distinguished from other common diseases, including Paget's disease, candidiasis, and malignant melanoma.

Treatment of LCH should be individualized according to the number and severity of organs involved. Therapeutic options should also prevent long-term side effects of medication. Topical and systemic corticosteroids, nitrogen mustard, methotrexate, psoralen plus ultraviolet-A radiation, narrow-band ultraviolet-B radiation (or excimer laser), thalidomide, interferon, and azathioprine can be considered for treatment depending on the extent of skin lesions[2]. Therefore, surgical resection of a single lesion should be considered. No single treatment has been effective in all patients.

CONCLUSION

The rarity of LCH in adults may have resulted in its overlooked diagnosis. Therefore, dermatologists should consider this disease, along with its varied presentation and treatment options.

FOOTNOTES

Co-first authors: Pan-Pan Yang and Su-Ye Hu.

Author contributions: Chai XY and Yang PP performed laboratory testing and clinical data collection; Shi XM and Liu LX performed pathological studies; Yang PP and Hu SY drafted the manuscript; Hu SY and Li LE critically revised the manuscript for important intellectual content; all authors have read and approved the final version. Yang PP and Hu SY contributed equally to this work as co-first authors. The reasons for designating Yang PP and Hu SY as co-first authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-first authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-first authors best reflect this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Yang PP and Hu SY contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Yang PP and Hu SY as co-first authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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CASE REPORT

Venous adventitial cystic disease is a very rare disease that can cause deep vein thrombosis: A case report

Miju Bae, Up Huh, Chung Won Lee, Jong Won Kim

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Abstract

BACKGROUND

Venous adventitial cystic disease (VACD) is a rare disease characterized by cysts, filled with a gelatinous mucous substance similar to joint fluid, in the adventitia of blood vessels adjacent to the joints. It is often misdiagnosed as deep vein thrombosis (DVT), femoral varices, venous tumors, or lymphadenopathy.

CASE SUMMARY

A 69-year-old woman visited our hospital with a complaint of swelling in the right lower extremity. The patient was diagnosed with DVT and prescribed apixaban at an outpatient clinic. After 3 wk, the patient was hospitalized again because of sudden swelling in the right lower extremity. We diagnosed VACD and performed surgery for cyst removal as well as patch angioplasty and thrombectomy of the right common femoral vein. The patient received anticoagulants for 6 mo and has been doing well without recurrence for 1 year postoperatively.

CONCLUSION

Recurrent VACD requires complete removal of the connections to the joint cavity to prevent recurrence.

Key Words: Adventitia; Cysts; Edema; Joints; Venous thrombosis; Case report

Core Tip: Venous adventitious cystic disease is a rare condition characterized by the occurrence of cysts filled with a gelatinous substance similar to synovial fluid in the outer layer of blood vessels adjacent to joints. It can be misdiagnosed as deep vein thrombosis, femoral varices, venous tumors, or lymphadenopathy. To prevent recurrence, it is important to completely remove the connections to the joint cavity.

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INTRODUCTION

Venous adventitial cystic disease (ACD) (VACD) is a rare malformation characterized by the accumulation of mucinous materials in cysts in the vascular adventitia[1]. According to an extensive literature review, only 53 cases have been reported to date[2]. Cysts usually occur in blood vessels around the major joints, and patients complain of severe swelling, tenderness, and pain[3].

We describe the case of a patient who was first diagnosed with deep vein thrombosis (DVT) and later diagnosed with VACD due to symptom recurrence during treatment. Recovery was achieved through surgical treatment.

CASE PRESENTATION

Chief complaints

Right leg swelling.

History of present illness

A 69-year-old woman visited our hospital complaining of swelling in the right lower extremity. The patient was diagnosed with DVT at a local hospital, and thrombolysis was performed. Venography was performed after thrombolysis, and it revealed focal stenosis in the right common femoral vein (CFV) area. Balloon angioplasty was performed, but the focal stenosis did not improve. The radiologist judged that the shape of the focal stenosis was not due to an intravenous thrombus but due to external pressure from a mass pressing on the vein. She was transferred to the emergency room of our hospital, but her symptoms improved. We prescribed a direct oral anticoagulant (apixaban) and observed her on an outpatient basis. After 3 wk, the patient was hospitalized again because of sudden swelling in the right lower extremity.

History of past illness

The patient had a history of hypertension.

Personal and family history

She had no relevant personal or family history.

Physical examination

The physical examination revealed no noteworthy abnormalities.

Laboratory examinations

Her D-dimer levels were elevated to 80 μg/mL (normal range 0-0.5 μg/mL). Other laboratory parameters were within the normal ranges.

Imaging examinations

Venography revealed a mass-like lesion (scimitar sign) located outside of and pressing on the right CFV (Figure 1A). A cystic mass was observed in the right CFV (Figure 1B). On ultrasonography, we did not observe flow to the right femoral artery (FV) because the cystic mass had blocked the right CFV (Figure 1C and D).

FINAL DIAGNOSIS

The patient was diagnosed with VACD and surgery was planned. After surgery, histological examination confirmed VACD. A cystic wall composed of fibrous tissue with increased proteoglycan levels and few elastic fibers was observed.

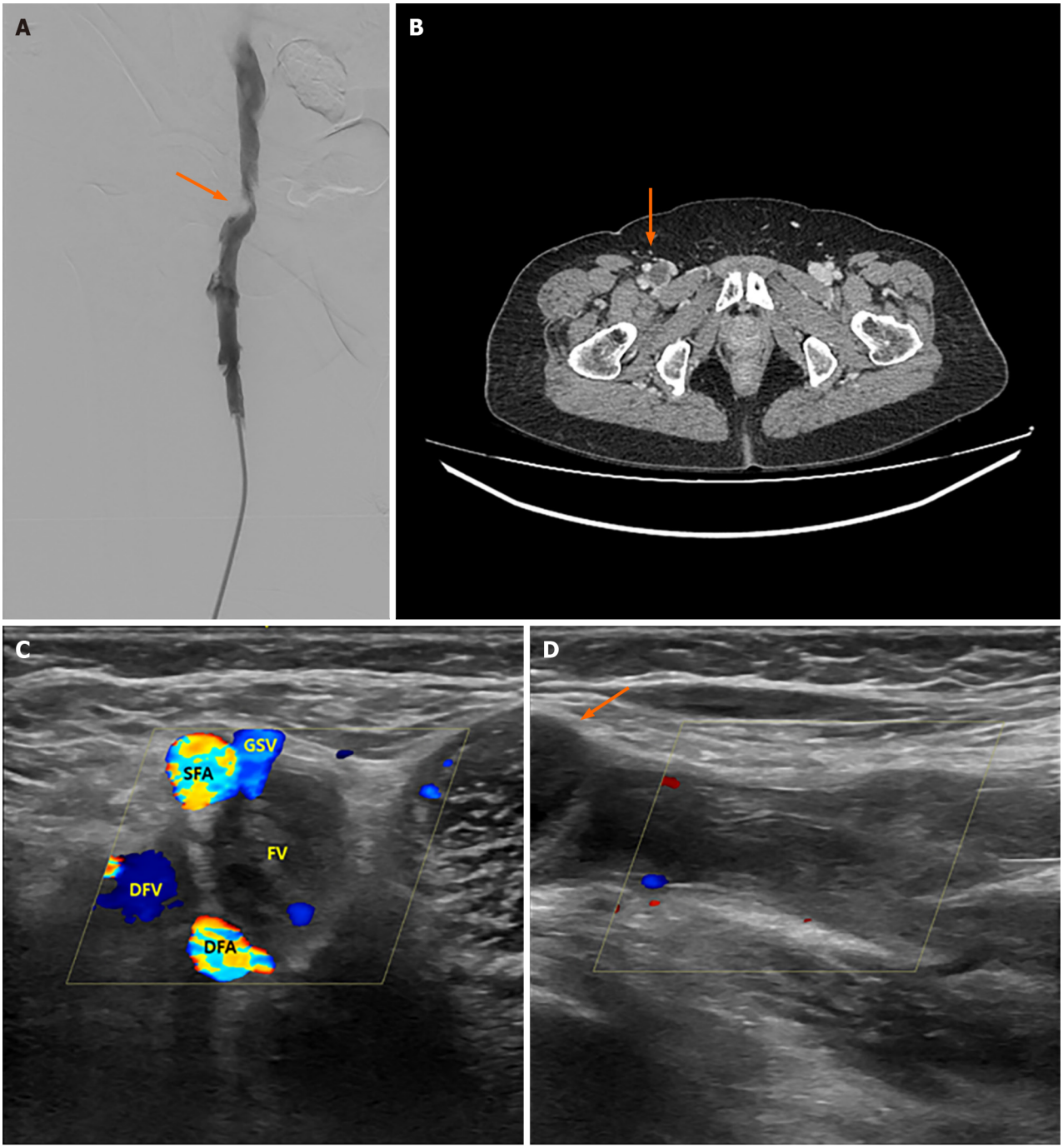

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Figure 1 Image study. A: Venography showing a mass-like lesion (scimitar sign) outside the blood vessel pressing on the right common femoral vein (FV) (CFV) (arrow); B: The cystic mass pressing on the right CFV (arrow); C and D: On ultrasonography, flow to the right FV cannot be observed because of a cystic mass blocking the right CFV; C: Transverse view; D: Longitudinal view. Arrows point to the cyst.

TREATMENT

The patient underwent surgery under general anesthesia. A longitudinal incision was made in the right groin. The distal external iliac vein above the branch of the great saphenous vein (GSV) was dissected into the GSV, proximal FV, and proximal deep femoral vein. In particular, to eliminate communication with the synovial fluid, the bottom wall of the vein was completely dissected and communication was removed (Figure 2). After venotomy, the cyst and the vein wall in the cystic area were removed. The right leg was squeezed to remove any remaining thrombus. The right posterior tibial vein was punctured, and a guidewire was moved to the CFV to facilitate thrombectomy, using a Fogarty catheter to remove as much of the remaining thrombus as possible. Patch angioplasty using the GSV was considered, but venous flow through the GSV was superior on preoperative ultrasound. Therefore, the vein was reconstructed using an Edwards bovine pericardial patch (Edwards Lifesciences Corp., Irvine, CA, United States).

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Figure 2 Right common femoral vein. Arrow: Venous adv.

OUTCOME AND FOLLOW-UP

The venous flow was restored, and the swelling of the right leg was completely recovered before discharge. Intravenous heparinization was performed for 7 d, after which the patient was switched to direct oral anticoagulants (apixaban). The inferior vena cava filter was removed on postoperative day 11, and the patient was discharged on postoperative day 12.

Apixaban was discontinued because DVT was no longer observed on computed tomography venography performed 6 mo after surgery. The patient is currently under follow-up as an outpatient and has been without recurrence for 1 year after surgery.

DISCUSSION

The present case report sheds light on the rare and often misdiagnosed entity of VACD. VACD is a rare condition, accounting for only 0.1% of all vascular diseases[4]; however, it is challenging to diagnose and manage due to its nonspecific clinical manifestations and resemblance to other vascular anomalies.

VACD is a benign vascular anomaly characterized by the formation of cystic structures within the adventitial layer of the veins. The presentation of this condition varies widely, ranging from asymptomatic incidental findings on imaging to cases with symptoms, such as pain, swelling, or compression of adjacent structures. Enlarged cysts can exert localized focal pressure on target vessels, leading to claudication or obstruction of venous outflow and limb swelling[3]. The rarity of this disease often leads to misdiagnosis or delayed diagnosis of DVT, femoral aneurysms, venous tumors, or lymphadenopathy, highlighting the need for clinical suspicion[5]. Over a period of 50 years (1963-2016), according to an extensive literature review on 45 cases of VACD, it was found that the femoral vein was the most common location of VACD lesions (56%), followed by the external iliac vein (24%), extra-saphenous vein (13%), and the popliteal vein (7%)[1]. The average age of patients participating in this study was 47 years, with 50% being male.

The pathogenesis of ACD is attributed to adventitial cystic degeneration caused by repetitive trauma, *de novo* adventitial degeneration caused by systemic processes, and resting residual mesenchymal cells[6]. The articular (synovial fluid) theory of the development of ACD has been proposed[2,7,8]. In particular, this theory about the cause of arterial ACD is predominant in the literature[8,9]. As the etiology of VACD is unclear and may differ from that of arterial ACD, adjacent structures must be thoroughly investigated during surgery to rule out events that are unlikely to be part of the underlying etiology of the disease.

Diagnostic imaging plays a pivotal role in confirming the presence of VACD and differentiating it from other vascular lesions. Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are commonly performed. VACD can be suspected upon careful examination of the duplex ultrasound; however, both CT angiography and MRI are usually needed to confirm the diagnosis and rule out other coincidental pathologies[10]. A venogram may reveal crescentic compression (the "scimitar sign") on the target vein, with distal venous distension[11,12]. Intravascular ultrasound has also been used to delineate lesions and estimate the degree of compression[13]. The increased sensitivity of CT and MRI in the venous phase has improved their use for making an accurate diagnosis, without the need for further invasive tools[3]. The characteristic features include well-defined cystic structures adjacent to the veins, which often show fluid–fluid levels on imaging.

In ACD, cysts tend to recur even after treatment[14]. Minimally invasive management of adventitial cysts by image-guided needle aspiration has been reported, but the recurrence rate is high because secondary cyst drainage is incomplete due to the high viscosity of the mucinous material in the cyst, and mucus-secreting mesenchymal cells remain in place[6, 11]. Endovascular treatment is also ineffective because it does not address the underlying cause of compression, and it can be problematic for cross-articular lines of stents and thrombosis of low-flow veins[15]. Therefore, physicians must use surgical intervention as the treatment of choice. If the patient's vein is intact and the lumen has no damage, transluminal or transadventitial evacuation of the cyst is performed prior to cyst wall excision. As the recurrence rate is 20%, surgeons must carefully perform thorough wall resection. If the wall is not properly excised, mesenchymal cells of the bursa may remain in the adventitia and secrete sufficient mucus leading to recurrence[1]. Vein resection with graft placement in either the great or small saphenous veins has a recurrence rate of 14.3%. However, this method should only be used when the vein being treated is damaged or when the surgeon is unable to visualize and operate on the vessel adequately[16].

CONCLUSION

VACD can be misdiagnosed as DVT, femoral varices, venous tumors, or lymphadenopathy. To prevent its recurrence, it is crucial to remove the connections to the joint cavity completely.

FOOTNOTES

Author contributions: Bae M, Huh U, and Lee CW contributed to subject assessment; Bae M, Huh U, Lee CW, and Kim JW contributed to drafting the manuscript and data interpretation; Bae M, Huh U, Lee CW, and Kim JW contributed to study conception, design, and supervision; All authors have read and approved the final manuscript.

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CASE REPORT

Rare case of lupus enteritis presenting as colorectum involvement: A case report and review of literature

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Abstract

BACKGROUND

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that can affect the gastrointestinal tract. Most cases of lupus enteritis (LE) involve the small intestine, while the involvement of the whole colon and rectum without the small intestine being affected is extremely rare.

CASE SUMMARY

A 35-year-old woman was diagnosed with colorectal LE after initially presenting with intermittent abdominal pain and vomiting for two months. She had a regular medication history for five years following the diagnosis of SLE but had been irregular in taking medications, which may have contributed to the onset of LE and led to her current hospital admission. According to the 2019 Classification criteria for SLE of the European League Against Rheumatism/American College of Rheumatology, this case scored 14. Additionally, abdominal computed tomography revealed significant wall edema of the colon and rectum, ischemia and hyperemia of the ascending colon intestinal wall, mesenteric vessel engorgement, increased mesangial fat attenuation, ascites, and bilateral ureter-hydronephrosis, all indicative of colon and rectum LE. Laboratory tests also showed lower levels of complement C3 and C4, with an antinuclear antibody titer of 1:100. Overall, it was clear that this case involved the colon and rectum without affecting the small intestine, representing a rare manifestation of SLE. The patient received treatment with 10 mg of methylprednisolone sodium succinate, 100 mL of 0.9% sodium chloride, hydroxychloroquine (100 mg), and nutrition support. After one week of methylprednisolone and hydroxychloroquine therapy, her SLE symptoms and disease activity improved significantly.

CONCLUSION
Although colorectal LE without small intestine involvement is very rare, early diagnosis and excellent management with corticosteroids prevented the need for surgical intervention. Physicians should be aware of colorectal LE without small intestine involvement as a manifestation of lupus flare.

Key Words: Lupus enteritis; Systemic lupus erythematosus; Colon and rectum; Target sign; Comb sign; Methylprednisolone and hydroxychloroquine; Case report

Core Tip: According to the 2019 Classification criteria for systemic lupus erythematosus of the European League Against Rheumatism/American College of Rheumatology classification criteria, the score of this case was 14. In addition, computed tomography of abdomen showed marked and dramatic wall edema of the whole colon and rectum, ischemia and hyperemia of ascending colon intestinal wall, engorgement of mesenteric vessels, increased attenuation of mesenteric fat, ascites and bilateral ureter-hydronephrosis, demonstrating colon and rectum lupus enteritis (LE). Moreover, laboratory tests revealed lower complement C3 and C4. The titer of antinuclear antibody was 1:100. Overall, whole colon and rectum LE invaded of this case without involving small intestine was clear which was one of the rare manifestations of Systemic lupus erythematosus (SLE). The patient was treated with 10 mg methylprednisolone sodium succinate and 100 mL of 0.9% sodium chloride, hydroxychloroquine (100 mg) and nutrition support. After one week therapy of methylprednisolone and hydroxychloroquine, her symptoms and disease activity of SLE were dramatically improved.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an immune disease which may involve almost every organ and system in the body, and it shows protean manifestations. The influence of SLE correlating with the digestive organs may show as dental ulcers, protein-losing enteropathy, intestinal pseudo-obstruction, autoimmune pancreatitis, hepatic damage, Lupus Enteritis (LE), and various other complications. The gastrointestinal (GI) system involved in SLE manifests as gastritis, enteritis, colitis, and appendicitis, among others. Approximately half of the SLE-related GI manifestations are abdominal pain, diarrhea, nausea, loss of appetite, and vomiting[1].

LE is an opportunistic complication affecting patients with active SLE. It occurs in critically ill patients who are likely to have a worse prognosis. At present, we use large dose corticosteroid to treat patients of LE successfully as a strategy, leading to symptom improvement and the absence of complications related to infection[2]. Most cases of LE in SLE develop after the diagnosis of SLE, involving the small intestine. Therefore, it is difficult to recognize whether LE involving the colorectum is associated with SLE. A 35 year old woman presented with involvement of the entire colorectum instead of the small intestine, who demonstrated symptom improvement and disease activity after the administration of high-dose corticosteroid therapy.

CASE PRESENTATION

Chief complaints

A 35 year old woman came to the hospital with unexplainable abdominal pain, accompanied by vomiting. The patient had been taking her medication regularly for five years after the diagnosis of lupus nephritis and had been taking medications irregularly until two months prior to the onset of LE. There was no history of intestinal diseases in her family. Our study was approved by the Medical Ethics Committee of Xinqiao Hospital of Army Medical University (No. 2022-125-01) and received informed consent from the patient.

The physical examination upon admission and the pressure of blood, temperature, pulse rate, respiratory rate was normal.

On physical examination, the patient had diffused abdominal pain and pressing pain, without rebound tenderness. Laboratory tests revealed a high antinuclear antibody titer (ANA 1:100) and lower titers of C3 and C4. According to the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria[3,4], which added antinuclear antibodies to the entry criterion and provided an improved SLE diagnosis of combined sensitivity and specificity, the admission criterion ANA was equal or greater (1:80), the kidney biopsy of International Society of Nephrology (ISN) class IV lupus nephritis (diffuse proliferative glomerulonephritis) was 10 score, lower

complement C3 and C4 was a score of 4, and the total score was 14 (≥ 10). The diagnosis of SLE was clear[5]. The sensitive indicator of active SLE often was a reduced level of complement C3[6].

An abdominal contrast enhancement computed tomography (CT) was performed the day after admission. CT showed that there was marked and dramatic whole colon and rectum edema with the target sign or doughnut sign (Figure 1)[7, 8], and the thickened intestinal wall was about 4mm to 13mm from the rectum to ascending colon. Ischemic and congestive changes were seen locally in the same bowel (Figure 1A-C), which could be seen as partially discontinuous with the ischemic segment intestinal wall, with gas shadows of a discontinuous mucosal line (Figure 1B). The mesenteric vessels were increased and thickened with the comb sign (Figure 1E)[8,9], which was accompanied by mesenteric fat attenuation (Figure 1A), bilateral ureter-hydronephrosis (Figure 1C) and ascites (Figure 1D).

In previous reports, an active disease of SLE was related to flares of LE, so LE was regarded as the expression in SLE. Consequently, we administered 10 mg of methylprednisolone sodium succinate and 100 mL of 0.9% sodium chloride, hydroxychloroquine (100 mg) and nutrition support. After one week of the treatment, the symptoms, laboratory tests, and intestinal abnormalities on CT images were improved. A follow-up CT was performed 7 d before discharge and revealed no abnormal findings (Figure 2). The patient has been treated with a methylprednisolone and hydroxychloroquine tapering. The timeline for treatments and efficacy evaluations of this case is summarized in Figure 3.

History of present illness

She had no family history of intestinal diseases.

History of past illness

The kidney biopsy of ISN class IV lupus nephritis (diffuse proliferative glomerulonephritis).

Personal and family history

She has no personal and family history.

Physical examination

On admission, the blood pressure was 93/72 mmHg, the body temperature was 36.5 °C, the pulse rate was 116/min, and the respiratory rate was 20/min.

On physical examination, diffuse abdominal pain and pressing pain, without rebound tenderness.

Laboratory examinations

The admission criterion ANA is equal or greater (1:80), the kidney biopsy of ISN class IV lupus nephritis (diffuse proliferative glomerulonephritis) was 10 scores, lower complement C3 and C4 was 4 scores, the total scores was 14(≥ 10). The diagnosis of SLE is clear. A reduced level of complement C3 is often a sensitive indicator of active SLE.

Imaging examinations

An abdominal contrast enhancement CT was performed the day after admission. CT showed that there was marked and dramatic whole colon and rectum edema with the target sign or doughnut sign (Figure 1)[7,8], and the thickened intestinal wall was about 4mm to 13 mm from the rectum to ascending colon. Ischemic and congestive changes were seen locally in the same bowel (Figure 1A-C), which could be seen as partially discontinuous with the ischemic segment intestinal wall, with gas shadows of a discontinuous mucosal line (Figure 1B). The mesenteric vessels were increased and thickened with the comb sign (Figure 1E)[8,9], which was accompanied by mesenteric fat attenuation (Figure 1A), bilateral ureter-hydronephrosis (Figure 1C) and ascites (Figure 1D).

FINAL DIAGNOSIS

The admission criterion ANA is equal or greater (1:80), the kidney biopsy of ISN class IV lupus nephritis (diffuse proliferative glomerulonephritis) was 10 scores, lower complement C3 and C4 was 4 scores, the total scores was 14 (≥ 10). The diagnosis of SLE is clear.

TREATMENT

Consequently, we administered 10 mg of methylprednisolone sodium succinate and 100 mL of 0.9% sodium chloride, hydroxychloroquine (100 mg) and nutrition support.

OUTCOME AND FOLLOW-UP

After one week of the treatment, the symptoms, laboratory tests, and intestinal abnormalities on CT images were improved. Follow-up CT was performed 7 d before discharge and revealed no abnormal findings. The patient has been treated with a methylprednisolone and hydroxychloroquine tapering.

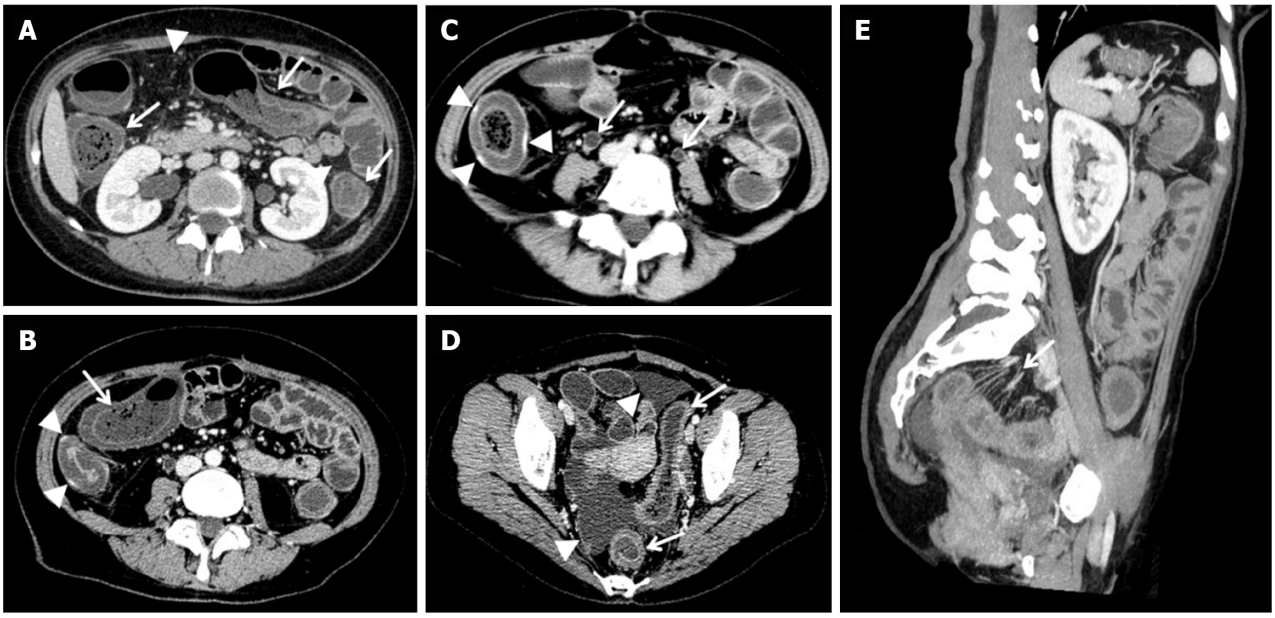

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Figure 1 Contrast-enhanced computed tomography scan of our patient shows severe whole colon and rectum wall thickening, with the target sign or doughnut sign (white arrows). A: The image shows the air-liquid level in the ascending colon, increased attenuation of mesenteric fat (white arrows head); B: The image shows the hyperemic ascending colon with obvious enhancement (white arrows head) and punctured gas breaking through the intestinal wall (white arrows); C: The image shows the ascending colon with ischemic and congestive changes in the same ascending bowel, which the hyperemic area showed obvious enhancement (white arrows head), and bilateral ureter-hydronephrosis (white arrows); D: The image shows rectum and sigmoid colon wall thickening with doughnut sign (white arrows), and ascites (white arrows head); E: The reconstructed coronal image shows mesenteric vessels enlargement with comb sign (white arrows).

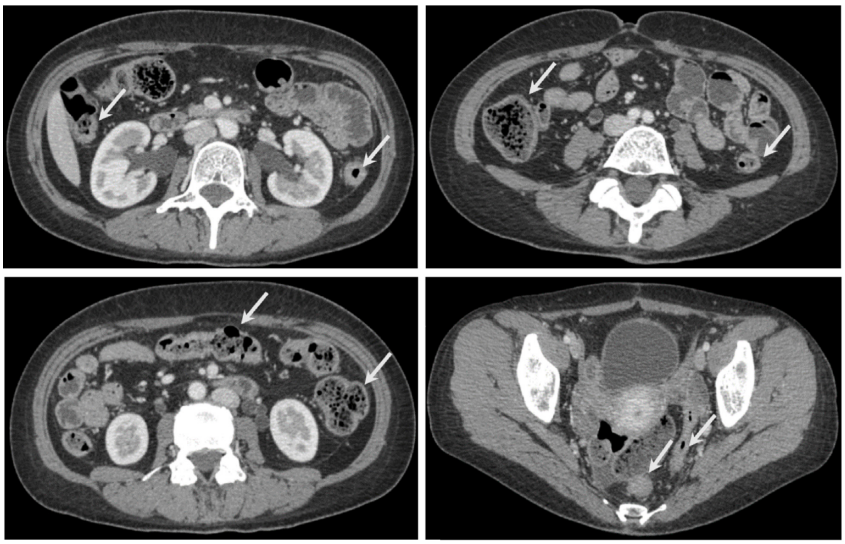

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Figure 2 Contrast-enhanced computed tomography scan of our patient shows all colon is normal after one week of treatment (white arrows).

However, at the most recent telephone follow-up, the patient presented for abdominal pain again in June 2023, considering the possibility of LE recurrence, the specific treatment was uncertain. Her recurrence was most likely associated with severe thickness of the bowel wall (> 8-9 mm), lupus nephritis and intestinal pseudo-obstruction in those with the large intestine-dominant type[10,11].

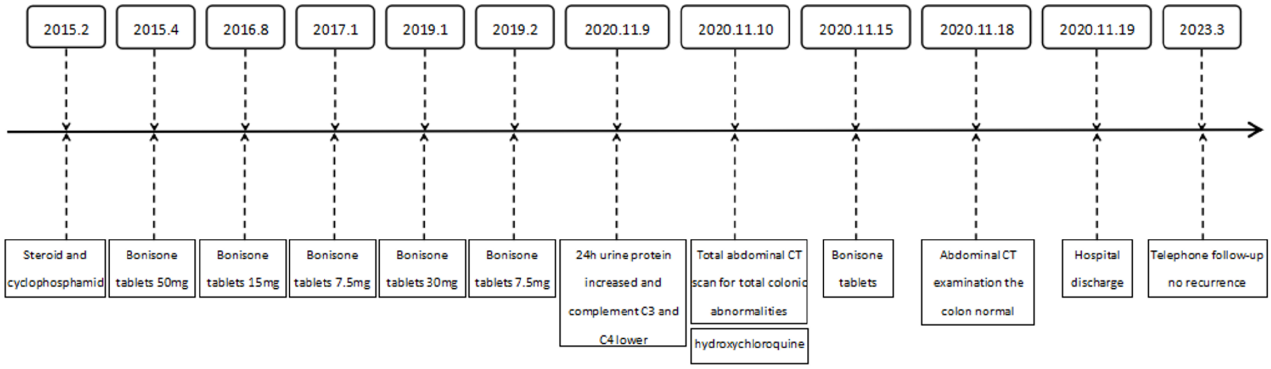

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Figure 3 The treatment process for this case. CT: Computed tomography.

DISCUSSION

SLE had different features and expressions in every organ, such as the skin, kidneys, joints, liver, pancreas, and GI system [12,13]. Various manifestations of vasculitis occur in association with SLE such as stomachache (97%), ascitic fluid (78%), sick (49%), vomitus (42%), diarrhoea (32%), mesenteric vasculitis, protein-losing enteropathy, intestinal pseudo-obstruction, intussusception, and bowel gangrene[14,15]. The diagnosis of SLE has been mostly proposed by the EULAR/ACR 2019 sorting criterion. According to this criterion, the score of our case presented as 14 (≥ 10). The diagnosis of SLE was clear. Based on the typical CT findings of the colon and rectum, the diagnosis of colon and rectum LE is reliable. LE is an intestinal ischemia and congestive disease due to SLE activity involving the intestine.

SLE can affect the entire GI tract, from the oral mucosa to the rectum. The percent of patients of GI tract related symptom is up to 40%-50%[14], but the development of LE is present in only about 0.2% to 5.8% of SLE patients[8,16]. LE involving the jejunum and ileum (83% and 84%, respectively) are relatively common[17,18], but involvement of the colon (19%) and rectum (4%) without involvement of the small intestine is extremely rare[14]. In previous reports, LE has been described as two types: Small intestine-dominant and large intestine-dominant. Small intestine-dominant LE is more frequently seen with biopsy-proven lupus nephritis, with the jejunum and ileum being the most usual involvements reported frequently in the literature. However, the advantage of colon and rectum with or without small intestinal involved) was usually seen in elderly people, as well as in the vesicoureter and conduit involved. This case is the type of large intestine-dominant with extra-intestinal symptoms, such as hydroureter, but the patient of our case also had biopsy-proven lupus nephritis, which is often seen in the small intestine-dominant type[10,11,18]. However, in our case, only the colon and rectum were involved, while the small intestine was uninvolved. As we know, the rectum has a rich and multiple blood supply with two or more different origin vessels, so rectal involvement has been very rarely reported in the PubMed database[19]. As can be seen from the above description, LE of the colon and rectum without small intestinal involvement is extremely rare.

Acute and chronic abdominal pain is always the main LE manifestation, which is present in approximately 50% of cases[7]. The main manifestation of our patient was stomachache and vomiting. The diagnosis of LE was based on the clinical manifestation, laboratory tests and CT images. Now CT scanning has become the gold standard for the diagnosis of LE, which can supply the non-invasive assessment of bowel loops and intestinal blood supply[20]. In our patient, CT showed edema of all the colon and rectum walls with the target sign or doughnut sign, ischemia and hyperemia of transverse colon, ascending colon and descending colon walls. In the arterial phase, obvious spot-enhanced and patchy enhanced areas could be seen in the same colon walls. Gas appears to break through the intestinal wall beneath the ascending colonic wall, which is highly suggestive of perforation. Bowel perforation occurs because of lupus mesenteric vasculitis, which leads to the vessel thrombosis causing bowel wall infarction and perforation[21]. We could also see the mesangial vascular pectinate sign, and the increase in density of mesangial fat, ascites or bilateral ureter-hydronephrosis [18]. The above signs are relatively typical except for ascites, which occurs in 8%-11% of adults with SLE[16].

The diagnosis of LE was not easy, with no obvious active characteristic in SLE. LE may be considered if three of the following signs are presented on CT: Fluid levels, bowel wall thickening of ≥ 3 mm, the target sign or doughnut sign, dilatation of intestinal segments, mesenteric edema, mesangial angiitis, pectinate sign, increased mesangial fat attenuation and ascitic fluid[21-24]. The patient of our case had a definite history of SLE for five years and typical CT findings of the colon and rectum. Other causes of acute abdomen non-SLE-related and relation of SLE had been screened out, so the consideration of colon and rectum LE was relatively easy.

However, the above CT findings of bowel wall and mesenteric ischemia are quite common and lack specificity because these signs can also be seen in inflammatory bowel disease such as Crohn's disease (CD), which can mimic LE. LE and CD have similar features like the "comb sign" and share clinical symptoms including abdominal pain and diarrhea. The endoscopic appearance and pathological examination are important ways to distinguish between the two diseases[25]. There were obvious characteristics with discrete areas of CD with cobblestoning. The common pathological features generally are focal crypt irregularity and inflammatory epithelial-giant cell granulomas. There are also some distinct features of CD on CT examination, such as bowel expansion, curve, and broadening of the mesareic arteries[9]. Also, the most common area of CD is the ileocecum. Colorectal involvement of CD is relatively rare and is often accompanied with

involvement of other parts.

Although we don't know the relationship between LE and angeitis completely, especially small or middle sized vessels injury causes, lupus mesenteric vasculitis (LMV), thrombosis, hypocomplementemia, inflammatory, immune-mediated diffuse smooth muscle dysfunction, immune dysregulation and SLE itself[7,26]. High disease activity and a long-standing history of SLE in patients usually causes LMV to occur[27]. Arteritis and venulitis of the colon and rectum may be the result of aggravation of SLE. Vasculitis is the most common cause of mucosal damage[22].The deposition of immune complexes in the vascular endothelium, arterial muscular and elastic elements by circulation autoantibodies may lead to leukocytoclastic vasculitis[10,24,28], thrombosis and vasculitis of vessels supplying of the intestine vessels walls and the target organ[8,29]. The involvement of the renal and intestinal small vessels may be the major cause due to the autoimmune disorder and active SLE, especially when other causes have been excluded[30]. There was also an article that suggested "visceral pseudo-obstruction" and vasculitis of the visceral smooth muscles leading to muscular damage may encompass the SLE GI involvement[26]. Among the extra-GI involvements, the urinary tract was the most frequently affected compartment[30]. Lupus nephritis can be concomitant with LE, which is present in about 65% of LE cases[8,15,22].

The patient had a history of immunosuppressive therapy for her SLE during the last five years. Irregularly taking medication for two months before the onset of LE was most likely the predisposing factor. A medication's side effects are also a factor causing LE[18]. Drug therapy leads to immune complex deposition, resulting in thrombosis of small mesenteric vessels, which causes submucosal edema and ischemia in the colon and rectum[19].

We observed thrombosis in this patient due to SLE. SLE patients are prone to thromboses and angeitis. Mesenteric inflammatory veno-occlusive disease is another rare cause of LE in patients, and it is detected on abdominal CT[2]. We considered that the angeitis may be the vital pathological features of our patient due to the marked improvement of the patient with hormone therapy.

There are few reports of secondary manifestations involving the colon and rectum of SLE. Generally, GI involvement is an important manifestation of reignition that occurs in someone with SLE. Typically, their average age range is 15-44 years[31]. Almost all patients were treated with high-dose corticosteroids and responded successfully to treatment.

The complication of SLE associated with LE involves high necrosis and perforation, and even death, with a mortality of 2.7%[15]. Due to the risk of eating tetter and treatment with large dose immune suppression treatment. LE patients have a higher rate (31.3%) of infectivity, as reported by the latest reported studies, which is one of the reasons for the majority of LE deaths[10]. The diagnose is difficult when it is only through the results of clinic and laboratorial, while CT manifestations are quite typical, so we should combine the CT images to improve the diagnosis accuracy. In the past, laparotomy or laparoscopy has been considered. However, corticosteroids play a crucial role in control of SLE symptoms of patients [32]. Corticosteroids therapy has been successfully used as the initial treatment, reducing surgical intervention. Hydroxychloroquine may reduce the risk of lupus flares and organ damage. Dose tapering should be slowed to avoid recurrence [13]. Most patients were in remission after treatment without recurrence. The literature reported that patients with bowel wall thickness ≥ 8-9 mm may experience recurrence, which is up to 23% of the LE cases. Koo *et al*[33] have identified colon and urinary tract involvement (especially lupus cystitis) was also the main risks factors of recurrence[5,10,33,34], because of lupus cystitis and LE, and there was a strong correlation in the pathogenesis[35]. According to the basic manifestations and danger elements, the patient was reposeful because of the significant improvement with drug treatment, and there were no confirmed recurrences during follow-up from November 2020 to May 2023. Large dose methylprednisolone and hydroxychloroquine may be the original strategies in LE of SLE. However, at the most recent telephone follow-up, the patient presented for abdominal pain again in June 2023; and after considering the possibility of LE recurrence, the specific treatment was uncertain. Her recurrence was most likely related to obvious intestinal wall thickness (> 9 mm), lupus nephritis and a pseudo bowel block in the colon and rectum[10,11].

CONCLUSION

The patient of our case presented with colorectal LE with main features of SLE. There was successful treatment by methylprednisolone and hydroxylation drugs. In spite of the rarity of SLE cases where the only GI involvement being due to colon and rectum LE, we should be aware of it and the severe activity of SLE, which can manifest as intestinal symptoms after exclusion of infection, and this can help avoid unnecessary ineffective interventions and potentially fatal complications[30]. Prolonged intestinal wall edema can lead to intestinal necrosis, intussusception, perforation, and an even more serious abdominal infection that can endanger the patient's life. As we know, SLE is a common autoimmune disease, and its important features are autoantibodies and autoreactive T lymphocytes that may be activated at any time [6]. Therefore, we should also closely observe the possible recurrence of patients, which may be the manifestation of enteritis, or the corresponding symptoms of involvement of other abdominal organs, such as autoimmune pancreatitis, liver damage, cholecystitis, and cystitis.

As the initial treatment for colon and rectum LE related to SLE, we can use high-dose methylprednisolone and hydroxychloroquine for treatment combining general manifestation and individual dangerous element. We should emphasize that colon and rectum involvement may occur independently in LE, so it is critical to diagnose it early to prevent devastating organ damage.

FOOTNOTES

Author contributions: Gan H wrote the article; Wang F drew a diagram; Gan Y collected data; and Wen L revised the article.

Informed consent statement: Our study was approved by the Medical Ethics Committee of Xinqiao Hospital of Army Medical University (No. 2022-125-01), and informed consent has been obtained from the patient for the publication of cases and pictures.

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

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CASE REPORT

Repeated atrial arrhythmia induced by cochineal red poisoning: A case report

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Abstract

BACKGROUND

Cochineal red is an organic compound widely used in food, cosmetics, pharmaceuticals, textiles, and other fields due to its excellent safety profile. Poisoning caused by eating foods containing cochineal red is rare, and repeated atrial arrhythmia due to cochineal red poisoning is even rarer.

CASE SUMMARY

An 88-year-old Asian female patient was admitted to hospital due to a disturbance of consciousness. Twelve hours prior to presentation, the patient consumed 12 eggs containing cochineal red over a period of 2 h. At presentation, the patient was in a coma and had a score of 6 on the Glasgow Coma Scale (E2 + VT + M4). The patient's skin and mucous membranes were pink. Electrocardiography (ECG) revealed rapid atrial fibrillation without any signs of ischemia. We prescribed cedilan and fluid replacement for arrhythmia correction. Shortly after admission, the atrial fibrillation corrected to a normal sinus rhythm. On the day 2 of admission, the patient had a sudden atrial flutter accompanied by hemodynamic instability and rapidly declining arterial oxygen saturation between 85% and 90%. The sinus rhythm returned to normal after two electrical cardioversions. Six days after admission, the skin color of the patient returned to normal, and the ECG results were normal. The patient was transferred out of the intensive care unit and eventually discharged after 12 d in hospital. At the 2-mo follow-up visit, the patient was in good health with no recurrence of arrhythmia.

CONCLUSION
Although cochineal red is a safe, natural food additive, excessive consumption or occupational exposure can induce cardiac arrhythmias.

Key Words: Cochineal red; Poisoning; Cardiac arrhythmias; Atrial fibrillation; Atrial flutter; Case report

Core Tip: Poisoning caused by eating foods containing cochineal red is rare, and repeated atrial arrhythmia caused by cochineal red poisoning is even rarer. For the first time, we report a case of repeated atrial arrhythmia caused by cochineal red poisoning. Through this case report, clinicians and the public will gain knowledge of the risks of excessive consumption of foods containing cochineal red pigment.

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INTRODUCTION

Cochineal red is a natural pigment extracted from female cochineal insects. In its natural state, it is powdered and reddish or purplish red[1]. As an organic compound, cochineal red is widely used in food, cosmetics, pharmaceuticals, textiles, and other fields because of its excellent safety profile[2]. In China, cochineal red is commonly used to dye eggs for good wishes during the Dragon Boat Festival. Poisoning due to eating foods containing cochineal red is rare, and repeated atrial arrhythmia caused by cochineal red poisoning is even rarer.

Here, we report a case of cochineal red poisoning that presented as tender pink skin, purple–red urine, and repeated atrial arrhythmia in an 88-year-old patient, which improved rapidly after active treatment. Through this case report clinicians and the public can become aware of the risks of excessive consumption of food containing cochineal red pigment.

CASE PRESENTATION

Chief complaints

An 88-year-old Asian female patient was admitted to the hospital due to a disturbance of consciousness. Twelve hours prior to presentation, the patient ate 12 eggs containing cochineal red over a period of 2 h.

History of present illness

The patient had a disturbance of consciousness after eating 12 red eggs containing cochineal red before her family rushed her to hospital. Considering the potential risk of respiratory failure, the emergency department physician immediately intubated the trachea, and the patient was admitted to the intensive care unit.

History of past illness

The patient was diagnosed with hypertension 10 years prior to presentation. She managed her blood pressure with oral nifedipine tablets (10 mg, tid). She also experienced a cerebral infarction 2 years prior to presentation. The muscle strength in her left limb was grade 3, she was able to independently walk and get out of bed, and her speech was clear.

Personal and family history

The patient had no significant personal or family history.

Physical examination

Upon physical examination, the patient's temperature was 36.9 ℃, heart rate 131 beats/min, respiratory rate 20 breaths/min, blood pressure 149/74 mmHg, and peripheral capillary oxygen saturation (breathing 30% oxygen) 96%. The patient was in a coma and had a score of 6 on the Glasgow Coma Scale (E2 + VT + M4). The patient's skin and mucous membranes were pink (Figure 1). The superficial lymph nodes were not enlarged. The pupils were equal in size and circular with a diameter of approximately 3 mm, and the light reflex was slow. The patient's exhaled air was not abnormal. The breath sounds of both lungs were coarse, and scattered wet rales were heard. The heartbeat rhythm was irregular without any other pathological signs.

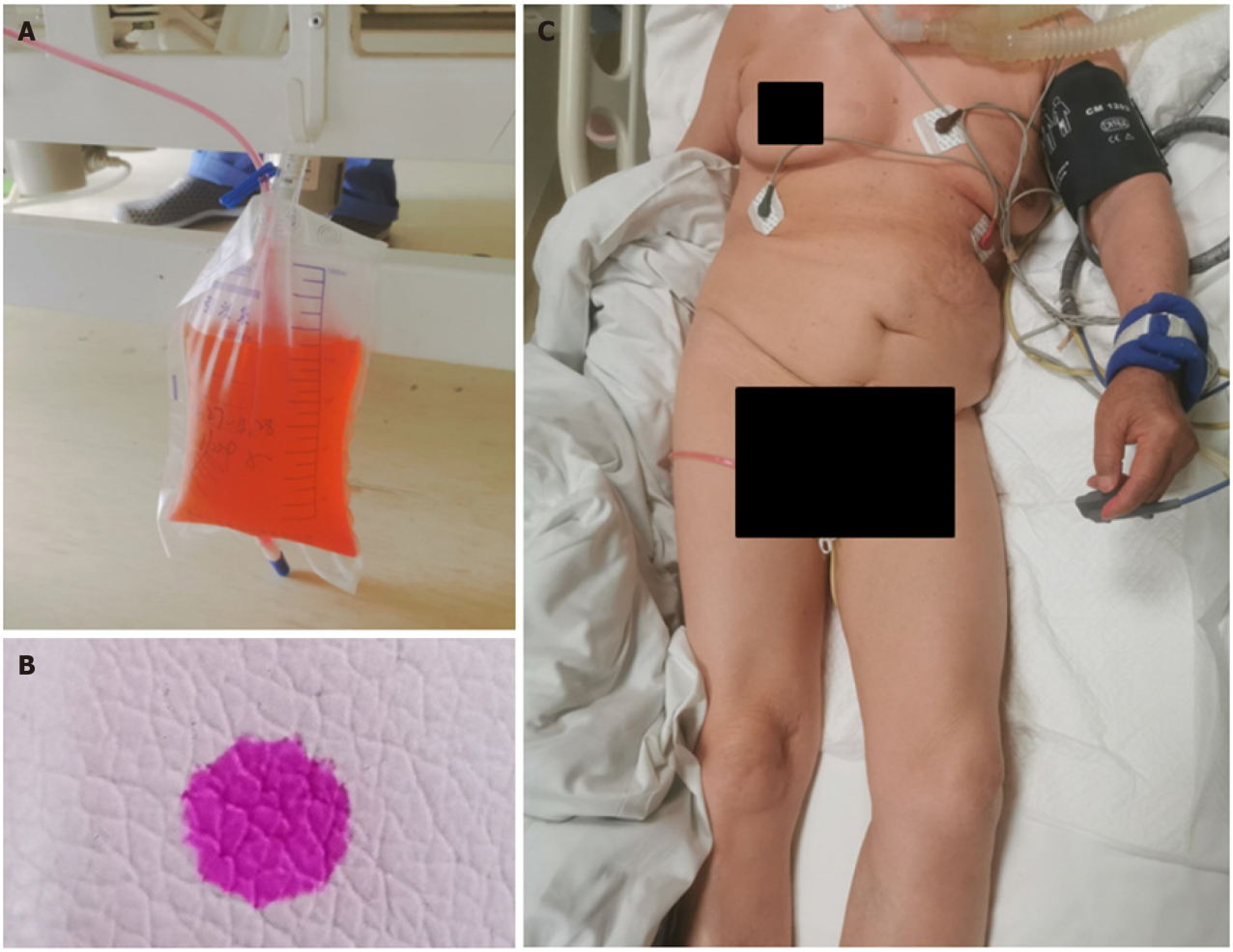

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Figure 1 Skin and urine color changes after cochineal red poisoning. A: The urine was pink; B: When the urine of patient was dripped on the white cloth it appeared purplish red; C: The skin of the patient was a delicate pink.

Laboratory examinations

Initial blood investigations revealed a total white blood cell count of 20.79 × 10^9/L (normal range: 4 × 10^9-10 × 10^9/L), neutrophil count 19.39 × 10^9/L (normal range: 2 × 10^9-7.5 × 10^9/L), hemoglobin 109 g/L (normal range: 110-160 g/L), platelet count 176.0 × 10^9/L (normal range: 100 × 10^9-300 × 10^9/L), C-reactive protein 7.20 mg/L (normal range: 0-5 mg/L), procalcitonin 0.14 ng/mL (normal range: 0-0.5 ng/mL), and glycated hemoglobin 6.5% (normal range: 3.9%-6.5%). Electrolyte, coagulation function, liver and kidney function, amylase, cholinesterase, myocardial enzymes, troponin, B-type natriuretic peptide, and blood lipids were all within the normal range. A routine urine test showed purple urine (Figure 1), while other values were normal. Arterial blood gas analysis showed a pH of 7.414 (normal range: 7.35-7.45), partial pressure of oxygen 167 mmHg (FiO_2: 35%, normal range: 83-108 mmHg), and partial pressure of carbon dioxide 30.2 mmHg (normal range: 35-48 mmHg). The residual base level was -4.3 mmol/L (normal range: -2.0 to 2.0 mmol/L), HCO_3 was 20.9 mmol/L (normal range: 22-28 mmol/L), and plasma lactate level 5.84 mmol/L (normal range: 0.5-1.6 mmol/L).

Imaging examinations

Echocardiography showed a left ventricular ejection fraction of 60% and no pericardial effusion. Electrocardiography (ECG) revealed rapid atrial fibrillation without any signs of ischemia (Figure 2A). Computed tomography of the brain, lung, and abdomen revealed no abnormalities.

FINAL DIAGNOSIS

The patient was diagnosed with acute cochineal red poisoning, hyperlactatemia combined with metabolic acidosis, and rapid atrial fibrillation.

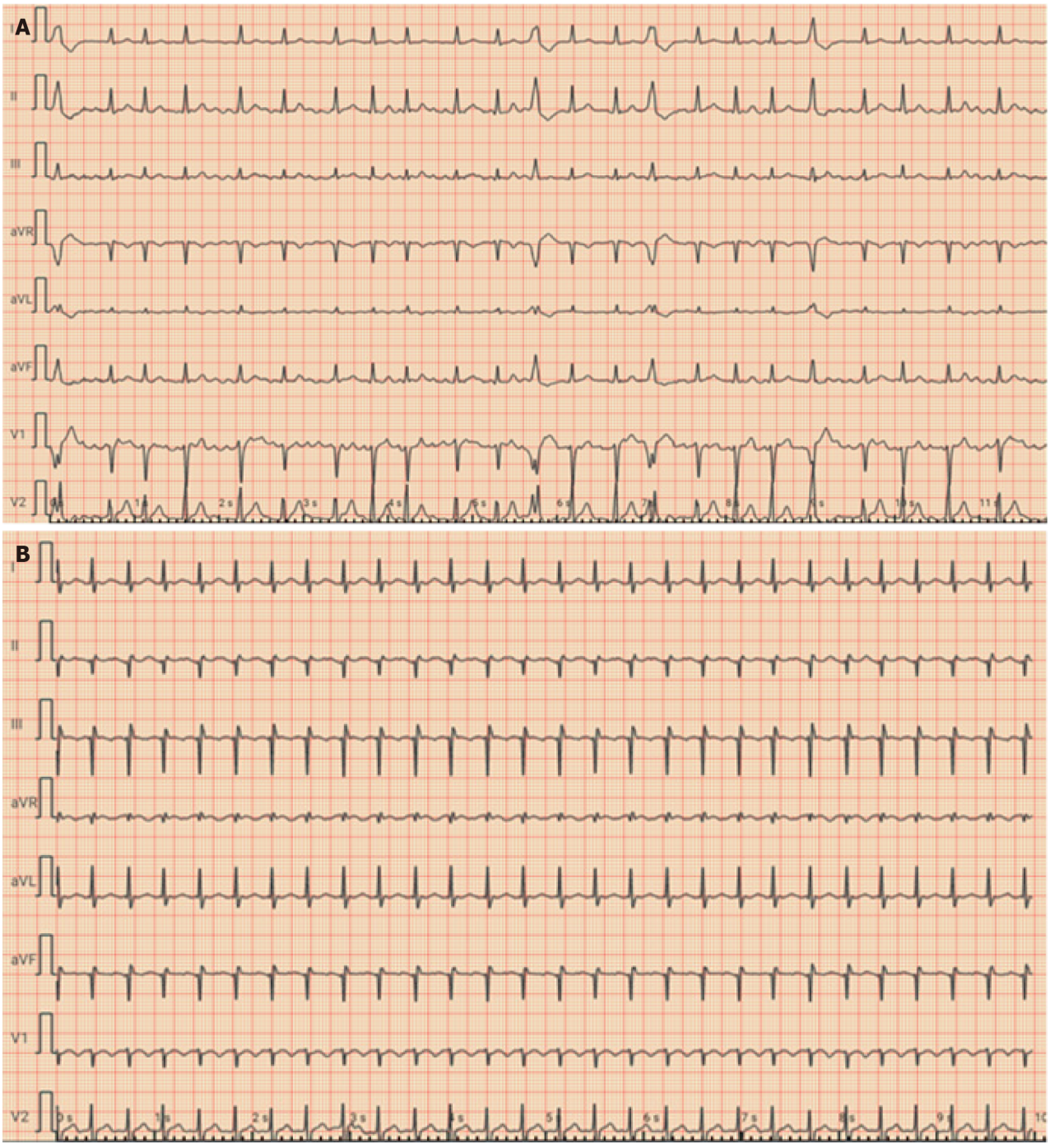

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Figure 2 Electrocardiograms showed atrial arrhythmia. A: Rpid atrial fibrillation with premature ventricular contractions without any signs of ischemia; B: Chest electrocardiography revealed an atrial flutter with rapid ventricular rate.

TREATMENT

The patient received fluid replacement and began cedilan for arrhythmia correction. Shortly after admission, the atrial fibrillation converted to normal sinus rhythm. The arterial blood gas analysis and plasma lactate level returned to normal 8 h after admission. Approximately 18 h after admission, the patient regained consciousness. At 09:35 h, the patient had a sudden atrial flutter (Figure 2B), accompanied by hemodynamic instability (systolic blood pressure: 80-90 mmHg; diastolic blood pressure: 40-55 mmHg) and a rapidly declining arterial oxygen saturation between 85% and 90%. The sinus rhythm returned to normal after two electrical cardioversions, and intravenous microinfusion of amiodarone was administered. Electrolytes, myocardial enzymes, and troponin were re-examined and showed no abnormalities. The tracheal intubation was removed, but the skin color of the patient was still pink. We observed that the patient's skin was slightly less pink on the day 3 after admission (Figure 3). Amiodarone was stopped on day 4 after admission because ECG showed a normal sinus rhythm (Figure 4).

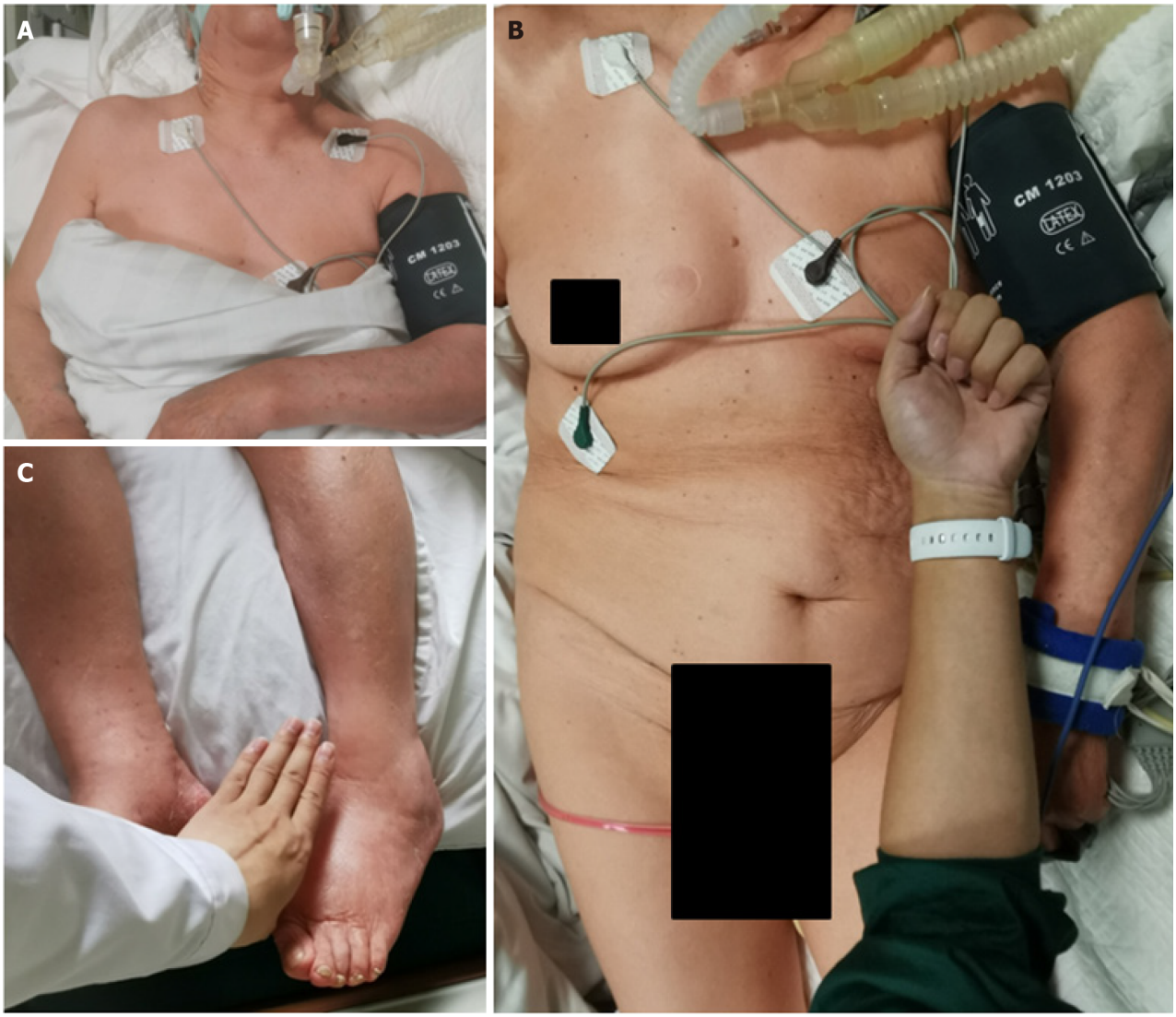

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Figure 3 The skin color of the patient was slightly less pink on day 3 after admission. A: The skin color of the neck and chest was pink, which was slightly less than at initial admission; B: The skin on the abdomen was more pink than normal skin; C: Compared with the skin color of normal hands, the lower limbs were pink, and the skin was delicate and colored.

OUTCOME AND FOLLOW-UP

Six days after admission, the pink tint in the patient's skin significantly subsided (Figure 5), and the blood routine tests, coagulation function, liver and kidney function, electrolytes, and ECG were normal. The patient was transferred out of the intensive care unit because her symptoms were continuously improving. She was discharged after 12 d of hospitalization. At the 2-mo follow-up the patient was in good health with no recurrence of arrhythmia.

DISCUSSION

Cochineal red is a natural anthraquinone pigment extracted from female cochineal beetles growing on cacti[1]. It appears as a red crystal or reddish-brown powder in its natural state and is easily soluble in water. Carminic acid is the main active component of cochineal red, which contains eight hydroxyl groups and one carboxyl group in each molecule[3]. The physicochemical properties of cochineal red are stable, and it is stable in light and heat and when exposed to oxidants [1]. As an excellent colorant, cochineal red pigment is widely used in food additives due to its high safety profile and good affinity for meat proteins. *In vitro* and *in vivo* tests have also shown that it has no toxicity nor teratogenicity[4].

Cochineal red contains nonpigment components, such as insect proteins and lipids. These components can vary from batch to batch and may lead to rare allergic reactions and diseases[5]. Cochineal-red-related anaphylaxis[5], urticaria[6], occupational asthma[7], and allergic contact dermatitis[8] have been reported, and the main mechanism is IgE-mediated anaphylaxis[9]. Cochineal red may be a potentially overlooked allergen in patients with chronic allergic diseases and in children[10,11]. Cochineal red is also a cause of occupational respiratory allergies[7]. Therefore, people with allergic

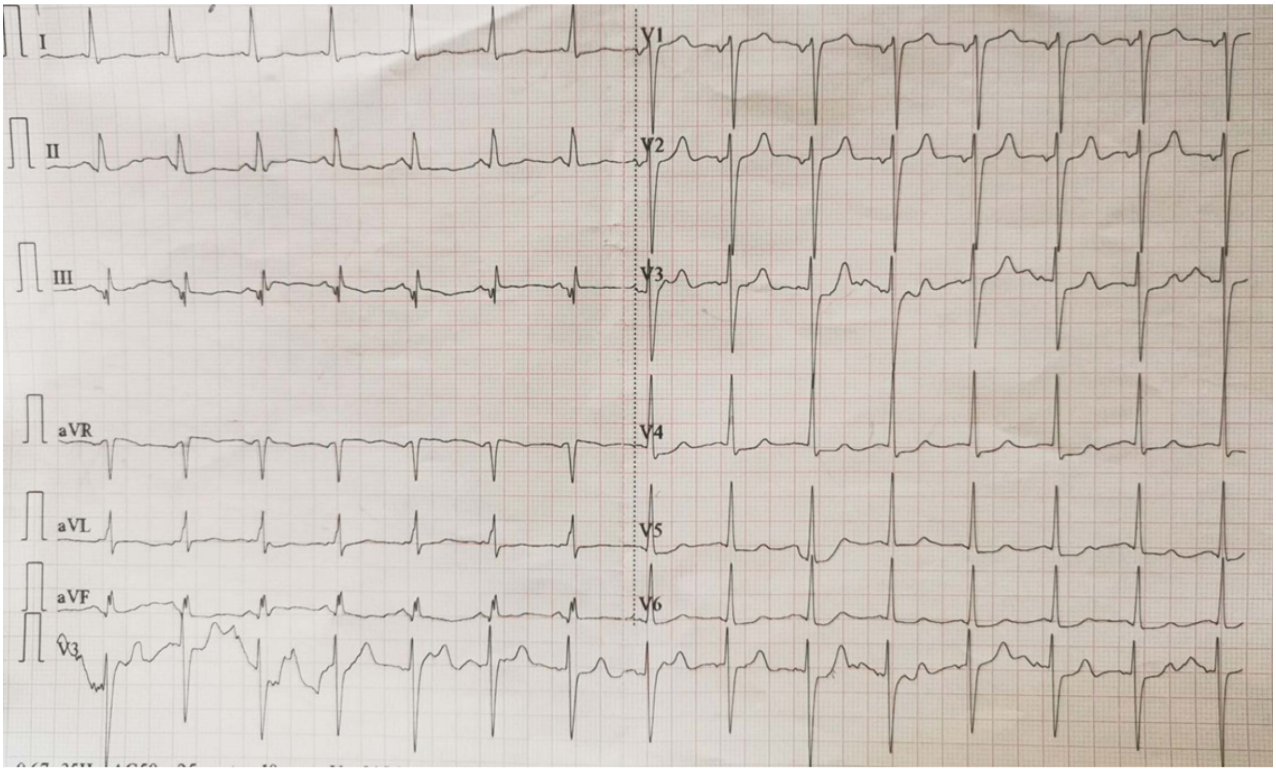

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Figure 4 Repeat electrocardiogram indicated a normal sinus rhythm on day 4 after admission.

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Figure 5 Six-days after admission, the skin color of the patient returned to normal.

diseases are at an increased risk of adverse reactions when eating food containing the pigment or when exposed to cochineal-red-related products.

There are few clinical reports available on adverse reactions caused by cochineal red. However, repeated atrial arrhythmia caused by cochineal red has not been reported to date. Therefore, the clinical characteristics, treatment, and prognosis of atrial arrhythmia caused by acute cochineal red poisoning remain limited. In our patient, coagulation function, liver and kidney functions, electrolytes, amylase, cholinesterase, myocardial enzyme profile, troponin, B-type natriuretic peptide, and blood lipids were all within the normal range at admission. Emergency arterial blood gas analysis suggested hyperlactatemia with acidosis, while the ECG revealed rapid atrial fibrillation. The lactate level and acidosis quickly returned to normal, and the ECG revealed a normal sinus rhythm after initial intravenous fluid rehydration, antiarrhythmic application, and symptomatic treatment.

However, the skin of the patient remained pink, suggesting that cochineal red was not completely cleared from the body. Hyperlactacidemia and acidosis were considered possible causes of hypoxia during transportation to the hospital. On day 2 of hospitalization, the patient had a sudden atrial flutter but returned to a sinus rhythm after electric

cardioversion. Re-examination of blood tests, liver and kidney functional electrolytes, myocardial enzymes, and troponin were normal, and intravenous fluids and symptomatic treatment were administered. On day 3 after admission, the pink color of the patient's skin decreased. By day 6 of admission, the patient's skin color returned to normal.

The patient had no previous history of arrhythmia. Initial ECG showed atrial fibrillation after admission, which was quickly resolved. The atrial flutter that occurred on the next day was also resolved quickly. According to the clinical manifestations, the patient was diagnosed with repeated atrial arrhythmia caused by cochineal red poisoning. After symptomatic treatment, the condition of the patient improved, and she recovered well with no recurrence of arrhythmia at the 2-mo follow-up.

To the best of our knowledge, this is the first reported case of repeated atrial arrhythmia associated with cochineal red poisoning. Therefore, for patients with cochineal red poisoning, routine fluid replenishment, diuresis, and maintenance of a stable internal environment can be performed. Blood purification therapy or hemoperfusion may also be performed to accelerate the internal excretion of cochineal red. However, evidence to show the effectiveness of this intervention is lacking.

The specific mechanism of repeated atrial arrhythmia caused by cochineal red remains unclear based on the limited literature. Some studies have suggested that cochineal red typically contains contaminating proteins, including a 38-kDa protein thought to be the primary allergen[2]. These proteins can induce an IgE-mediated food allergy and/or allergic diseases in patients using these products[12]. The toxicity of cochineal red in rats suggested that acute oral toxicity is low. The only adverse effect noted by the study was an unusual color[13]. Therefore, we hypothesize that repeated atrial arrhythmia may be caused by cochineal red allergy. However, more research on the safety and toxicity of cochineal red is needed to clarify the mechanism in the future.

There were some limitations to this study. Quantitative analysis of relevant toxicants can provide further information regarding the severity and prognosis of the disease. However, due to the limitations of objective conditions in our hospital, we were unable to obtain the concentration or specific metabolic components of cochineal red in the patient's gastrointestinal tract, blood, or urine. The lack of cochineal red toxicological test results led to certain defects in the diagnosis of this patient.

CONCLUSION

Cochineal red is a safe, natural food additive. In China, it is widely used for red-dyed eggs. However, excessive consumption of food containing cochineal red or occupational exposure to the cochineal red pigment may induce allergic reactions, urticaria, allergic asthma, and cardiac arrhythmias. Therefore, clinicians and the public should know about the health risks of cochineal red.

FOOTNOTES

Author contributions: Wang YJ, Yang H, and Xu BP contributed to conception and design of the study; Yang H and Xu Q provided study materials or recruited patients; Xu BP contributed to collection, analysis, and interpretation of data; Xu BP, Yang H, Peng HW, Xu Q, Yu HB, and Wang YJ contributed to manuscript writing and editing; Yang H, Peng HW, and Yu HB contributed to administrative support; all authors read and approved the final manuscript.

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CASE REPORT

Anti-glial fibrillary acidic protein antibody and anti-aquaporin-4 antibody double-positive neuromyelitis optica spectrum disorder: A case report

Ting-Yu Jin, Bing-Tong Lin, Li-Jv Dai, Xia Lu, Han Gao, Jin Hu

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Abstract

BACKGROUND

A case of neuromyelitis optica spectrum disorder (NMOSD) with positive cerebrospinal fluid (CSF) anti-aquaporin-4 antibody (AQP4-IgG) and anti-glial fibrillary acidic protein IgG (GFAP-IgG) at the time of relapse was reported. The exact roles of GFAP-IgG in NMOSD are not fully understood and are the subject of ongoing research. This study revealed the possible connection between GFAP-IgG and the occurrence or development of diseases.

CASE SUMMARY

A 19-year-old woman was admitted to the hospital due to a constellation of symptoms, including dizziness, nausea, and vomiting that commenced 1 year prior, reoccurred 2 mo ago, and were accompanied by visual blurring that also began 2 mo ago. Additionally, she presented with slurred speech and ptosis, both of which emerged 1 mo ago. Notably, her symptoms deteriorated 10 d prior to admission, leading to the onset of arm and leg weakness. During hospitalization, magnetic resonance imaging showed high T2-fluid attenuated inversion recovery signals, and slightly high and equal diffusion-weighted imaging signals. The serum antibody of AQP4-IgG tested positive at a dilution of 1:100. CSF antibody testing showed positive results for GFAP-IgG at a dilution of 1:10 and AQP4-IgG at a dilution of 1:32. Based on these findings, the patient was diagnosed with NMOSD. She received intravenous methylprednisolone at a daily dose of 500 mg for 5 d, followed by a tapering-off period. Afterward, the rate of reduction was gradually slowed down and the timely use of immunosuppressants was implemented.

CONCLUSION

The CFS was slightly GFAP-IgG-positive during the relapse period, which can aid in the diagnosis and treatment of the disease.

Key Words: Anti-glial fibrillary acidic protein antibody; Neuromyelitis optica spectrum disorder; Anti-aquaporin-4 antibody; Cerebrospinal fluid; Case report

Core Tip: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disorder that affects the central nervous system. Here, a case of NMOSD with positive cerebrospinal fluid aquaporin-4 antibody and anti-glial fibrillary acidic protein antibody (GFAP-IgG) at the time of the relapse was reported. The exact role of GFAP-IgG in NMOSD remains a subject of debate and research, with some studies suggesting it is pathogenic and plays a role in disease development or progression. This case reveals the potential role of GFAP-IgG in NMOSD. The findings suggest a possible association between GFAP-IgG and the initiation or advancement of the disease.

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INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disorder affecting the central nervous system (CNS), specifically the optic nerves and spinal cord. It is characterized by immune-mediated inflammation and demyelination of the affected tissues, classified as a humoral immune spectrum disease. In 2005, Lennon *et al*[1] discovered anti-neuromyelitisopica antibody in the serum of NMOSD patients, which was later confirmed to target anti-aquaporin-4 antibody (AQP4-IgG). This finding became one of the primary diagnostic criteria for NMOSD. The main diagnostic basis of NMOSD includes six core symptoms: optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, acute diencephalic clinical syndrome, and symptomatic cerebral syndrome[2]. Glial fibrillary acidic protein (GFAP) serves as the main intermediate filament of the astrocyte skeleton[3]. Increased levels of GFAP in the cerebrospinal fluid (CSF) of NMOSD patients indicate astrocyte injury and are considered a biomarker[4]. Notably, elevated CSF-GFAP levels in patients with multiple sclerosis (MS) are associated with higher disability and worsening disability, particularly in late-stage patients[5]. It is indicated that CSF-GFAP partially reflects reactive astrogliosis[6].

Anti-GFAP antibodies (GFAP-IgG) refer to antibodies that are directed against GFAP and have been observed in the blood and CSF of patients with autoimmune diseases such as neuromyelitisopica, NMOSD, encephalitis, and other neurological disorders, suggesting an immune attack against astrocytes, leading to CNS inflammation and damage. While the detection of GFAP-IgG has been used as a diagnostic tool, its specificity and sensitivity require further research [7]. Zhang *et al*[8] reported a case of an NMOSD patient who tested negative for AQP4-IgG but positive for GFAP-IgG in 2020. In this report, we present a case of an NMOSD patient with positive AQP4-IgG and GFAP-IgG in the CSF during a relapse.

CASE PRESENTATION

Chief complaints

A 19-year-old woman was admitted to the hospital due to a constellation of symptoms, including dizziness, nausea, and vomiting that commenced 1 year prior, reoccurred 2 mo ago, and were accompanied by visual blurring that also began 2 mo ago. Additionally, she presented with slurred speech and ptosis, both of which emerged 1 mo ago. Notably, her symptoms deteriorated 10 d prior to admission, leading to the onset of arm and leg weakness.

History of present illness

One year ago, the patient experienced dizziness, nausea, and vomiting, leading her to seek examination by a gastroenterologist at a nearby hospital. Gastrointestinal endoscopy was performed and revealed no significant abnormalities. Her symptoms were completely alleviated with proton pump inhibitor treatment.

Two months prior to admission, she had a recurrence of dizziness, nausea, vomiting, and mild visual blurring. She was re-examined by the gastroenterology department, where another endoscopic examination showed no obvious abnormalities. Additionally, she visited the ophthalmology clinic for an eye exam and visual acuity test, which revealed nearsightedness in both eyes, with a naked eye visual acuity of 0.4 in her left eye and 0.6 in her right eye, and a corrected visual acuity of 1.0 in both eyes. No evident abnormalities were found in her eye fundus. Her symptoms slightly improved after receiving antacid and antiemetic medication, leading to her discharge from the hospital.

One month prior to admission, her symptoms worsened, characterized by increased dizziness, nausea, vomiting, and visual blurring, as well as the development of slurred speech and drooping eyelids. She was subsequently admitted to the local hospital's neurology department. The patient had previously sought medical attention at a local grass-roots hospital, where her magnetic resonance imaging (MRI) was reviewed and revealed new findings. It is worth noting that the limited expertise of radiologists at such hospitals may contribute to potential inaccuracies in the diagnosis. Her brain MRI report initially indicated no obvious abnormalities, but upon further review, the MRI showed abnormal T1-weighted imaging (T1WI) signals (Figure 1A-D), high T2-fluid attenuated inversion recovery (T2-FLAIR) signals (Figure 1E-H), slightly high and equal diffusion-weighted imaging (DWI) signals (Figure 2A-D), and normal apparent diffusion coefficient (ADC) values (Figure 2E-H).

Ten days prior to admission, her symptoms worsened further, and she developed weakness in her arms and legs. As a result, she was transferred to our hospital's neurology department.

History of past illness

The patient had no previous history of similar conditions.

Personal and family history

The patient denied any family history of similar conditions.

Physical examination

A neurological examination revealed both vertical and horizontal nystagmus, slurred speech, drooping eyelids, and muscle strength of grade 4 in the bilateral lower extremities according to the muscle strength grading scale (maximum score 5); her Expanded Disability Status Scale (EDSS) score was 7 points. She had hyperactive reflexes in the biceps, triceps, knees, and Achilles tendons, and positive bilateral Babinski's sign.

Laboratory examinations

Laboratory tests for various antibodies were performed, including serum anti-nuclear antibodies, anti-double-stranded DNA antibodies, anti-neutrophil cytoplasmic antibodies, anti-cardiolipin antibodies, anti-myelin oligodendrocyte glycoprotein antibody (MOG-IgG), anti-myelin basic protein antibody (MBP-IgG), GFAP-IgG, and anti-autoimmune encephalitis antibodies, all of which yielded negative results. However, the serum antibody of AQP4-IgG tested positive at a dilution of 1:100. Lumbar puncture revealed an opening pressure of 115 mm water, with normal levels of CSF protein, glucose, and leukocyte count, and undetectable oligoclonal bands. CSF antibody testing showed positive results for GFAP-IgG at a dilution of 1:10 and AQP4-IgG at a dilution of 1:32, while CSF MBP-IgG, MOG-IgG, and autoimmune encephalitis antibodies were negative. The antibody detection test employed a transfected cell assay, which was further confirmed by the normality of the negative control from the same period.

Imaging examinations

The patient had previously sought medical attention at a local grass-roots hospital, where her MRI was reviewed and revealed new findings. It is worth noting that the limited expertise of radiologists at such hospitals may contribute to potential inaccuracies in the diagnosis. Her brain MRI report initially indicated no obvious abnormalities, but upon further review, the MRI showed abnormal T1WI signals (Figure 1A-D), high T2-FLAIR signals (Figure 1E-H), slightly high and equal DWI signals (Figure 2A-D), and normal ADC values (Figure 2E-H).

One month after the patient's initial MRI scan, a follow-up scan was performed, which showed low signal intensity on T1WI (Figure 3A-D), high signal intensity on T2-FLAIR (Figure 3E-H), slightly high and equal signal intensity on DWI (Figure 4A-D), and normal ADC values (Figure 4E-H) in the medulla oblongata. The location of the abnormal signals remained consistent with the first scan but showed a reduced range and decreased high signal intensity on T2-FLAIR. Additionally, a spinal MRI was conducted, yielding normal results.

FINAL DIAGNOSIS

Based on these findings, the patient was diagnosed with NMOSD.

TREATMENT

She received intravenous methylprednisolone at a daily dose of 500 mg for 5 d, followed by a tapering-off period. During treatment, her limb weakness, vision blurriness, dizziness, slurred speech, and blepharoptosis went into remission. After 2 wk of treatment, her EDSS score decreased to 5 points. Upon discharge, she was prescribed oral prednisone at a daily dose of 60 mg. The dose was gradually decreased from 10 mg to 30 mg daily over the course of each subsequent week. Afterward, the rate of reduction was gradually slowed down and timely use of immunosuppressants.

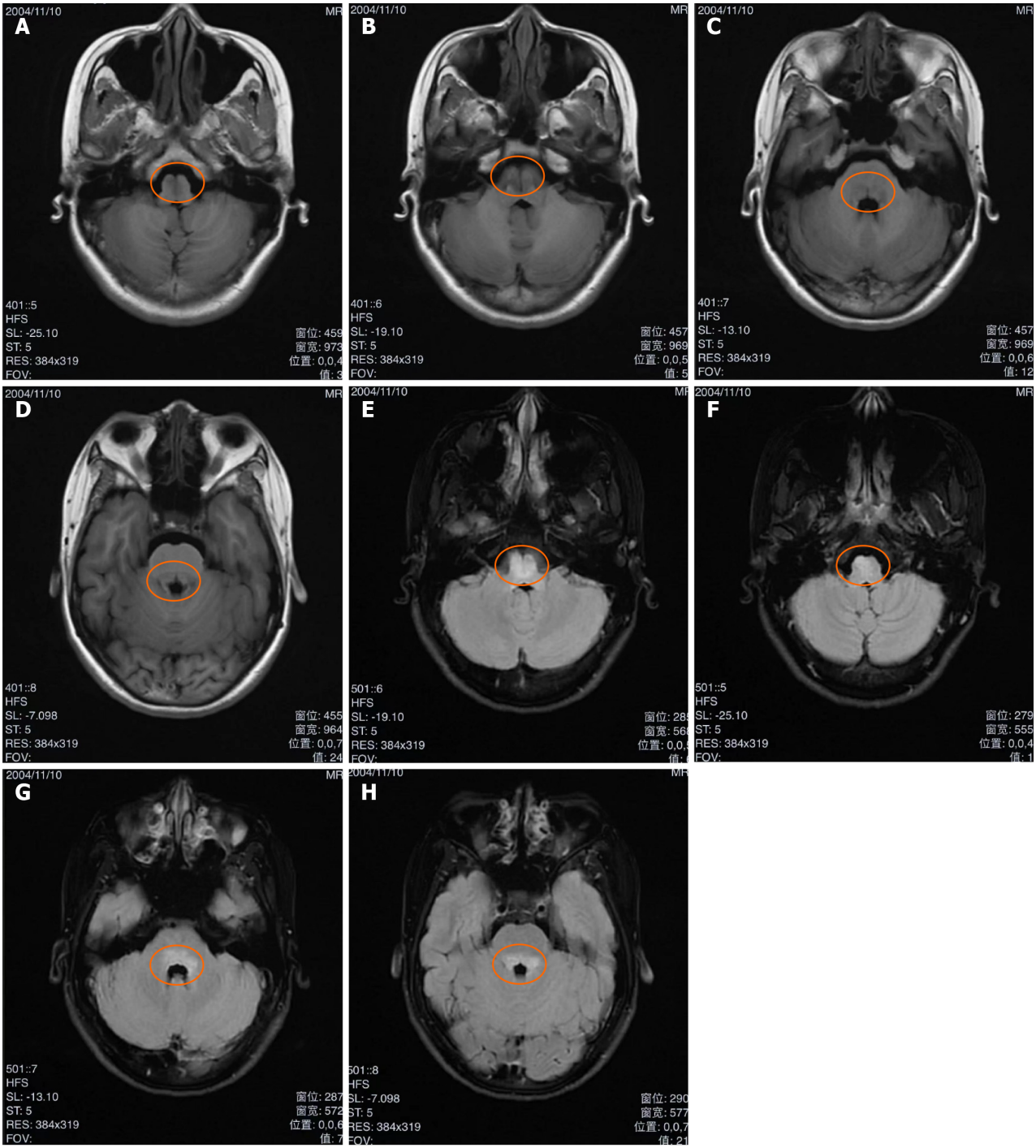

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Figure 1 Patient's first brain magnetic resonance imaging. A-D: Four slices of T1-weighted imaging showing low signals in the medulla oblongata; E-H: Four slices of T2-fluid attenuated inversion recovery showing high signals in the medulla oblongata.

OUTCOME AND FOLLOW-UP

Based on their expertise in NMOSD treatment, we plan to maintain her on corticosteroids for a minimum duration of 6 mo, with follow-up appointments scheduled every 1 to 2 mo. Through August 2023, the patient's condition did not recur and her EDSS score increased to 1 point.

DISCUSSION

The demand for predictive and disease-active biomarkers in NMOSD patients has been widely recognized, leading to an increase in biomarker studies. Among the potential biomarkers investigated, GFAP, an astrocyte protein, appears to be

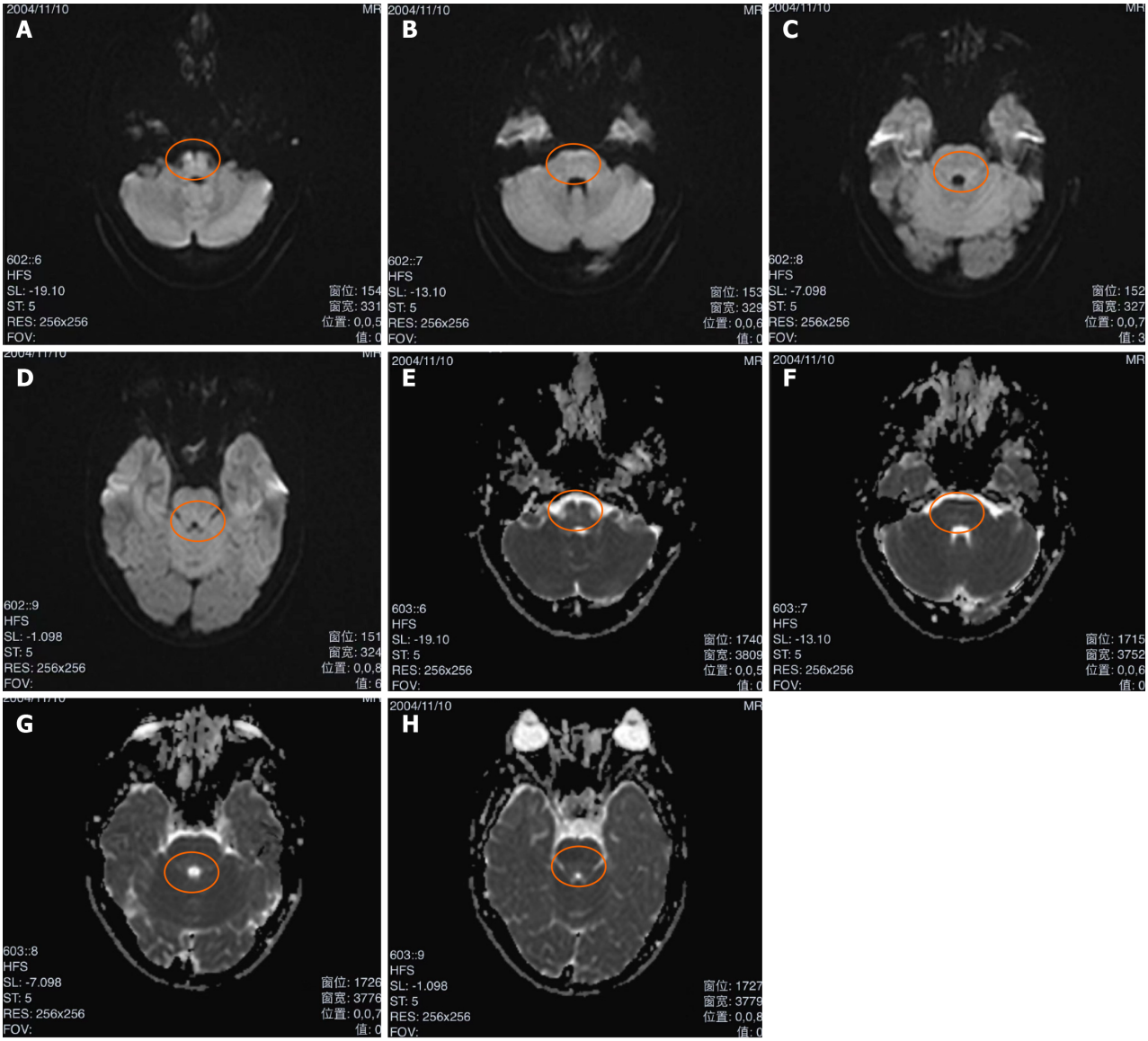

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Figure 2 Patient's first brain magnetic resonance imaging. A-D: Four slices of diffusion-weighted imaging showing slightly high and equal signals in the medulla oblongata; E-H: Four slices of apparent diffusion coefficient showing normal value in the medulla oblongata.

one of the most promising alternatives. In healthy astrocytes, GFAP is expressed moderately, but it is significantly upregulated during brain injury. This increase indicates reactive astrocyte proliferation[9]. Reactive astrocyte hyperplasia is a process caused by various types of brain injury, such as traumatic, metabolic, and inflammatory injury. Transient or permanent morphological and functional changes in astrocytes can result in the formation of glial scars[10].

Current evidence shows that the concentration of GFAP in the CSF and blood of NMOSD patients during an acute attack is higher compared to healthy individuals and patients with MS. In NMOSD, CSF and blood GFAP concentrations increase at the onset, decrease with immunotherapy, and are associated with disability. Furthermore, serum GFAP concentrations in clinically stable NMOSD patients can predict future seizures[10]. Importantly, there is growing evidence to support the predictive value of blood GFAP concentrations for present and future disease activity, particularly in AQP4-IgG-positive NMOSD. GFAP elevation in NMOSD can be explained by lysis of astrocytes and subsequent astrogliosis. Thus, GFAP concentrations in the blood of AQP4-IgG-positive NMOSD patients during clinical remission may reflect ongoing subclinical disease activity, potentially increasing the risk of further attacks[11].

However, the exact roles of GFAP-IgG in NMOSD are still not fully understood and are the subject of ongoing research. It is suggested that these antibodies may be involved in the onset or progression of the disease, but this has yet to be established conclusively. Some studies have proposed that GFAP-IgG can serve as biomarkers for diagnosing NMOSD and distinguishing it from other similar conditions. Others suggest that these antibodies may target and damage specific cells in the CNS, contributing to the disease's pathogenesis[12].

The exact role of GFAP-IgG in NMOSD remains a topic of debate and ongoing research. Some studies argue that they are epiphenomenal and do not directly contribute to the disease, while others suggest their pathogenic involvement in its development or progression[13].

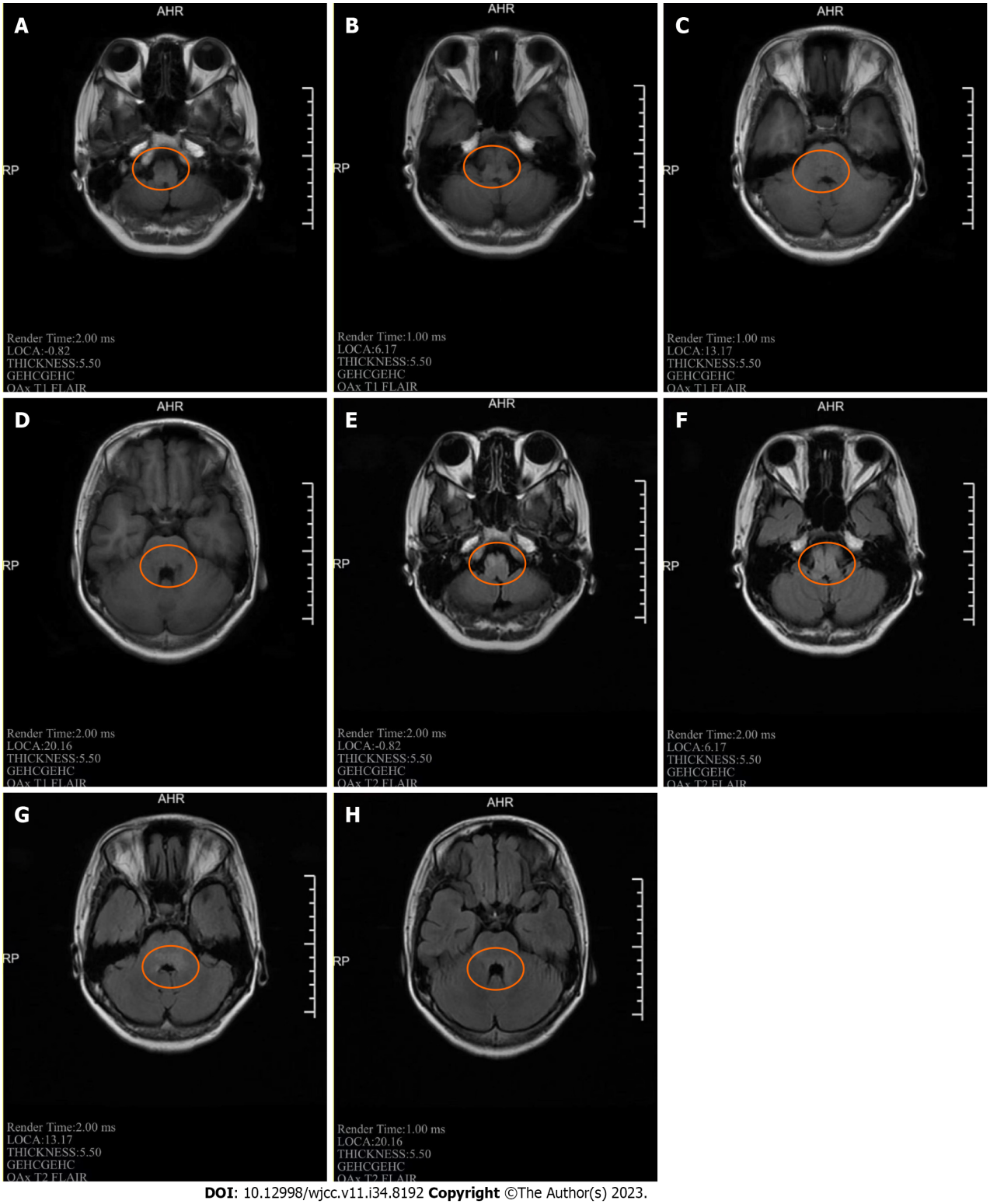

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Figure 3 Patient's second brain magnetic resonance imaging. A-D: Low signal intensity on four slices of T1-weighted imaging in the medulla oblongata; E-H: High signal intensity on four slices of T2-fluid attenuated inversion recovery in the medulla oblongata.

CONCLUSION

The disease described in this study exhibited a pattern of remission and relapse. Notably, during the relapse period, the CSF showed slight positivity for GFAP-IgG. This finding can be valuable in the diagnosis and treatment of the disease.

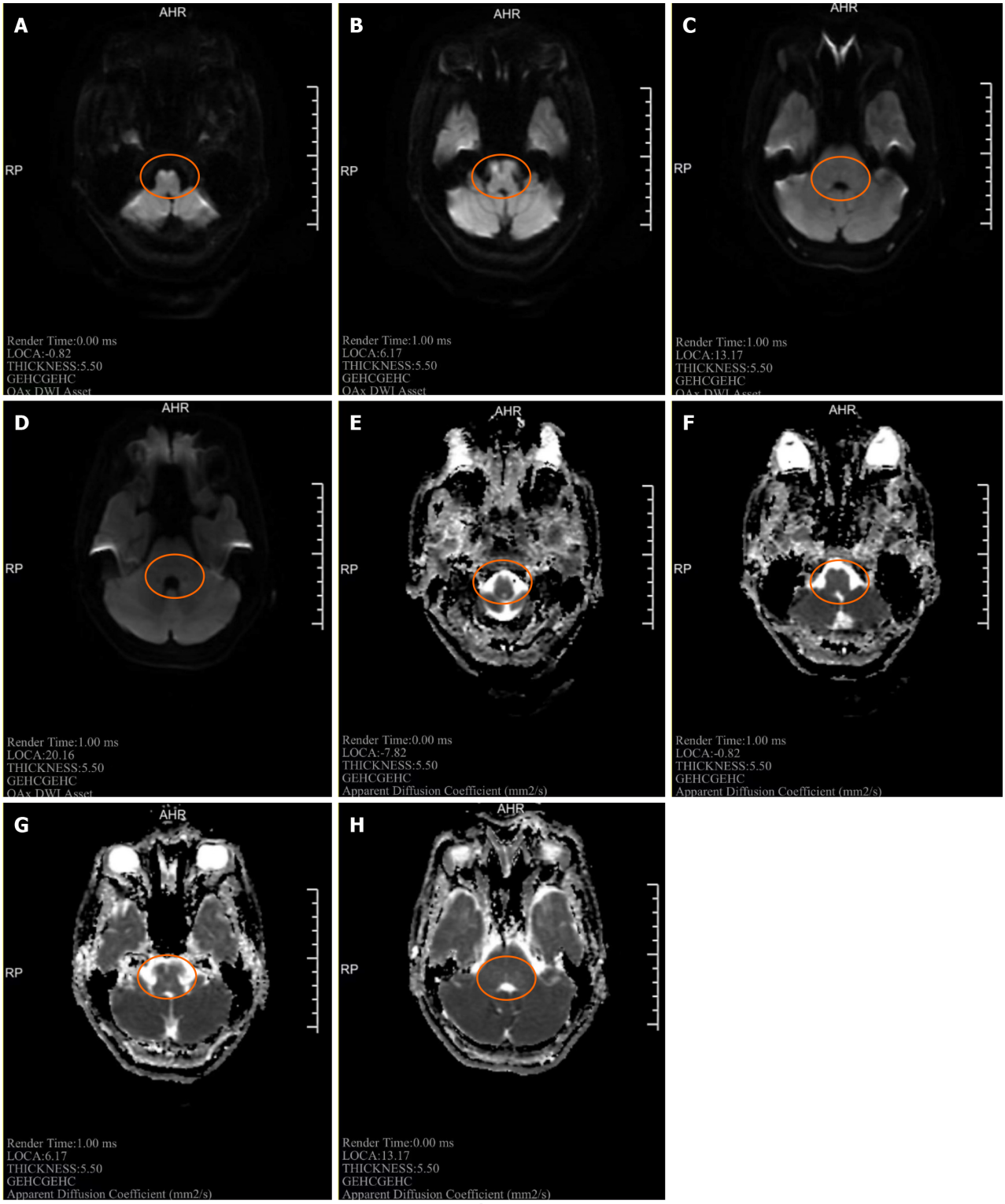

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Figure 4 Patient's second brain magnetic resonance imaging. A-D: Slightly high and equal signal intensity on four slices of diffusion-weighted imaging in the medulla oblongata; E-H: Four slices of apparent diffusion coefficient showing normal value in the medulla oblongata.

FOOTNOTES

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CASE REPORT

Thoracic duct cannulation during left internal jugular vein cannulation: A case report

Geal Hong Hwang, Woosik Eom

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Abstract

BACKGROUND

Central venous catheter insertion is an invasive procedure that can cause complications such as infection, embolization due to air or blood clots, pneumothorax, hemothorax, and, rarely, chylothorax due to damage to the thoracic duct. Herein, we report a case of suspected thoracic duct cannulation that occurred during left central venous catheter insertion. Fortunately, the patient was discharged without any adverse events related to thoracic duct cannulation.

CASE SUMMARY

A 46-year-old female patient presented at our department to undergo cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. During anesthesia, we decided to insert a central venous catheter through the left internal jugular vein because the patient already had a chemoport through the right central vein. During the procedure, blood reflux was observed when the needle tip was not within the ultrasound field of view. We did not try to find the tip; however, a guide wire and a central venous catheter were inserted without any resistance. Subsequently, when inducing blood reflux from the distal port of the central venous catheter, only clear fluid, suspected to be lymphatic fluid, was regurgitated. Further, chest X-ray revealed an appearance similar to that of the path of the thoracic duct. Given that intravenous fluid administration was not started and no abnormal fluid collection was noted on preoperative chest X-ray, we suspected thoracic duct cannulation.

CONCLUSION

It is important to use ultrasound to confirm the exact position of the needle tip and guide wire path.

Key Words: Central venous catheter insertion; Left internal jugular vein; Thoracic duct; Lymph; Ultrasound; Case report

Core Tip: Central venous catheter insertion is an invasive procedure that requires detailed knowledge of the anatomy and attention of the proceduralist. It is recommended to use the right internal jugular vein for this procedure to avoid damaging the thoracic duct. However, regardless of right or left insertion, it is important to use ultrasound to confirm the exact position of the needle tip and guide wire path.

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INTRODUCTION

Central venous catheter insertion is performed to secure the route of administration of intravenous fluids and transfusions as well as to administer medications and measure central venous pressure[1]. The internal jugular, subclavian, and femoral veins are most commonly used for this procedure. Notably, central venous catheter insertion is an invasive procedure that can lead to various complications, including infections, embolism due to air or blood clots, arrhythmia, hematoma, arterial puncture, pneumothorax, hemothorax, and cardiac tamponade[2]. Thoracic duct injury can rarely occur as a complication of left internal jugular or subclavian vein cannulation; thus, cannulation of right-sided veins is preferred[3].

Notably, complications caused by central venous catheter insertion are decreasing because of the use of ultrasound[4]. Herein, we report a case of suspected thoracic duct cannulation despite central venous catheter insertion performed through the left internal jugular vein using ultrasound.

CASE PRESENTATION

Chief complaints

A 46-year-old female patient presented at our department to undergo cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) with chief complaints of intra-abdominal recurrence and metastasis of a sigmoid colon tumor.

History of present illness

In the preoperative assessment, the patient's vital signs were stable and complete blood test results were within the normal range. Further, chest X-ray findings were unremarkable, except for the presence of a chemoport through the right central vein. Meanwhile, electrocardiogram revealed a normal sinus rhythm of 60 beats per minute.

History of past illness

The patient reported that she had undergone laparoscopic anterior resection of the colon 3 years ago. She also reported having the same medical conditions and undergoing CRS and HIPEC 2 years ago.

Personal and family history

The patient had no family or genetic history of the disease.

Physical examination

Given that the patient had a chemoport through the right central vein, during anesthesia in the operating room, we decided to insert a central venous catheter through the left internal jugular vein. The location of the left internal jugular vein was confirmed using ultrasound, and the needle was inserted after confirming the course of the vein.

Although the internal jugular vein was distinctly visible on the ultrasound scan, blood reflux was noted when the needle tip was not within the ultrasound field of view. The guide wire was pushed through the needle, and we confirmed that it entered without resistance. Further, a 7-Fr 2-lumen central venous catheter was inserted along the guide wire without resistance. After inserting the catheter up to 15 cm, the guide wire was removed. Then, to remove the air, we regurgitated blood from the catheter and assessed blood reflux. However, after approximately 1 cc of blood was refluxed, we found that when blood reflux was induced, only clear fluid regurgitated from the 16-G distal port of the central venous catheter, but no blood regurgitated from the 18-G proximal port of central venous catheter. Because intravenous fluid administration was not started and no abnormal fluid collection was noted on preoperative chest X-ray, thoracic duct cannulation was suspected. Thus, we determined that central venous catheter could not be used as a central line. Accordingly, we reinserted the central venous catheter through the left subclavian vein under ultrasound guidance.

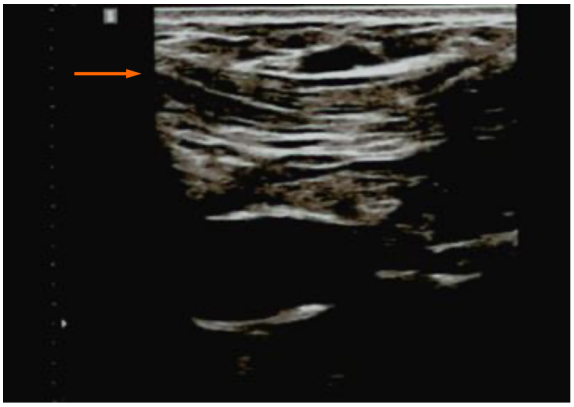

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Figure 1 Guide wire in the subclavian vein.

Further, while carefully monitoring the needle tip and guide wire, we easily inserted the central venous catheter (Figure 1). The patient's vital signs were stable. Meanwhile, the position of the tip of the internal jugular central venous catheter that was initially inserted was unclear. However, we determined that the catheter was unlikely to affect vital signs and that removing it without checking its position could cause problems. Therefore, we decided to leave it in the same position and checked its position after surgery.

Laboratory examinations

Postoperative complete blood test results were within the normal range.

Imaging examinations

In the recovery room, a chest X-ray was obtained (Figure 2A), which revealed an appearance similar to that of the path of the thoracic duct.

FINAL DIAGNOSIS

The patient was diagnosed with thoracic duct cannulation. On preoperative chest X-ray, no abnormal fluid collection that could lead to clear fluid was noted. Further, during the procedure (*i.e.*, during central venous catheter insertion through the left internal jugular vein), intravenous fluid administration was not started through the central venous catheter. From an anatomical perspective, the only structure that can produce clear fluid where the central venous catheter is located is the thoracic duct, which joins the left venous system. In addition to the abovementioned findings, given the clinical feature that only clear fluid suspected to be lymphatic fluid regurgitated when blood reflux was induced from the distal port of the central venous catheter and that the patient's chest X-ray revealed an appearance similar to that of the path of the thoracic duct, we considered that the central venous catheter was inserted through the thoracic duct opening.

TREATMENT

Although the patient's vital signs were stable, she was transferred to the intensive care unit for observation owing to the possibility of pneumothorax and chylothorax. She exhibited no respiratory symptoms, such as shortness of breath, cough, or phlegm. Moreover, her condition remained unchanged and her vital signs were stable overnight. The next day, after consultation with the thoracic surgery department, the internal jugular central venous catheter was removed, and the patient was transferred to the general ward because her chest X-ray revealed no findings of chylothorax or pneumothorax. Furthermore, chest X-rays obtained on postoperative day 2 revealed no abnormalities (Figure 2B), and the patient was observed in the general ward.

OUTCOME AND FOLLOW-UP

The patient experienced no other significant complications postoperatively, and she was discharged on postoperative day 14. At that time, her chest X-ray revealed no abnormalities (Figure 2C).

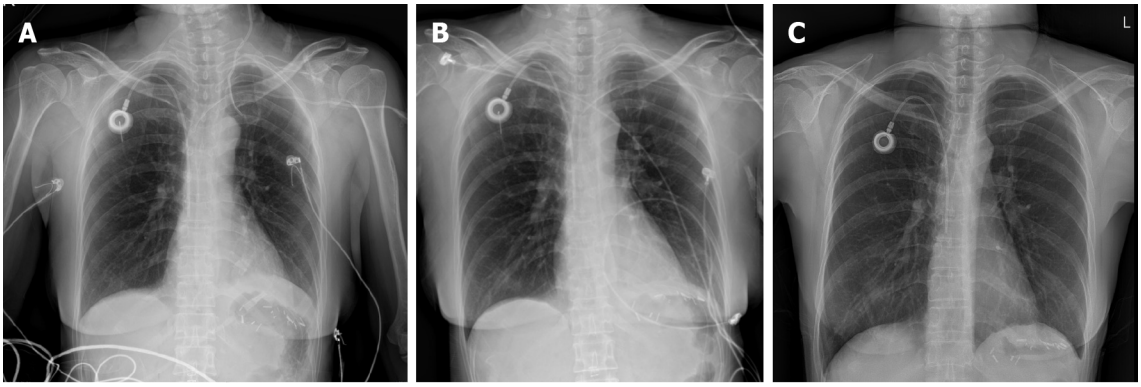

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Figure 2 Patient's chest X-ray. A: In the recovery room; B: On postoperative day 2; C: On postoperative day 14.

DISCUSSION

In the present case, fortunately, there were no complications leading to the suspicion of chylothorax. However, caution should always be exercised in such cases because chylothorax may occur if the thoracic duct is damaged due to thoracic duct cannulation.

The anatomy of lymphatics varies widely. Normally, the thoracic duct is 38-45 cm long and 2-3 mm thick. It extends from the cisterna chyli at the L2 level to the neck and passes behind the aortic arch and the left subclavian artery. Further, thoracic duct forms an arch 3-5 cm above the clavicle, makes an acute angle near the left subclavian vein and the left internal jugular vein, and joins the venous system[5].

The flow rate of chyle is approximately 2.4 L/d. This rate is dependent on diet, activity level, and intestinal function and can increase with a triglyceride-rich diet. Conversely, the amount of chyle is significantly reduced if patients are immobilized, starved, or constantly suctioned with a nasogastric tube. This is why bowel rest is used as a treatment for chylothorax[6,7].

Chylothorax can be treated conservatively with bowel rest, somatostatin/octreotide medication to reduce chyle production, and drainage through a chest tube or catheter. However, patients who fail to respond to conservative treatment may require surgical intervention[6,7].

In the present case, a clear fluid regurgitated through the inserted catheter, and postoperative chest X-ray findings led to the suspicion of direct cannulation of the thoracic duct into the opening at the site where it joins the subclavian or internal jugular vein. For a more accurate diagnosis, the regurgitated fluid should be analyzed for triglyceride concentration to detect the presence of chyle; alternatively, computed tomography or lymphangiography may be needed.

Initially, the following cases were considered for cannulation of the thoracic duct: (1) Direct puncture from outside the thoracic duct; and (2) double puncture of the thoracic duct through the internal jugular vein**.** However, after removing the catheter, there were no remarkable findings, including chylothorax or pneumothorax, chylocele at the site of thoracic duct inlet, and hematoma. Thus, the catheter was thought to be directly cannulated through the thoracic duct opening, where the thoracic duct connects to the internal jugular or subclavian vein.

To avoid thoracic duct cannulation during central venous catheterization, it is important to use ultrasound to accurately identify the position of the needle tip and guide wire path during needle entry because the thoracic duct is located 3−5 cm above the clavicle. Moreover, the proceduralist should be alert and have a clear understanding of the anatomy.

CONCLUSION

Central venous catheter insertion is an invasive procedure requiring accurate knowledge of anatomy and proceduralist alertness. During this procedure, it is recommended to use the right internal jugular vein to avoid damage to the thoracic duct. Regardless of right or left insertion, it is important to use ultrasound to confirm the exact position of the needle tip and guide wire path.

FOOTNOTES

Author contributions: Hwang GH and Eom W were the physicians; Hwang GH reviewed the literature and contributed to manuscript drafting; Hwang GH and Eom W were responsible for the revision of the manuscript; all authors issued final approval for the version to be submitted.

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CASE REPORT

Long-term survival of the Sister Mary Joseph nodule originating from breast cancer: A case report

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Abstract

BACKGROUND

A Sister Mary Joseph nodule (SMJN) is an uncommon cutaneous metastasis found in the umbilicus, indicating an advanced malignancy. SMJNs typically originate from intra-abdominal sources, rarely from breast cancer. Diagnosis suggests a poor prognosis with a median survival of approximately 8 mo after detection. Managing patients with SMJNs is challenging, as most receive limited palliative care only. The optimal strategy for long-term survival of these patients remains unclear.

CASE SUMMARY

A 58-year-old female, previously diagnosed with right breast cancer 17 years ago and underwent breast-conserving surgery, adjuvant radiotherapy, and endocrine therapy, presented with a 2-cm umbilical nodule. Thirteen years previously, metastases were detected in the right supraclavicular, infraclavicular, hilar, and mediastinal lymph nodes. An umbilical nodule emerged four years before the date of presentation, confirmed as a skin metastasis of primary breast cancer upon excisional biopsy. Despite initial removal, the nodule recurred and grew, leading to her referral to our hospital. The patient underwent extensive excision of the umbilical tumor and immediate abdominal wall reconstruction. Endocrine therapy was continued postoperatively. Five years later, no local recurrence was observed, and the patient continued to work full-time, achieving over 9 years of survival following SMJN diagnosis.

CONCLUSION

This case study aimed to identify the optimal strategy for achieving extended survival outcomes in patients with SMJN through comprehensive treatment. We presented a case of the longest survival in a patient after undergoing a multidisciplinary treatment regimen. Our findings underscore the significance of adopting

a multimodal treatment approach comprising timely and wide excision along with adjunctive therapy. This approach can control the disease, prolong survival, and improve the quality of life in patients with SMJN.

Key Words: Sister Mary Joseph nodule; Breast cancer; Cutaneous metastasis; Long-term survival; Abdominal wall reconstruction; Case report

Core Tip: Sister Mary Joseph nodules (SMJN) typically present as firm, irregular periumbilical nodules, which are uncommon yet significant symptoms that indicate an advanced stage of malignancy with a poor prognosis. Although most patients receive limited treatment, the optimal systemic treatment strategy for long-term survival remains controversial. While treatment decisions should be based on the patient's overall health and condition, a multimodal treatment approach comprising timely and wide excision along with adjunctive therapy has the potential to control the disease, prolong survival, and improve the quality of life of patients with SMJNs without peritoneal dissemination.

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INTRODUCTION

The Sister Mary Joseph nodule (SMJN) is an unusual cutaneous metastasis in the umbilicus. It originates from intra-abdominal or pelvic sources and is rarely associated with breast cancer[1]. On physical examination, SMJN is an uncommon yet significant sign indicating an advanced stage of malignancy and a poor prognosis. The median survival duration after SMJN diagnosis was 7.9 mo, with a 95% confidence interval of 6.7 to 9.1 mo[2]. Because managing patients with SMJN is challenging, they generally receive limited treatments, such as palliative surgery or best supportive care. However, the optimal systemic treatment strategy for long-term survival remains controversial. This report presents a rare case of a patient diagnosed with SMJN originating from breast cancer who survived for over 9 years after receiving treatment with a multidisciplinary approach. The patient remained active in society, working full-time.

CASE PRESENTATION

Chief complaints

A painless 2-cm hard nodule with erosions in the umbilical region, which was first detected four years ago.

History of present illness

At age 41 (17 years ago), she underwent a right breast-conserving surgery (invasive ductal carcinoma, ER+, PR+, HER−, T2N2M0). The patient was treated with adjuvant chemotherapy (four cycles of Epirubicin and Cyclophosphamide), followed by adjuvant radiotherapy (50Gy/25Fr) and endocrine therapy (Tamoxifen). At age 45 (13 years ago), metastases were detected in her right supraclavicular to infraclavicular lymph nodes, right hilar lymph nodes, and mediastinal lymph nodes on positron emission tomography–computed tomography (PET-CT). Consequently, she was prescribed an LH-RH agonist (Leuprorelin) with Tamoxifen as a second-line treatment. Over time, the tumor showed a trend of reduction in both lymph node and lung metastases compared to their state before treatment, leading to the discontinuation of Leuprorelin. At age 53 (5 years ago), Tamoxifen was switched to Anastrozole as progressive enlargement of the right supraclavicular lymph node was found. One year later, Leuprorelin was resumed because the CT scan showed an increasing number of nodules in both the upper and lower lobes of the right lung. At age 54 (4 years ago), an umbilical nodule emerged, for which an excisional biopsy was performed, confirming skin metastasis originating from the primary breast cancer (adenocarcinoma, metastatic, ER+, PR+, HER−). Although endocrine therapy with Leuprorelin and Exemestane was initiated, the nodule recurred and gradually increased in size, leading to her referral to our hospital.

History of past illness

The patient has no significant medical history.

Personal and family history

No notable abnormalities: Never smoked, no alcohol consumption, and no known allergies to drugs or food.

Physical examination

A hard, localized, and poorly mobile nodule accompanied by erosion was detected in the umbilical region. The nodule measured approximately 2 cm in diameter, with no redness, heat, pain, or tenderness (Figure 1A and B). A lymph node approximately 2 cm in diameter was palpable subcutaneously above the right clavicle, with no other palpable lymph nodes including the axillary or inguinal regions.

Laboratory examinations

Her laboratory results were normal, with the carcinoembryonic antigen level at 3.1 ng/mL (normal reference value: 5 ng/mL), except for a slight elevation in the carbohydrate antigen (CA) 15-3 Level to 59 U/mL (normal reference value: 21 U/mL).

Imaging examinations

PET scans revealed increased 18F-fluorodeoxyglucose uptake in the umbilicus (SUVmax, 4.0), right supraclavicular fossa (SUVmax, 7.2), and bilateral lung fields (SUVmax, 1.2) (Figure 1C). Additionally, the PET-CT scan indicated no evident nodules suggesting tumor metastasis to the peritoneum in the abdominal cavity, nor was there any evidence of abdominal or pelvic fluid (Figure 1D).

FINAL DIAGNOSIS

A puncture biopsy was performed, resulting in a diagnosis of recurrent metastatic adenocarcinoma originating from breast cancer. Histological examination confirmed adenocarcinoma with a foamy tubular arrangement (Figure 2). Immunohistochemistry was positive for ER and GCDFP-15, negative for PR and HER, and showed a low proliferative index of 7% for neoplastic cells on Ki67.

TREATMENT

The tumor was excised with a 15 mm horizontal margin, involving combined resection of the peritoneum and falciform ligament (Figure 3A). No tumor was exposed to the abdominal cavity (Figure 3B and C), and no adhesions were observed in the intra-abdominal organs. There was no evidence of peritoneal dissemination. Given the large size of the defect, simple closure was challenging; therefore, we reconstructed the abdominal wall using a component separation technique (Figure 3D-F). Postoperative endocrine therapy with Toremifene citrate was initiated followed by adjuvant radiation therapy (45Gy/15Fr) for the enlarged right subclavian lymph nodes.

OUTCOME AND FOLLOW-UP

The wound healed completely, enabling the patient to return to work. Five years postoperatively, there was no evident local recurrence in the umbilical region, and the patient continued to work full-time, five days a week (Figure 4).

DISCUSSION

This report presents a case of long-term survival in a patient with an SMJN originating from breast cancer. SMJNs typically present as firm, irregular periumbilical nodules, usually measuring 0.5–2 cm. They may be painful, ulcerated, bloody, or suppurative[3]. For patients presenting with an umbilical nodule, the differential diagnosis should include primary umbilical neoplasms, metastatic umbilical nodules, umbilical hernias, umbilical endometriosis, keloids, pyoderma gangrenosum, and foreign bodies. Notably, SMJN may be the sole presenting complaint in some otherwise healthy patients. However, other patients may present with a poor clinical state and additional physical signs, such as ascites and pleural effusion[4]. A focused history and examination of the chest, abdomen, and regional lymph nodes can help identify the source of the primary neoplasm. Patients presenting with SMJN after treatment for a known neoplasm should be evaluated for recurrence. Biopsy of the umbilical nodule offers a convenient method for obtaining tissue samples for histological diagnosis. CT scan and magnetic resonance imaging can determine the extent of the malignancy.

Cutaneous metastases occur in up to 9% of malignancies, with only 10% localized to the umbilicus[5,6]. SMJN is typically associated with primary neoplasms of the gastrointestinal and genitourinary tracts. Other reported primary sites include the lungs, pancreas, liver, gallbladder, breast, kidney, prostate, and testicle[7,8]. However, the source of the primary neoplasm may remain unidentified in up to 30% of patients[5]. Only 1.7% of umbilical metastases originate from breast tissues[9].

The etiology of SMJN remains unclear. Proposed hypotheses include direct extension of the tumor to the umbilicus as well as lymphatic or hematogenous spread[10]. A literature review showed that 21 out of 23 (91%) patients with SMJN at presentation experienced peritoneal dissemination[11]. Although the mechanism of tumor spread from the breast to the umbilicus remains unclear, extensive vascular and lymphatic connections between the umbilicus and axillary and

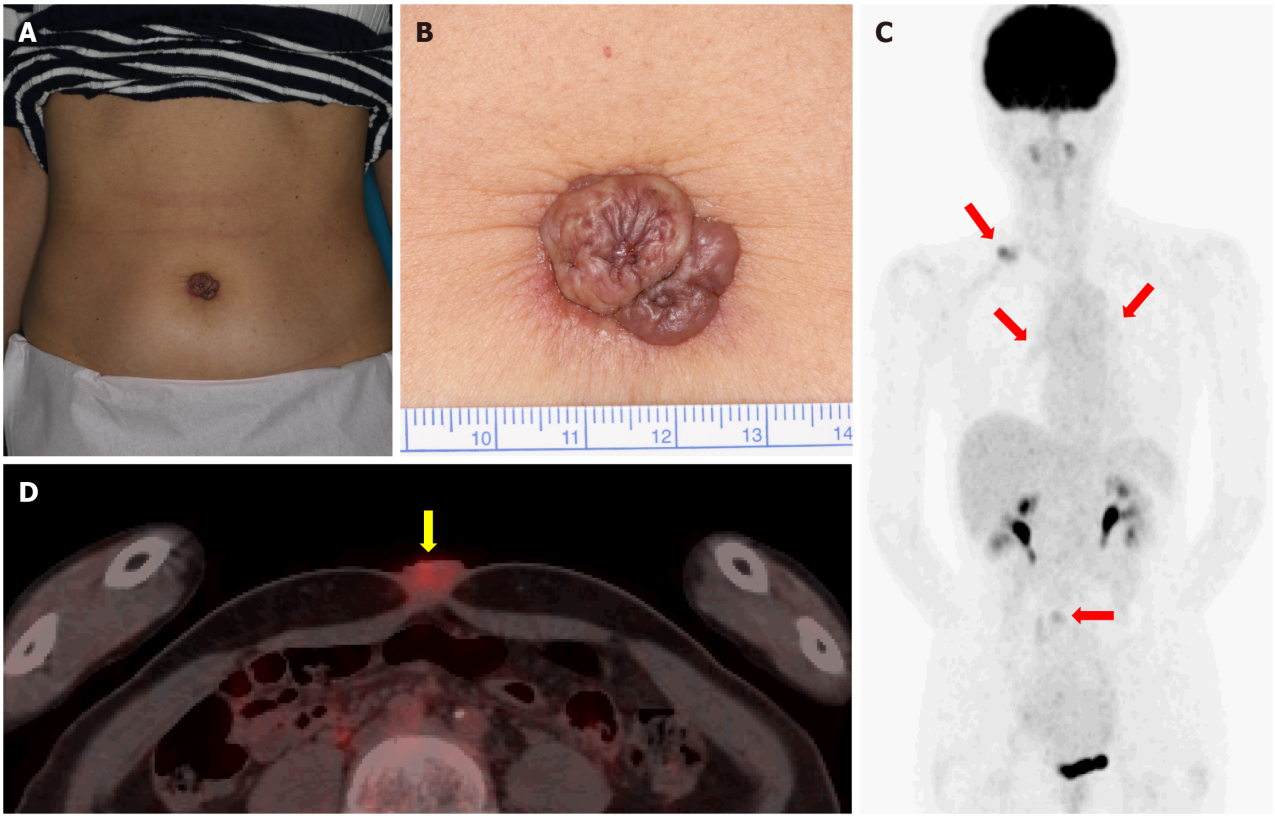

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Figure 1 A 58-year-old woman presented with Sister Mary Joseph's nodule. A and B: A 2-cm hard, localized, and painless nodule with erosions observed in the umbilical region; C: Positron emission tomography (PET) demonstrates increased 18F-fluorodeoxyglucose uptake in the umbilicus, right supraclavicular fossa, and bilateral lung fields (red arrow); D: PET-computed tomography scan revealed increased 18F-fluorodeoxyglucose uptake in the umbilicus (yellow arrow), but there were no nodules or abdominal/pelvic fluid suggesting tumor metastasis to the peritoneum.

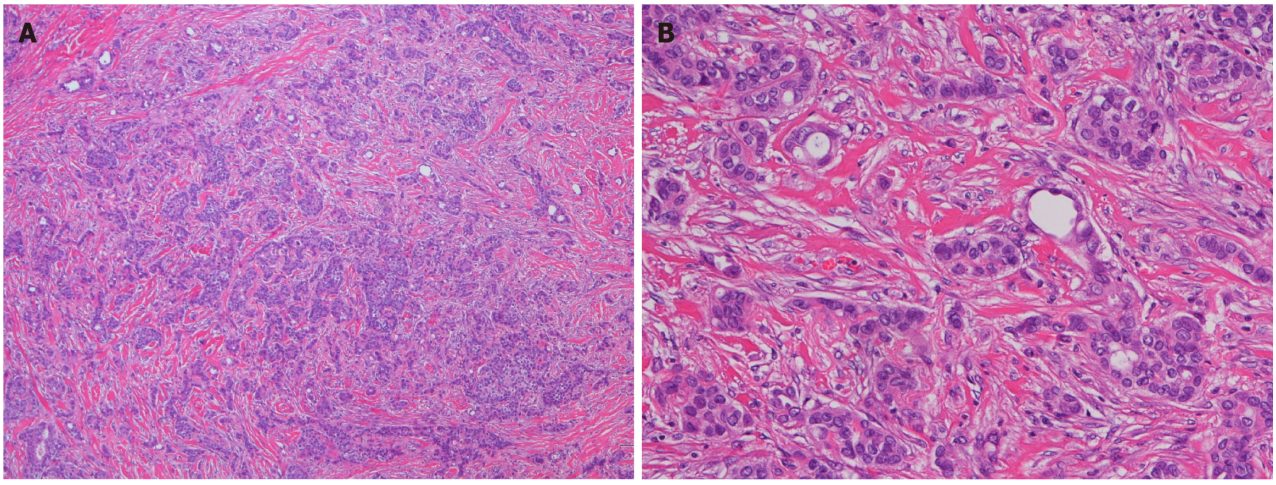

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Figure 2 Pathology of the metastatic specimens. A: Morphology (Hematoxylin and eosin, × 40); B: Morphology (Hematoxylin and eosin, × 200) confirming an adenocarcinoma in a foamy, tubular arrangement in metastatic lesions.

thoracic regions may facilitate the migration of breast tumor cells[5,6,12,13].

Patients diagnosed with SMJN typically have a poor prognosis: fewer than 30% of treated patients survive beyond 1 year, and fewer than 15% survive beyond 2 years[12]. To our knowledge, no report has described a patient with SMJN who survived for over 9 years. The recommended treatment approaches for SMJN remain controversial. Some physicians advocate an aggressive regimen combining surgery with adjunctive therapy[12,14], while others recommend avoiding surgery due to the poor prognosis[15]. Majmudar *et al*[12] demonstrated that an aggressive multimodality treatment approach, including both surgery and chemotherapy, improved survival (average survival 17.6 mo) compared to those

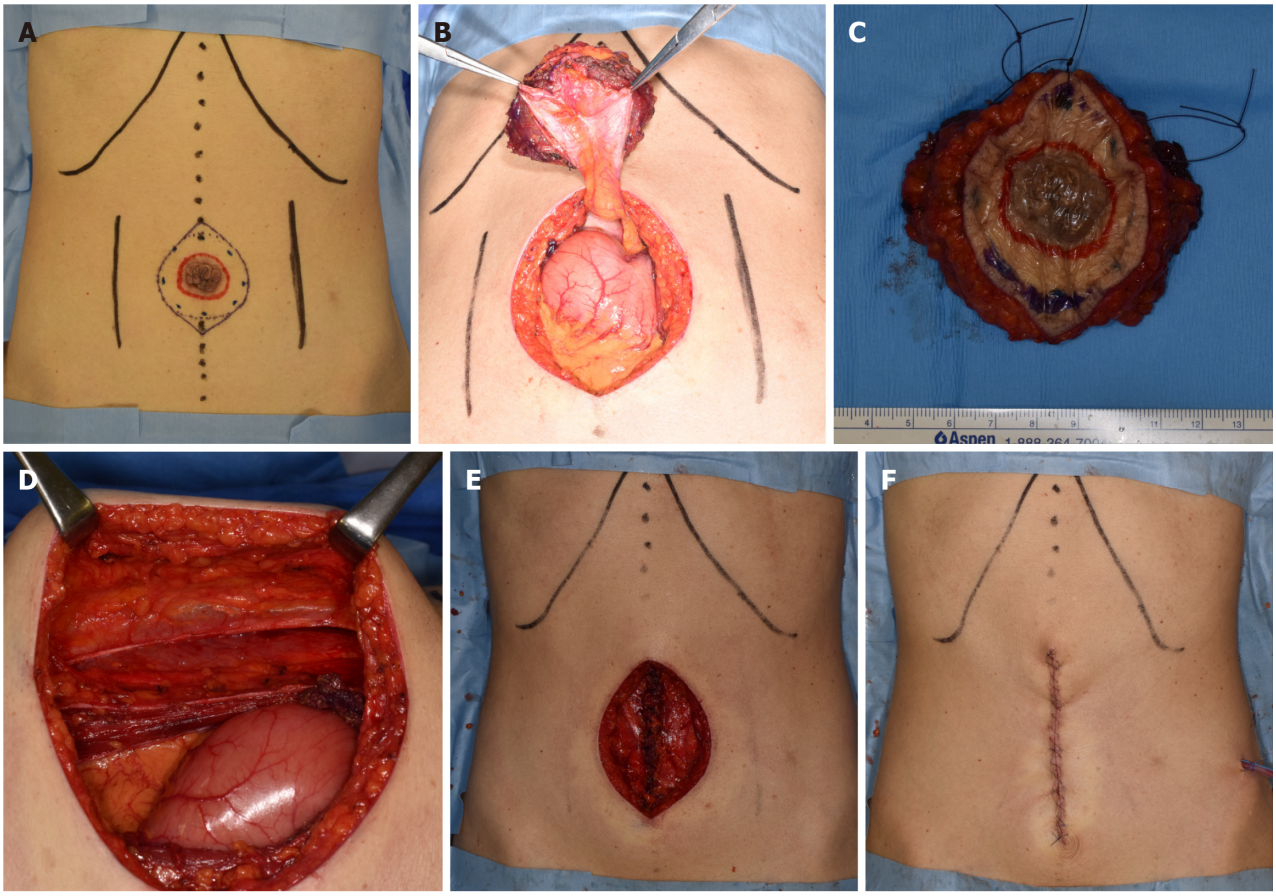

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Figure 3 Perioperative images of tumor resection and immediate abdominal wall reconstruction. A: Tumor excision with a 15 mm horizontal margin, encompassing a combined resection of the peritoneum and the falciform ligament; B: Image showing no exposure of the tumor to the abdominal cavity; C: Macroscopic image of the resected tissue; D–F: Abdominal wall reconstruction using a component-separation technique.

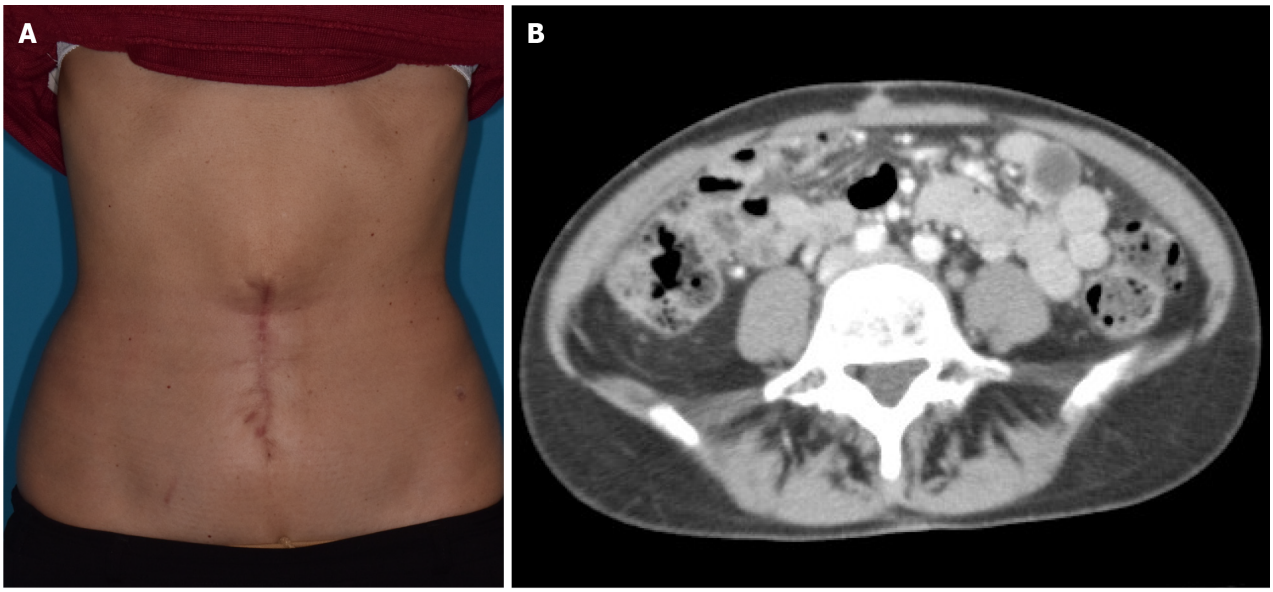

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Figure 4 Five-year postoperative images. A: No evident local recurrence in the umbilical region; B: Computed tomography scan shows no nodules, suggesting tumor recurrence in the umbilical region or metastasis to the peritoneum in the abdominal cavity.

treated with either surgery alone (average survival 7.4 mo) or adjunctive therapy alone (average survival 10.3 mo); patients who received no therapy had the lowest average survival of 2.3 mo. The prognosis of patients with SMJN is variable and may be most directly affected by the primary tumor type and location. Patients with a primary tumor originating from the pancreas had the poorest prognosis, with a median overall survival rate of approximately 3 mo from the date of diagnosis of umbilical metastasis, while those with primary tumors originating from the ovaries or endometrium had a median survival rate of approximately 10 mo[2].

When determining a management strategy, it is crucial to consider the patient's preferences, clinical condition, and the etiology of the primary malignancy. Although palliative care may be the only viable option for certain patients, others, when carefully selected, may benefit from more aggressive interventions such as surgery, chemotherapy, and radiotherapy. In the present case, the initial approach was local resection followed by endocrine therapy. However, due to disease progression, more extensive surgery was required. Timely and wide excision can prevent peritoneal dissemination and treat patients with SMJN. Peritoneal dissemination often distresses patients, manifesting as abdominal distension, constipation, pain, nausea, and vomiting. As the disease progresses, the patient's quality of life (QOL) can be impaired as a result of poor oral intake due to bowel obstruction, jaundice resulting from bile duct stenosis, and hydronephrosis caused by ureteral constriction. While such treatment decisions must align with the patient's overall health and condition, this strategy has the potential to control the disease, extend survival, and enhance the QOL in patients with SMJN.

The current study has limitations; as this is a report on just one patient's outcome, the results may not be generalizable to the broader population of patients with SMJNs originating from breast cancer. Additional studies with larger sample sizes are needed. Future studies could investigate potential biomarkers or clinical factors that could help identify SMJN patients who are more likely to respond positively to aggressive treatment approaches, similar to the case presented. This could lead to more personalized treatment plans.

CONCLUSION

This case study aimed to identify the optimal strategy for achieving extended survival outcomes in patients with SMJN through comprehensive treatment. We presented a case of the longest survival in a patient after undergoing a multidisciplinary treatment regimen. Our findings underscore the significance of adopting a multimodal treatment approach comprising timely and wide excision along with adjunctive therapy. This approach can control the disease, prolong survival, and improve the QOL in patients with SMJN.

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FOOTNOTES

Author contributions: Kanayama K designed the case report and drafted the manuscript; Tanioka M, Hattori Y, and Iida T collected patient data; Okazaki M provided the administrative support; The final version of the manuscript was approved by all authors.

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CASE REPORT

Hemophagocytic lymphohistiocytosis with jaundice as first manifestation: A case report

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Abstract

BACKGROUND

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening condition. It is an immune-mediated disease that has a wide range of causes, elicits a hyperinflammatory response, and results in multiple organ damage. Clinical presentations vary, and in some cases, jaundice occurs as the first symptom.

CASE SUMMARY

We report the case of a 71-year-old female patient who presented with jaundice. She was admitted to our hospital because of the occurrence of "jaundice for half a month", and upon examination, obstructive jaundice with choledocholithiasis and gallstones was suggested. Cholecystectomy and choledocholithotomy were performed. However, the jaundice did not improve after surgery. We found splenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, and elevated ferritin. Bone marrow biopsy revealed hemophagocytosis. Later, cardiac arrest occurred when she returned 3 wk after the surgery. We considered that HLH was triggered by septic shock. The patient's condition deteriorated rapidly, with multiple organ dysfunction and severe gastrointestinal bleeding. Corticosteroid therapy and symptomatic treatment failed to save her life.

CONCLUSION

Jaundice rarely presents as the first symptom in HLH patients. The HLH in this case was triggered by septic shock with jaundice as the first symptom. Clinicians should try hard to reduce missed diagnoses and misdiagnoses.

Key Words: Hemophagocytic lymphohistiocytosis; Jaundice; Common bile duct stones; Bile duct obstruction; Septic shock; Case report

Core Tip: We report the case of a 71-year-old female patient who presented with jaundice. Obstructive jaundice with choledocholithiasis and gallstones was suggested. Then, we found splenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, and elevated ferritin. Bone marrow biopsy revealed hemophagocytosis. Later, cardiac arrest occurred when she returned after the surgery. We considered that hemophagocytic lymphohistiocytosis (HLH) was triggered by septic shock. The patient's condition deteriorated rapidly, with multiple organ dysfunction. Corticosteroid therapy and symptomatic treatment failed to save her life. Jaundice rarely presents as the first symptom in HLH patients. Elevated direct bilirubin was associated with prognosis. Clinicians should try to reduce missed diagnoses and misdiagnoses.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of immunomodulatory abnormalities caused by aberrant activation of lymphocytes, monocytes, and macrophages, which release a large amount of inflammatory cytokines, eliciting an excessive inflammatory response. HLH can be classified as primary or secondary. This rapidly progressive disease has a low incidence, but the case fatality rate is high, with a more than 50% mortality rate in severe patients. Therefore, early recognition is crucial to improve the survival of patients with this disorder. We report a patient with HLH who presented with jaundice as the first symptom.

CASE PRESENTATION

Chief complaints

A 71-year-old woman was admitted to our emergency department after experiencing jaundice for half a month and was admitted to the hepatological surgery department in the first stage on February 7, 2023. She was admitted to the emergency department again 3 wk after receiving surgery for cardiac arrest on March 2, 2023.

History of present illness

First stage: In the previous 2 wk prior to her first admission to the hospital, the patient found that her skin and sclera turned yellow, accompanied by chills, but without fever. Obstructive jaundice was considered and treated with medication. However, the treatment did not work, and her jaundice worsened. Therefore, she was admitted to our hospital.

Second stage: Three weeks later, the patient returned to the hepatobiliary surgery department for follow-up. The patient entered cardiac arrest and was admitted to the emergency department.

History of past illness

The patient had a history of gallstones and choledocholithiasis.

Personal and family history

The patient had no remarkable personal or family history.

Physical examination

The physical examination revealed a temperature of 37.1°C, pulse of 56 beats per minute, respiration rate of 23 breaths per minute, and blood pressure measured at 163/99 mmHg. Her skin and sclera were yellow, her abdomen was soft, with no tenderness or rebound pain, and Murphy's sign was negative.

Laboratory examinations

The results of a routine blood test were as follows: White blood cell count 4.67 × 10^9 /L; hemoglobin 153 g/L; and platelet count 127 × 10^9 /L. The biochemical test results were as follows: Alanine aminotransferase 309.4 U/L; aspartate aminotransferase 313.1 U/L; total bilirubin 193.9 μmol/L; direct bilirubin 162.4 μmol/L; albumin 32.2 g/L; cholinesterase 4739 U/L; blood urea nitrogen 4.4 mmol/L; creatinine 48 μmol/L; lactate dehydrogenase 419 U/L. Tumor markers were assessed as follows: Carbohydrate antigen-153 26.5 U/mL; alpha-fetoprotein 100.57 ng/mL; carbohydrate antigen-125 77.2 U/mL. Coagulation function results were as follows: Prothrombin time 14.3 s; prothrombin activity 59.2%; activated partial thromboplastin time 35 s; fibrinogen 1.07 g/L; D-dimer 1.19 mg/L; fibrinogen degradation products 3.59 mg/L. The myocardial enzyme series values were within normal limits.

Imaging examinations

Magnetic resonance cholangiopancreatography showed gallstones with cholecystitis, and there were stones in the common bile duct. The common bile duct was mildly dilated. The spleen was also enlarged.

After the patient entered cardiac arrest and was admitted to emergency, imaging examinations were as follows: Acute cerebrovascular lesions were not identified *via* head computed tomography(CT); chest CT indicated inflammation in the lower lobe of the right lung; abdominal CT showed no dilation of bile ducts inside or outside the liver, abnormal density, or splenomegaly.

Treatment

The patient's liver did not function normally since she was admitted to our emergency. Combined with the imaging results and elevated aminotransferases, gallstones with cholecystitis were considered. The patient underwent laparoscopic cholecystectomy and common bile duct exploration. During the operation, it was revealed that the gallbladder wall was hyperemic and edematous, and the common bile duct was widened, with a diameter of approximately 12 mm. The stones in the common bile duct were removed completely, and the T-tube was drained. The average drainage from the T-tube was 305 mL per day.

However, the jaundice worsened, and elevations in direct bilirubin were observed (Table 1). Other laboratory chemistry findings were as follows: Cytopenia affecting three lineages in the peripheral blood, hypertriglyceridemia, and hypofibrinogenemia. Re-examination of magnetic resonance cholangiopancreatography did not indicate dilation or obstruction in the intrahepatic and extrahepatic bile ducts. A series of tests, such as bone marrow morphology tests, were completed after hematologist consultation, and the patient was discharged from the hospital. Other relevant results were as follows: Ferritin 3881 μg/L; hemophagocytosis was found in the bone marrow (Figure 1); and normal results for immunoglobulin, complement, antinuclear antibodies, extractable nuclear antibodies, thyroid function, human parvovirus B19 (DNA), cytomegalovirus (nucleic acid), and Epstein–Barr virus (nucleic acid). We informed the patient's family that further diagnosis and treatment would be needed, and they intended to go to another hospital. When she returned to the hepatobiliary surgery department for follow-up, cardiac arrest occurred.

FINAL DIAGNOSIS

We considered septic shock, with a high possibility of biliary infection. Imipenem/cilastatin sodium (1 g per 8 h) was administered as an anti-infective, as well as for organ support. Considering that the T-tube was in place, T-tube drainage was continued. Later, peripheral blood culture and bile culture results indicated the presence of *Klebsiella acidogenes* (treated with cefoperazone sodium/sulbactam sodium, minimum inhibitory concentration 8 mg/L) and *Enterococcus faecium* with high levels of aminoglycoside resistance (HLAR) (treated with vancomycin, minimum inhibitory concentration 0.5 mg/L). According to the results regarding drug sensitivity, the anti-infection regimen was adjusted to cefoperazone sodium/sulbactam sodium combined with vancomycin.

We consulted a hematologist again. Since the patient showed signs such as cytopenia affecting three lineages in the peripheral blood, hypertriglyceridemia, hypofibrinogenemia, ferritin > 500 ng/L, and hemophagocytosis in the bone marrow, HLH was considered. An examination of soluble interleukin-2 receptor alpha subunit and natural killer cell activity revealed that the soluble interleukin-2 receptor alpha subunit level was 22616 pg/mL (normal reference range < 6400 pg/mL) and natural killer cell activity was 8.14% (normal reference range ≥ 15.11%) (Figure 2), leading to a clear diagnosis of hemophagocytosis[1] (Table 2).

TREATMENT

According to the consultation, HLH-1994 was suggested. For the patient, her general condition was extremely poor and complicated with severe gastrointestinal bleeding. She could not tolerate etoposide, so only corticosteroids were administered. Multiple organ support therapy was continued.

OUTCOME AND FOLLOW-UP

The patient continued to deteriorate and died on March 8, 2023.

DISCUSSION

HLH was first reported in 1939 by Scott and Robb-Smith as "medullary histiocytic reticulocytosis"[2], and since then, doctors have gradually learned more about the disease. HLH is characterized by fever, splenomegaly, and other atypical symptoms, and organ dysfunction occurs as the disease deteriorates. The pathogenesis of HLH involves systemic inflammation and severe cytokine storms caused by impaired natural killer cells and CD8+ cytotoxic cells[3,4]. HLH is classified as primary HLH and secondary HLH. Primary HLH is an autosomal or sex chromosomal recessive hereditary disease,

Table 1 Laboratory results on key dates

Item	Feb. 7	Feb. 10	Feb. 14	Feb. 21	Mar. 2	Mar. 3	Mar. 5	Mar. 8
Hb (g/L)	153	126	108	84	59	88	35	27
WBC (× 10^9/L)	4.67	3.36	6.24	2.07	38.68	19.79	2.47	7.2
PLT (× 10^9/L)	127	88	88	71	211	143	20	8
ALT (U/L)	309.4	205	102.2	36	78.2	183.5	105.1	409.6
AST (U/L)	313.1	215	117.4	55.3	265.4	871.2	367.6	2215
TBIL (μmol/L)	193.9	131.2	94	222.5	425.2	521.2	355.2	245
DBIL (μmol/L)	162.4	112.7	81	174.8	373.3	422.6	276.9	169.5
PTA (%)	68.2	59.2	70	67.3	22.5	28.3	35.4	8.3
Cre (μmol/L)	48	40	55	31	118	73	58	117
LDH (U/L)	419	367	245	413	793	1440	1182	3753
Ferritin (μg/L)	-	-	-	3881.0	-	-	> 8000	-
TG (mg/dL)	-	2.89	2.38	-	-	-	-	-
Fib (g/L)	1.05	1.07	2.04	1.58	1.49	1.34	0.8	0.74

Hb: Hemoglobin; WBC: White blood cell count; PLT: Platelet count; AST: Aspartate aminotransferase; TBIL: Total bilirubin; DBIL: Direct bilirubin; PTA: Prothrombin activity; Cre: Creatinine; LDH: Lactate dehydrogenase; Fib: Fibrinogen; TG: Triglycerides; ALT: Alanine aminotransferase.

Table 2 Diagnostic guidelines for hemophagocytic lymphohistiocytosis in 2004

Diagnostic criteria	
1	Molecular diagnosis consistent with HLH
2	Five of the following eight criteria are fulfilled
	Fever
	Splenomegaly
	Cytopenias affecting at least two of the three lineages in the peripheral blood; hemoglobin < 90 g/L; platelets < 100 × 10^9; neutrophils < 1 × 10^9
	Hypertriglyceridemia and/or hypofibrinogenemia
	Hemophagocytosis in bone marrow, spleen, or lymph nodes
	Low or absent natural killer cell activity
	Hyperferritinemia
	Soluble interleukin-2 receptor alpha subunit ≥ 2400 U/mL

while secondary HLH is triggered by infections, tumors, or autoimmune diseases[5]. Most studies on HLH involve pediatric patients, while few epidemiological data on adults have been published[6]. An international study in Japan that included children and adults showed that the incidence of HLH was 1/800000[7]. In adults, the proportion of secondary HLH can be as high as 90%. Malignancy, especially lymphoma and leukemia, is the main trigger factor[8]. The 30-d case fatality rate for HLH is approximately 27%[9], while it can reach 53%-57% in the intensive care unit, with sepsis as the main underlying factor[10,11].

HLH lacks typical symptoms in the clinic, resulting in a delay in diagnosis and treatment in most affected patients. Patients may present with persistent high fever, splenomegaly, lymph node enlargement, neurological symptoms, abnormal liver function, and coagulation dysfunction, which deteriorate rapidly to critical illness and shock[12,13]. Statistics on adult HLH show that it takes 1-93 d from the first symptom to diagnosis, and the average time to diagnosis is 10 d[14]. Among these patients, 93%-98% have fever, 84%-86% have splenomegaly, 36%-61% have hepatomegaly, 33%-50% have respiratory dysfunction, 31%-39% have neurological symptoms, and jaundice is present in only 11% of patients [8,14]. Therefore, few HLH patients present with jaundice as the first symptom, and it is crucial to recognize HLH with atypical symptoms and laboratory tests to avoid a delay in treatment.

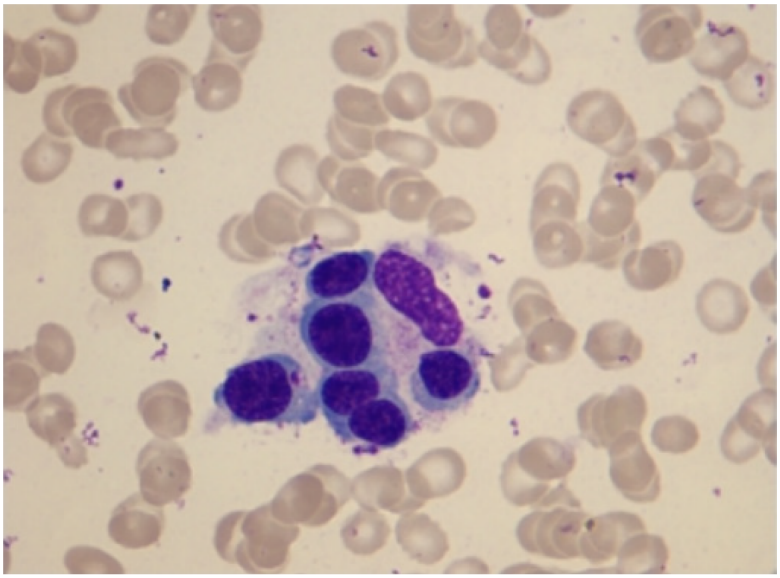

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Figure 1 Hemophagocytosis was identified in the bone marrow.

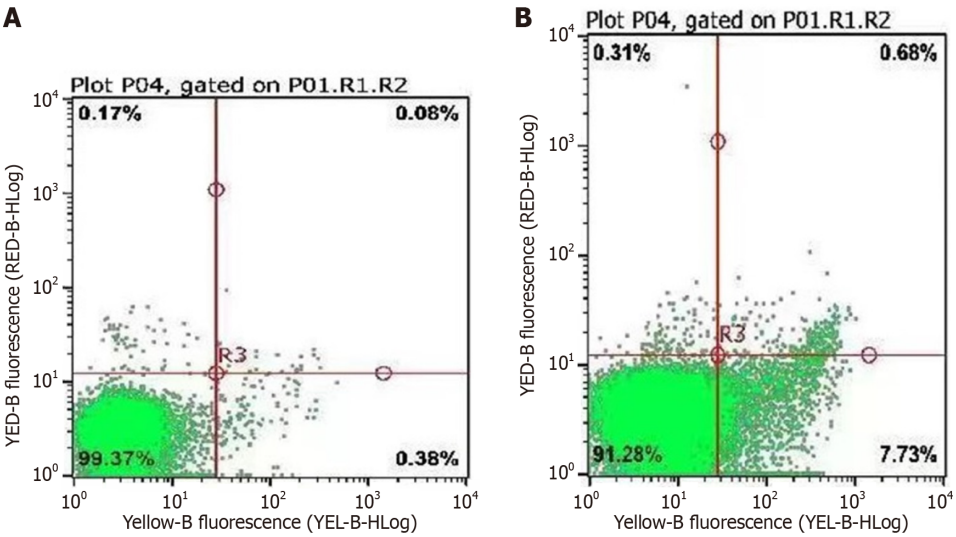

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Figure 2 Natural killer cell activity was significantly decreased. A: Background of natural apoptosis of target cells; B: The killing ratio of natural killer cells to target cells.

The patient in this case report presented with jaundice as the first symptom. Since her elevated aminotransferase and bilirubin levels indicate that her liver did not function normally, we could not exclude the possibility that the jaundice was caused by biliary diseases; however, the jaundice and elevated aminotransferase persisted after the obstruction was resolved and progressively worsened. We consider HLH to be a more critical cause. Only two cases of HLH secondary to cholecystitis were retrieved. One of them did not record elevated bilirubin, and the other reported HLH with gallstones and elevated direct bilirubin, but details were not provided[12,15]. We consulted the literature and found that elevated aminotransferase could be found in the early phase of HLH and was associated with periportal vein lymphocyte infiltration, which means activation of the disease[16]. Elevated direct bilirubin was found in nearly 50% of HLH patients[17-19] and was found to be associated with prognosis[18,20,21]. Higher levels of direct bilirubin are associated with shorter patient survival[22]. A pathological study of liver damage in patients with primary HLH found[23] that lymphocyte-mediated bile duct damage was present in all specimens from HLH patients, and circumferential or clusters of monocytes or lymphocyte cells were interposed between the epithelium and its basal layer. Specimens from some patients showed cholestasis. The injury to the bile duct epithelium was mediated by infiltrating CD8+ and CD4+ T lymphocytes. The bile duct and portal inflammation observed in these specimens were similar to that in primary sclerosing cholangitis or primary cholestatic cirrhosis but without manifestations such as granuloma or bile duct sclerosis.

Treatment mainly follows three approaches[14]: (1) Immunosuppressants such as glucocorticoids, immunoglobulin, alemtuzumab, or etoposide are used to deplete immune cells and interrupt immune activation; (2) organ function support and the prevention of severe bleeding are initiated; and (3) treatment aims to mitigate trigger factors. The diagnosis of HLH was clear in our patient, and the trigger factor was sepsis. Blood culture and bile cultures obtained from the patient were consistent, with both indicating the presence of *Klebsiella acidogenes* and *Enterococcus faecium* (HLAR). Effective anti-infective treatment is crucial[24]. Bergsten's studies have shown that etoposide is effective in improving patient outcomes and can be used as a first-line therapy[25]; however, recent studies have shown that the use of etoposide does not significantly improve survival[26]. In addition, etoposide could suppress immune function, which aggravates infection. For this reason, only glucocorticoids were used to treat the patient in the current study. The patient admitted to our hospital was of advanced age, was in extremely poor general health, had many comorbidities, and died.

CONCLUSION

HLH patients have low morbidity and a high mortality rate, and most of them have nonspecific symptoms. Many patients visit the emergency department first, so it is particularly important to improve the recognition of HLH. Few HLH patients have jaundice as the first symptom. In this patient, the jaundice was thought to be caused by biliary obstruction at first stage, causing elevated aminotransferase and bilirubin, but surgical treatment is ineffective. As the disease progressed, we found that the patient developed fever, splenomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, and elevated ferritin, and her HLH presented jaundice as the first symptom and was triggered by septic shock. We ultimately failed to save her. Clinicians should try hard to discover HLH as early as possible because early diagnosis can improve prognosis.

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FOOTNOTES

Author contributions: Wu S and Kong BB Participated in the treatment process and tried hard to save this patient; Wang DD wrote the manuscript; Wu S and Song LL revised this manuscript; all authors have read and approved the final manuscript.

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CASE REPORT

Comprehensive treatment of deep frostbite of multiple fingers after trauma: A case report

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Abstract

BACKGROUND

Frostbite is becoming increasingly common in urban environments, and severe cases can lead to tissue loss. The treatment goal is to preserve tissue and function; the sooner appropriate treatment is administered, the more tissue can be saved. However, not every patient with deep frostbite seeks medical care promptly.

CASE SUMMARY

We report the case of a 73-year-old male patient who was lost in the wilderness for 2 d due to trauma and confusion. He experienced deep frostbite on multiple fingers. Treatment should not be discontinued for patients with deep frostbite who present after the optimum treatment timing. Bullae that no longer form (bloody) blisters within 24 h of aspiration should be removed. Mucopolysaccharide polysulfate cream has clinical value in frostbite treatment. The patient was transferred to Chinese Academy of Medical Sciences and Peking Union Medical College Hospital 12 h after being rescued. The patient had contraindications for thrombolysis, the most effective treatment, due to intracranial hemorrhage and presenting past the optimum treatment timing. We devised a comprehensive treatment plan, which involved delayed use vasodilators and high-pressure oxygen therapy at day 49 post-injury. We experimented with mucopolysaccharide polysulfate cream to treat the frostbite. The aim of the treatment was to safeguard as much tissue as possible. In the end, the fingers that suffered from frostbite were able to be partially preserved.

CONCLUSION

The case indicated that patients with severe frostbite who missed the optimal treatment time and had contraindications for thrombolysis could still partially

preserve the affected limbs through comprehensive treatment.

Key Words: Frostbite; Wound care; Mucopolysaccharide polysulfate cream; Case report

Core Tip: Frostbite, increasingly common in urban areas, requires swift treatment for tissue preservation. Not all deep frostbite cases receive prompt medical attention. A 73-year-old male, lost in the wilderness for 2 d post-trauma, presented with deep frostbite on multiple fingers. Despite a 12-h delay, he received comprehensive, delayed treatment at the Chinese Academy of Medical Sciences and Peking Union Medical College Hospital. Contraindications for thrombolysis led to an alternative plan, including extended vasodilator use and high-pressure oxygen therapy from day 49 post-injury. This case emphasizes the vital importance of timely frostbite treatment and offers insights into managing delayed cases with contraindications.

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INTRODUCTION

Frostbite is damage caused by the acute freezing of tissues exposed to extremely low temperatures. The severity of the injury depends on the temperature gradient of the skin surface and the duration of exposure. Severe cases can lead to permanent damage or even be life-threatening[1]. In recent decades, the incidence of frostbite has shifted from military personnel to the general population, particularly among those residing in cold environments. Frostbite is more frequent in persons with alcohol use disorder, mental health challenges, those with accidental injuries, and socially disadvantaged groups[2]. Currently, no consistent grading system exists for frostbite. One approach classifies it into first to fourth degrees based on the depth of tissue freezing[3]. For clinical purposes, frostbite is more commonly classified into superficial (grades 1 and 2) and deep frostbite (grades 1 and 2)[4]. Two distinct time periods characterize the response to frostbite: The pre-response period (stage of cold exposure that lasts until the tissue warms up) and the response period, which is further subdivided into the early response period (from tissue rewarming to the first day) and the late-response period (from the second day onward)[5]. Frostbite is best treated with consistent and effective treatment plans during the pre-response and early response periods. However, treatment plans for late-response frostbite vary widely and involve a long treatment cycle with an unclear prognosis. For deep frostbite, the treatment aims to reduce the area of the limb affected and improve limb function as much as possible. Studies have shown that most deep frostbite cases result in amputation[6-8]. Thrombolytic therapy within 24 h of frostbite can significantly reduce tissue damage[9]. Here, we report a case involving severe frostbite of several fingers of a 73-year-old man who had faced trauma and went missing for 48 h.

CASE PRESENTATION

Chief complaints

A 73-year-old man went missing following a car accident. When the rescue team found him, he had severe facial swelling, purple bruising, and scabbing. He could not open his eyes voluntarily, had frozen hands, and could not make a fist.

History of present illness

On January 18, 2023, at 06:00 PM, the patient was admitted to our emergency department after he had been missing for 2 d following a car accident. He experienced retrograde amnesia and impaired localization of function after being hit on the head on January 16, 2023, at around 03:00 PM. He went missing and was found by a rescue team in a neighboring village after 2 d. The incident occurred in winter, with the lowest nighttime temperature reaching -18 °C. Upon presentation at our emergency department, the patient underwent a head computed tomography (CT) scan, which revealed a left frontal lobe contusion, a small hematoma, left frontal bone and bilateral orbital fractures, and a subarachnoid hemorrhage, suggesting contraindication for thrombolysis. Additionally, the patient had frostbite on all ten fingers and a soft tissue contusion in the left orbit. The patient had no history of smoking or drinking and no other medical history except for a self-reported untreated twist injury on the right ring and little fingers. The medical history was confirmed by his daughter.

The patient was dehydrated and weak, having not drunk or eaten in the 2 d when he was missing. He fell asleep in a thicket and was found wearing a cotton hat, clothes, and shoes, with only his hands exposed. When the rescue team found the patient, he had severe facial swelling, purple bruising, and scabbing. He could not open his eyes voluntarily,

had frozen hands, and could not make a fist. Due to limited medical treatment in the area, the patient was transported by ambulance for 8 h. During this time, he received peripheral intravenous glucose and sodium chloride, and his hands were placed under his family member's armpits for rewarming.

The patient was admitted to the general surgery ward at night and received an intramuscular injection of 250 IU tetanus human immunoglobulin. Laboratory tests were immediately performed; the abnormal results are listed in Table 1.

Physical examination revealed swollen joints in the patient's hands. His fingers were frostbitten to varying degrees, with all ten fingers having cool skin and dark purple fingertips. Severe water blisters were observed on all five fingers of the right hand. The patient's fingers were cleaned and wrapped with gauze after the ulcer was cleaned and then covered with a warm blanket. The patient received continuous intravenous fluid therapy and ertapenem. The following morning, the patient's hands were severely swollen. All ten fingers were clubbed with large, tense, and bloody blisters (Figure 1A and B). The first, second, and fifth fingers of the left hand and the first finger of the right hand had superficial frostbites, whereas the third and fourth fingers of the left hand and the second to fifth fingers of the right hand had deep frostbites. We conducted a multidisciplinary consultation with the Departments of Plastic Surgery, Dermatology, and Vascular Medicine, and a wound specialist nurse intervened in the treatment.

History of past illness

The patient had no history of smoking or drinking and no other medical history except for a self-reported untreated twist injury on the right ring and little fingers.

Physical examination

Physical examination revealed swollen joints in the patient's hands. His fingers were frostbitten to varying degrees, with all ten fingers having cool skin and dark purple fingertips. Severe water blisters were observed on all five fingers of the right hand.

Laboratory examinations

Laboratory examinations showed the following results: Lymphocytes (%) 6.2 (reference range: 20.0-40.0); C-reactive protein 30.40 (≤ 8.00) mg/L; neutrophils (%) 85.6 (50.0-75.0); amylase 537 (35-135) U/L; white blood cell count 9.95 (3.50-9.50) × 10^9/L; total bilirubin 43.6 (5.1-22.2) μmol/L; red blood cell count 3.14 (4.00-5.50) × 10^{12}/L; direct bilirubin 16.3 (≤ 6.8) μmol/L; hemoglobin 115 (120-160) g/L; myoglobin 1043 (≤ 110) μg/L; prothrombin time 12.9 (10.4-12.6) s; creatine kinase 3022 (24-195) U/L; D-dimer 3.18 (0-0.55) mg/L fibrinogen equivalent units; creatine kinase-mass 43.3 (≤ 5.0) μg/L.

Imaging examinations

Upon presentation at Chinese Academy of Medical Sciences and Peking Union Medical College Hospital emergency department, the patient underwent a head CT scan, which revealed a left frontal lobe contusion, a small hematoma, left frontal bone and bilateral orbital fractures, and a subarachnoid hemorrhage.

Magnetic resonance imaging (MRI) revealed a small effusion in the second to fifth metacarpophalangeal joints on the left side, subcutaneous soft tissue swelling on the palmar side of the left hand, and cystic changes in the proximal phalanx of the middle finger of the left hand. Multiple cystic lesions were observed at the proximal and distal ends of the first metacarpal bone and the distal end of the second proximal phalanx of the right hand. Effusion was observed in the second, third, and fourth metacarpophalangeal joints, and soft tissue swelling was observed around the second and third metacarpophalangeal joints.

FINAL DIAGNOSIS

Traumatic brain injury and deep frostbite of multiple fingers.

TREATMENT

On day 1, after iodine disinfection, a suction bubble solution and low-position drainage were applied to protect the blistered skin. The blister fluid on the left hand was yellow, clear, and transparent, whereas the blister fluid on the right hand was slightly blood-tinged, clear, and transparent. The patient's hands were soaked in 50 mL of chlorhexidine acetate solution and 1000 mL of warm water at 37 °C-40 °C twice daily. After a warm water bath, mupirocin cream was externally applied, and the ulcer was wrapped with gauze. The patient reported no numbness or pain.

On day 2, the water-like blisters on the left hand and blood blisters on the right hand were still present, and the purple color had improved. The edges retreated towards the fingertips. The blister fluid was suctioned daily, and mupirocin and burn moist cream (MeiBao, MEBO) were externally applied. The patient reported experiencing sensation when his ten fingers were scraped with a cotton swab (Supplementary Figure 1). When the patient went to the examination room for CT, he accidentally injured the skin on their right index finger. The comprehensive treatment plan is highlighted in Table 2.

On day 3, the patient could not undergo tissue plasminogen activator (tPA) treatment due to anticoagulation contraindications and was administered an alprostadil injection (10 μg IV qd) for 12 consecutive days. On day 4, he was also

Table 1 Abnormal laboratory results at the patient's first admission

Item	Value	Reference range
Lymphocytes (%)	6.2	20.0-40.0
Neutrophils (%)	85.6	50.0-75.0
White blood cells (L)	9.95×10^9	3.50-9.50
Red blood cells (L)	3.14×10^{12}	4.00-5.50
Hemoglobin (g/L)	115	120-160
Prothrombin time (s)	12.9	10.4-12.6
D-dimer (mg/L FEU)	3.18	0-0.55
C-reactive protein	30.40	≤ 8.00
Amylase (U/L)	537	35-135
Total bilirubin (μmol/L)	43.6	5.1-22.2
Direct bilirubin (μmol/L)	16.3	≤ 6.8
Myoglobin (μg/L)	1043	≤ 110
Creatine kinase (U/L)	3022	24-195
Creatine kinase-mass (μg/L)	43.3	≤ 5.0

Table 2 Treatment plan for the patient's injured right index finger

Date	Therapeutic process
Day 2	The wound appeared red and well-circumscribed. After applying a thick layer of bacitracin ointment, it was covered with petroleum gauze, and the dressing was changed daily
Day 3-6	Epidermal growth factor gel, silver ion gel, and povidone-iodine were used to cover the calcium alginate dressing to prevent wound infection. Ulcer oil gauze and plain gauze were wrapped around the wound (Figure 1C and D)
Day 7	Epithelialization of the wound was performed (Figure 2C).
Day 9	The newly regenerated epidermis underwent crust formation (Figure 2D)
Days 12-16	The scab gradually shed off from initial formation to complete detachment (Figure 3D)

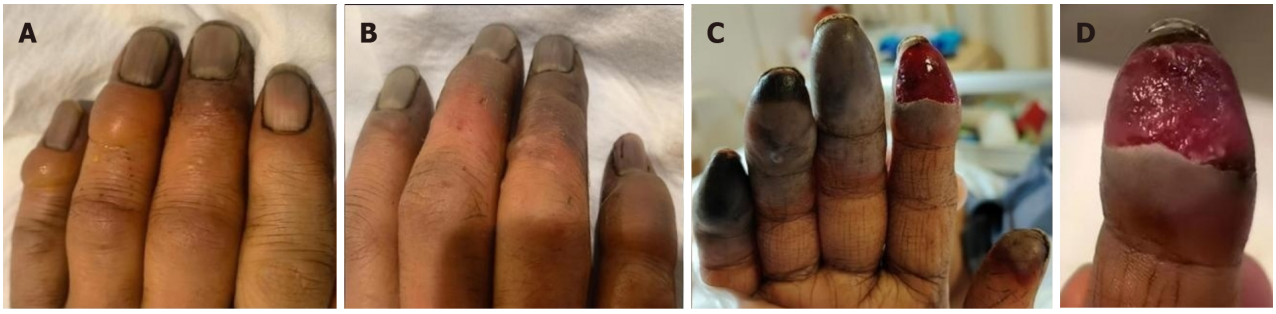

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Figure 1 Changes in frostbite during one week in hospital. A and B: On day 1, after 24 h of rewarming, there was noticeable swelling in the fingers accompanied by the presence of large blisters or blood blisters, but no reported pain; C: On day 4, there was a scab on the tips of the right fourth and fifth fingers, and the skin on the index finger was red where it was broken; D: On day 5, new tissue growth was observed at the site of broken skin on the index finger.

orally administered 60 mg of loxoprofen sodium every 12 h. The tips of the third, fourth, and fifth fingers of the right hand turned black (Figure 1C). On day 5,there was no sign of infection on the index finger of the right hand (Figure 1D). The blister fluid was suctioned daily until it disappeared on day 7. The black area gradually expanded near the first finger joint. The frostbite on the tips of the left fingers gradually formed a dark red soft shell (Supplementary Figure 2).

On day 8, mucopolysaccharide polysulfate cream was applied to the abnormally colored skin of the ten fingers, and the patient was administered oxygen *via* a nasal cannula at a rate of 2 L/min. The patient's fingertips were dry, wrinkled, and

had reduced volume (Figure 2A). Therefore, total parenteral nutrition was administered. On day 9, the patient took mecobalamin (0.5 g) orally three times daily, and we found that the new epithelium of the right index finger had turned into a black scab (Figure 2B). On day 12, the chlorhexidine acetate warm water bath was discontinued, and Sanyrenewas externally applied (Figure 2C).

On day 13, the patient underwent MRI and radiography of both hands. The radiographic image was normal. The MRI revealed a small effusion in the second to fifth metacarpophalangeal joints on the left side, subcutaneous soft tissue swelling on the palmar side of the left hand, and cystic changes in the proximal phalanx of the middle finger of the left hand. Multiple cystic lesions were observed at the proximal and distal ends of the first metacarpal bone and the distal end of the second proximal phalanx of the right hand. Effusion was observed in the second, third, and fourth metacarpophalangeal joints, and soft tissue swelling was observed around the second and third metacarpophalangeal joints.

On day 15, the black and hard scabs on the first joint of the back of the left hand were removed, and the patient could make a fist. The patient reported occasional pain in the little finger of the right hand and was administered 50 mg of etoricoxib tablets orally every 12 h. On day 16, the scabs on the back and fingertip of the left hand and the index finger of the right hand were removed after soaking them in warm water (Figure 2D; Supplementary Figure 3), and subsequently, the patient was discharged.

OUTCOME AND FOLLOW-UP

After discharge, the dry and hard scabs at the edges were gradually removed by the patient, and the nails gradually fell off (Figure 3A). On day 22, the broken index finger on his right hand has healed (Figure 3B). By day 27, the patient experienced noticeable constriction and swelling in the ring and little fingers of the right hand. The blackened edge of the scab was removed, revealing fresh tissue at the bottom. The edge of the black scab was shaved using a blade to relieve pressure (Supplementary Figure 4). Between day 49 and day 67, the patient underwent 20 sessions of hyperbaric oxygen therapy (HBOT) (Figure 3C). On day 90, the tips of the third finger of the right hand turned black and were deformed, necessitating a planned self-amputation (Supplementary Figure 5). On day 180, the tips of the fourth and fifth fingers of the right hand were amputated (Figure 3D).

DISCUSSION

Historically, frostbite injuries have occurred primarily during large-scale military operations. However, in recent years, it has impacted individuals living in cold environments in peaceful areas[1]. In China, people residing in temperate plains rarely experience frostbites[5,8]. Consequently, many hospitals, including the one mentioned in this report, lack established frostbite treatment protocols and experience, resulting in treatment delays for patients. On the second day after the patient was admitted to our hospital, we organized a multidisciplinary consultation involving neurosurgeons, orthopedics, vascular surgeons, dermatologists, plastic surgeons, general surgeons, and wound care nurses to devise a treatment plan led by the wound care nurses. We believe that treatment should not be discontinued for patients with deep frostbite who present after the optimum treatment timing. Bullae that no longer form (bloody) blisters within 24 h of aspiration should be removed. Mucopolysaccharide polysulfate cream has clinical value in frostbite treatment.

Frostbites can cause both cellular and ischemic vascular damage. Continuous freezing of body tissues leads to the formation of ice crystals in the extracellular fluid, which damages the cell membrane and alters the osmotic pressure of the cells, resulting in cell damage. When exposed to cold conditions, the body undergoes a physiological reaction to protect the limbs from cold-induced damage through a system of alternating vasoconstriction and vasodilation processes, known as the "hunting reaction". However, this physiological reaction causes severe damage, including progressive thrombosis and tissue ischemia[2,3]. When formulating a treatment plan, it is essential to determine the patient's exposure time to the cold. Unfortunately, in this case, the patient was lost for 2 d, and the exposure time to cold could not be determined. Therefore, we calculated the frostbite time and exposure time to the cold from the first day when he went missing until the patient was sent to the ambulance, which was approximately 36 h. The day of admission was designated as day 0 after the frostbite.

Unlike other skin injuries, the extent of frostbite gradually becomes apparent upon tissue rewarming, and the initial photographs do not show the extent of the injury[10]. Injuries are clinically classified into four grades according to the depth of the tissue frostbite[3]. Grade 1 injuries involve only the superficial skin layer frostbite, exhibiting white spots at the center surrounded by redness. Grade 2 injuries involve full-thickness skin freezing, resulting in the development of large clear blisters with redness and swelling around them within 24 h of rewarming. Grade 3 injuries involve subcutaneous tissue freezing, leading to tissue necrosis, hemorrhagic blisters, bluish-gray wax-like skin appearance, and black scab formation. Grade 4 injuries involve muscle, tendon, and bone freezing, resulting in the formation of hard black scabs and tissue mummification, ultimately necessitating amputation[3,4,11]. Another simple grading system includes superficial (grades 1-3) and deep injuries (grades 3 and 4). Superficial injuries rarely involve tissue loss, whereas deep injuries result in more extensive tissue loss and a generally poor prognosis[12]. Studies have shown that fluorescence microscopy angiography in the emergency department can rapidly identify perfusion defects after frostbite[13]. The accuracy of evaluating amputation levels can reach 84% when Technetium-99 bone scanning is performed on the second day after rewarming from frostbite[14]. Unfortunately, only an MRI scan was performed in this case.

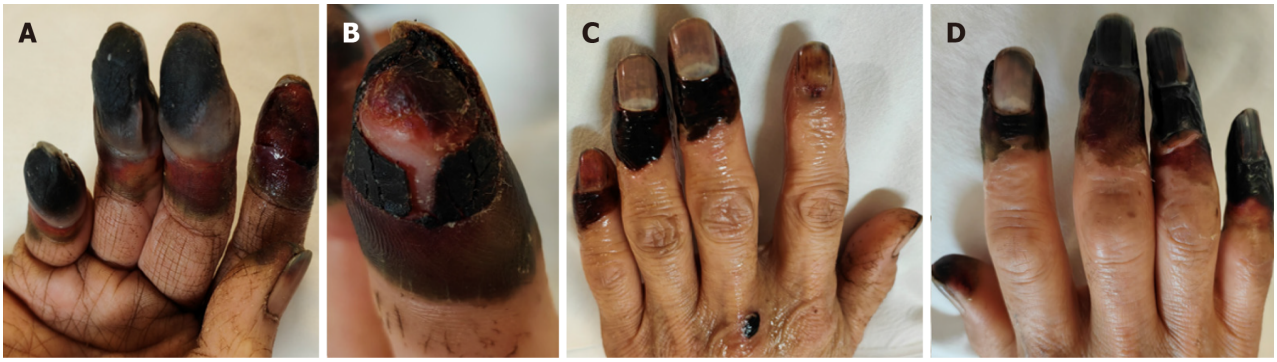

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Figure 2 Frostbite changes from one week after hospitalization to discharge. A: On day 8, the skin on the right third, fourth, and fifth fingers wrinkled and shrank, and the area covered by scabs rapidly expanded; B: On day 9, new tissue formed. It created a scab on the tip of the index finger, which eventually fell off after drying; C: On day 12, there was a hard black scab on the back of the left hand and a slightly softer, dark red scab on the palm; D: On day 16, when the patient was discharged, the tips of his right finger were covered in hard, black scabs.

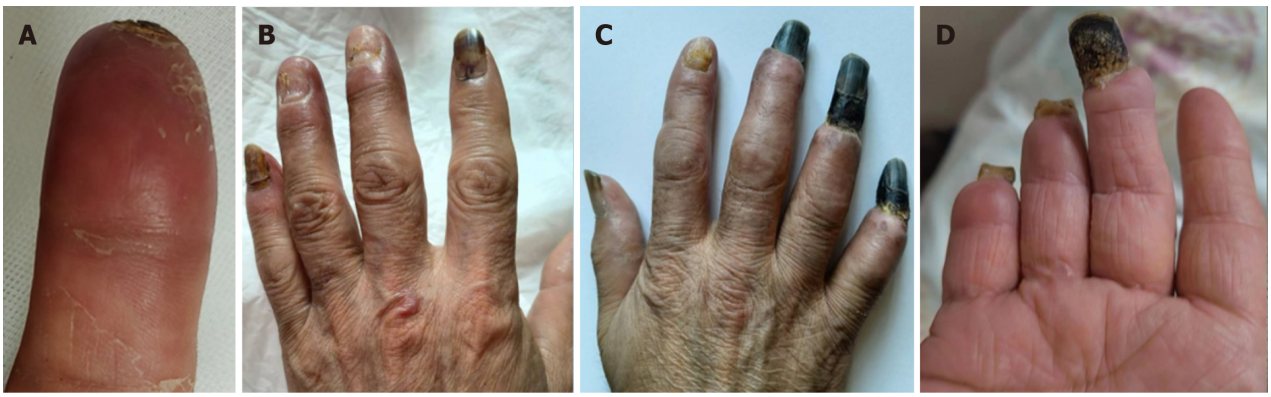

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Figure 3 Progression of frostbite outcomes. A: The nails on the fourth and fifth fingers of the left hand fell off, and the nail on the index finger was about to fall off; B: On day 22, the injury to the patient's right index finger completely healed; C: On day 67, after hyperbaric oxygen therapy, the tips of the right third, fourth, and fifth fingers had dried and shrunk; D: Six months after the injury, the patient's right fourth and fifth fingers were amputated, and the third finger was about to fall off.

Utilizing a water bath at 37 ℃-39 ℃ is generally recommended to prevent further damage to soft tissues during the rewarming stage for frostbite on-site[12]. Currently, there is no evidence-based protocol for frostbite hydrotherapy regarding the temperature, time, frequency, and duration after rewarming. In the present case, the patient underwent hydrotherapy on the first day after admission. The hydrotherapy treatment plan involved soaking the affected area in 1000 mL of warm water at 37 ℃-40 ℃ with a chlorhexidine acetate solution for 20 min, twice daily, for 12 d. Although no infections occurred during this treatment, its impact on promoting frostbite rehabilitation was found to be insignificant.

Frostbite is a thrombotic injury, and an increasing number of medical teams are attempting to use thrombolysis within 6-24 h after frostbite to salvage tissue in affected patients[9,15]. Early treatment with tPA can prevent amputation in 85%-90% of cases[16]. The Helsinki frostbite management protocol recommends the combined use of tPA and iloprost (a prostacyclin analog) to improve the prognosis of severe frostbite[17]. Cauchy *et al*[7] found that iloprost treatment alone for 8 d effectively prevents tissue loss.

The combination of aspirin and prostacyclin for stage 3 or higher frostbite is recommended, especially within 48-72 h of rewarming[18,19]. However, this patient had contraindications for thrombolysis due to combined trauma and intracranial hemorrhage; therefore, the thrombolysis treatment plan was abandoned. Iloprost was unavailable due to the limitations of the medicine used in our hospital. Consequently, prostaglandin E1, which is another vasodilator, was administered at a dosage of 10 μg/d approximately 80 h after rewarming.

The formation of blisters represents a distinct characteristic in the degree of the injury. Drainage is recommended because blister fluid contains high concentrations of anti-inflammatory substances, such as prostaglandin F2 alpha and thromboxane A2, which prevent the healing of the lower skin layers. However, controversy exists regarding the treatment of bleeding blisters, as there is a risk of bleeding during debridement[1,4]. In this case, both transparent and bleeding blisters were aspirated, and the blister skin was preserved. However, on the second day following the frostbite incident, the blistered skin on the patient's right index finger was accidentally torn during an outpatient CT examination. After using anti-infective dressings for 7 d, a black scab formed on the newly generated epidermis of the patient's right index finger. The scab eventually detached, and the finger completely healed without any tissue loss. Blood-blistered skin

on the third, fourth, and fifth fingers of the same hand also developed into hard black scabs. On day 24, the patient experienced significant constriction pain in the fourth and fifth fingers of the right hand. Subsequently, on day 26, the hard black scab near the junction was thinned using a blade, leading to a significant reduction in the patient's pain. Simultaneously, the hard black scab was divided into two layers, with dry blood scabs in between. This observation may indicate that third-degree frostbite had damaged the dermis layer, and despite the newly formed epidermis, the skin layer turned black and scabbed. This scab combined with the dry blistered skin, forming a hard black scab that hindered the growth of new tissue. Therefore, if no new blisters formed within 24 h of aspiration treatment, debridement of the blistered skin would have been considered.

The 2019 Clinical Practice Guidelines[12] for the prevention and treatment of frostbite released by the Wilderness Medical Society suggests that the topical application of aloe vera gel can reduce the formation of prostaglandins and thromboxanes, thereby improving frostbite outcomes. However, aloe vera gel only benefits superficial injuries and does not penetrate deeply into tissues. In this case, the mucopolysaccharide polysulfate cream was used for external treatment, marking the first report of its application in frostbite treatment. The main active ingredient of mucopolysaccharide polysulfate cream is mucopolysaccharide polysulphate (MPS), which is chemically similar to heparin, being described as heparin-like. It accelerates the recovery of the permeability barrier and hydration of the stratum corneum, thus exerting antithrombotic and anti-inflammatory effects[20]. The study by Livaoğlu *et al*[21] showed that local application of mucopolysaccharide polysulfate cream could improve the survival rate of rat skin flaps. MPS can penetrate the human skin, with trace amounts entering the circulation, thereby affecting the coagulation system. In this case, the mucopolysaccharide polysulfate cream was externally applied for 14 consecutive days after the patient's intracranial hemorrhage had stabilized (day 8). Mucopolysaccharide polysulfate cream promotes the resolution of edema and bruises[22]. Mucopolysaccharide polysulfate cream is used to treat venous inflammation at our hospital. Further investigation into the potential therapeutic effects of early mucopolysaccharide polysulfate cream application post-frostbite rewarming should be explored.

HBOT is an important adjunct for frostbite treatment. During HBOT, patients inhale high concentrations of oxygen within a pressurized chamber. This oxygen dissolves in the plasma and increases the oxygen partial pressure to over 20 times that of breathing indoor air at normal atmospheric pressure, resulting in hyperoxygenated plasma. This hyperoxygenated plasma can then be transported to hypoxic or ischemic tissues, promoting angiogenesis, reducing edema, and increasing the basal metabolic rate[23]. Masters *et al*[24] reported a 90% survival rate in a patient with severe frostbite after 20 sessions of HBOT combined with thrombolysis. Additionally, Kemper *et al*[25] reported a case where delayed HBOT treatment (21 d) resulted in positive outcomes for a patient with deep frostbite in the toes. However, HBOT for frostbite has potential side effects, including ear barotrauma, nausea, vomiting, anxiety, oxygen toxicity, and myopia changes[26]. Therefore, its application should be carefully considered based on the patient's condition. In this case, the patient received HBOT on day 49 after the frostbite incident and reported significant pain in the affected finger during the treatment period, possibly related to increased blood circulation at the injury site. Therefore, delayed HBOT may be beneficial for wound healing; this merits further investigation.

CONCLUSION

Treatment timing plays a crucial role in frostbite recovery, and prompt treatment should be provided for deep frostbite with a risk of tissue loss. For blisters that are no longer filled within 24 h, de-roofing of the blisters can be attempted while maintaining a moist wound environment to prevent infection. Amputation should be carefully considered, as some medical institutions lack the necessary equipment to detect tissue perfusion at the injury site. Conservative observation of dry black scabs may reveal viable tissues, warranting patients with such scabs to await self-amputation of necrotic tissues. Mucopolysaccharide polysulfate cream has application value in frostbite treatment and can be externally applied to intact frostbite tissues after rewarming. This case provides insights into managing deep frostbite with contraindications for thrombolysis or missed optimal treatment timing. During the 6-mo follow-up post-injury, we found that the patient was anxious due to the uncertainty of the time of self-amputation. Attention should be paid to the patient's psychological state.

FOOTNOTES

Co-first authors: Xi-Hua Wang and Min Li.

Co-corresponding authors: Guo-Le Lin and Wei-Nan Liu.

Author contributions: Wang XH supported the management of this case, collated information for and drafted this report, and managed manuscript revisions; Li M and Cheng Y supported the management of this case and collated information for and drafted this report; Wang XH, Li M, and Cheng Y contributed equally to this work; Lin GL and Liu WN supported in the management of this case and were responsible for revising the manuscript; Wang GJ supported the management of this case; all authors issued final approval for the submission of the manuscript; Wang XH supported the management of this case (was in charge of the care of this case), collated information for and drafted this report, and managed manuscript revisions (revised the manuscript); Li M supported the management of this case (was also in charge of the patient) and collated information for and drafted this report; Wang XH and Li M contributed equally to this work. Wang XH and Li M work together in the same department for a long time. Li M is the leader of this department. They had a graduate advisor in common. Wang XH and Li M are both enterostomal therapists, dedicated to the treatment of wounds and ostomies.

In this case, Wang XH and Li M worked together to review the data, and develop and validate treatment plans. They followed this case for 6 mo. Both of them drafted this report. Lin GL is the chief physician and the primary person in charge of the treatment of this case, providing medical guidance and oversight. Liu WN is the deputy chief nurse, an expert in surgical nursing, and the leader of the surgical nursing team, giving guidance and oversight on the nursing plan. In the treatment process of this case, we tried new treatment methods. Lin GL and Liu WN gave us help in the feasibility and effectiveness of the treatment process. They were jointly responsible for the review and revision of this article and the whole process of submission. Lin GL and Liu WN contributed equally to this work.

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CASE REPORT

Bilateral snapping triceps syndrome: A case report

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Abstract

BACKGROUND

Snapping triceps syndrome (STS) is a rare disease, while occurrence of bilateral STS is extremely rare. It is usually accompanied by dislocation of the ulnar nerve and double snapping is a clinically important feature. However, to the best of our knowledge, there has been no report of bilateral STS in young active patient.

CASE SUMMARY

A 23-year-old male presented with a complaint of discomfort and snapping on the medial side of both elbows while performing push-ups. On physical examination, two distinct snaps that were both palpable and audible were detected on additional clinical examination. Dynamic ultrasonography showed that the ulnar nerve and the medial head of the triceps were dislocated anteriorly over the medial epicondyle of the elbow during flexion motion. Finally, he was diagnosed as dislocation of the ulnar nerve and STS. Staged anterior subcutaneous transposition of the ulnar nerve combined with partial resection of the snapping portion of the triceps was performed. The patient's pain and snapping symptoms were resolved immediately after surgery. Three months later, the patient was completely asymptomatic and returned to normal activity.

CONCLUSION

STS should be included in the differential diagnosis for active young patients who present with painful snapping on the medial side of the elbow joint, particularly when dislocation of the ulnar nerve is detected. Dynamic sonography is used to assist in accurate diagnosis and differentiation between isolated dislocation of the ulnar nerve and STS.

Key Words: Triceps; Triceps snapping syndrome; Ulnar nerve; Elbow; Dynamic sonography; Case report

Core Tip: Snapping triceps syndrome (STS) is a rare disease, while occurrence of bilateral STS is extremely rare. It is usually accompanied by dislocation of the ulnar nerve and double snapping is a clinically important feature. Dislocation of the ulnar nerve typically occurs first, at approximately 70 to 90 degrees of elbow flexion, followed by dislocation of the triceps at approximately 100 to 110 degrees of elbow flexion. Dynamic sonography is used to assist in accurate diagnosis and differentiation. Here we reported on the case of a patient who underwent surgery for treatment of bilateral STS.

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INTRODUCTION

Snapping triceps syndrome (STS), a relatively rare disease, was first described by Rolfsen in 1970. It is defined as a dynamic phenomenon involving dislocation of the distal portion of the triceps over the medial epicondyle of the elbow[1-3]. Risk factors include cubital valgus or varus, hypertrophy or prominence of the distal triceps muscle, or accessory head of the triceps. STS is more common in abnormal triceps position as well as individuals who perform manual work related to hypertrophy of the triceps muscle through training[4,5]. Movement of the bulked medial triceps is more medial, which causes translocation (snapping) of a portion of the triceps over the medial epicondyle with flexion of the elbow[4].

Patients usually complain of local tenderness and a snapping sensation or sound around the medial side of the elbow. Because the condition usually involves coexistence with ulnar nerve dislocation, neuropathy of the ulnar nerve may also be observed. Two distinct snapping sounds can be detected in patients with typical STS. Dislocation of the ulnar nerve typically occurs first, at approximately 70 to 90 degrees of elbow flexion, followed by dislocation of the triceps at approximately 100 to 110 degrees of elbow flexion[6]. Confirmation of two characteristic snapping sounds around the medial side of the elbow during flexion is important. Recently, dynamic sonography is used to assist in accurate diagnosis and differentiation from diseases around elbow[7-11].

To the best of our knowledge, no previous cases of bilateral STS have been reported. Here we reported on the case of a patient who underwent surgery for treatment of bilateral STS.

CASE PRESENTATION

Chief complaints

A 23-year-old male, an amateur bodybuilder, presented with a complaint of discomfort and snapping on the medial side of both elbows while performing push-ups for three years.

History of present illness

His symptoms had worsened over the past two months. The pain, along with the snapping sound, then became constant with development of an intermittent tingling sensation on the ulnar side forearm and 5th finger area. In particular, the symptoms were aggravated by both resisted elbow flexion and resisted elbow extension.

History of past illness

Because he primarily regarded his symptoms as an inconvenience, he did not undergo treatment.

Personal and family history

The patient was a college student with no history of elbow surgery, and there was no history of trauma or sport injury as well. There was no other past illness or family history.

Physical examination

On physical examination, tenderness over the medial epicondyle of the elbow was not observed and there were no clinical findings indicative of ulnar nerve compression. Two distinct snaps that were both palpable and audible were detected on additional clinical examination. The first snap had developed at approximately 90 degrees of elbow flexion and the second snap had developed at above 100 degrees of elbow flexion.

Laboratory examinations

The results of preoperative laboratory tests were normal.

Imaging examinations

No bony abnormality such as cubitus varus or valgus was observed on the plain radiographs. A T2-weighted magnetic

resonance image (MRI) showed a high signal change and swelling of the ulnar nerve (Figure 1). Dynamic ultrasonography showed that the ulnar nerve was dislocated anteriorly over the medial epicondyle of the elbow in flexion of the elbow by 90 degrees and the medial head of the triceps was also dislocated anteriorly over the medial epicondyle in flexion of the elbow by 100 degrees (Figure 2).

FINAL DIAGNOSIS

The final diagnosis of the presented case was bilateral STS of elbow joints.

TREATMENT

Conservative treatment was initially considered. However, the patient was an amateur bodybuilder who usually participated in several sports activities, and he wanted to anticipate returning to participation in sports as soon as possible. Therefore, surgery on the left elbow, which showed more severe symptoms, was planned. Anterior subcutaneous transposition of the ulnar nerve combined with partial resection of the snapping portion of the triceps was our surgical treatment of choice. After inflating a tourniquet, an 8 cm incision was made from 4 cm proximal to 4 cm distal of the medial epicondyle. During performance of the subcutaneous dissection, the medial antebrachial cutaneous nerve was located, and care was taken to avoid damaging it. The ulnar nerve was thickened and dislocated from the posterior to the anterior of the medial epicondyle with flexion of the elbow by 90 degrees (Figure 3). Neurolysis was performed using a vessel loop and the ulnar nerve was mobilized sufficiently to transpose it anteriorly without tension. With further flexion of the elbow, the leading edge of the medial head of the triceps was dislocated over the medial epicondyle. The minimum extent of the dislocated medial head of the triceps was measured by repeat passive flexion of the elbow and the medial head of the triceps, and was located over the medial epicondyle, was resected (Figure 4). After resection, it was confirmed that flexion of the elbow did not cause any dislocation of the triceps. Hemostasis was performed after the tourniquet was delated. Postoperatively, passive motion was subsequently initiated as pain permitted. Active mobilization was allowed after one week and no snap was observed on physical examination. He had no complaint of discomfort after three months of follow up, therefore, surgery on the right elbow was planned. The surgical method was the same as that used for the left side. The ulnar nerve was also thickened and dislocated from the posterior to the anterior of the medial epicondyle with flexion of the elbow by 80 degrees. After dissection and mobilization of the anterior of the ulnar nerve, the bulked-leading edge of the medial head of the triceps was also dislocated over the medial epicondyle with further flexion of the elbow (Figure 5) (Video 1). The minimum extent of the dislocated medial head of the triceps was measured by repeat passive flexion of the elbow and the medial head of the triceps, measuring 3 cm, located over the medial epicondyle, was resected. After resection, anterior transposition of the ulnar nerve was performed (Figure 6).

OUTCOME AND FOLLOW-UP

The patient's pain and snapping symptoms showed significant improvement after surgery. Dynamic ultrasonography showed that the ulnar nerve and triceps were not dislocated during flexion and extension of the elbow at six weeks postoperatively. Three months later, the patient was completely asymptomatic and returned to participation in sports. And during the one-year follow-up, there were no symptoms in both elbows.

DISCUSSION

This case involves a rare disorder with STS in a bilateral elbow joint. STS with dislocation of the ulnar nerve can be easily overlooked when dislocation of the ulnar nerve and triceps occurs simultaneously at a similar angle during flexion of the elbow, resulting in detection of only one snapping sound, or when the second snapping sound is missed on physical examination. In particular, in cases where this disease is not considered, it is often misdiagnosed as isolated dislocation of the ulnar nerve.

Isolated dislocation of the ulnar nerve is relatively common, occurring in approximately 16.2% of healthy adults (subluxation: 12%, complete dislocation: 4%)[12] Causes include congenital general laxity, hypoplasia of the trochlea, and dislocation of the medial head of the triceps with or without cubitus varus/valgus deformity[13-15]. Also, several authors insisted that cubitus varus or valgus, fourth muscular head of the triceps, or accessory triceps tendon and hypertrophy of the medial head of the triceps are risk factors for STS[14-16]. However, in our case, there were no risk factors such as congenital general laxity, bony abnormalities or anatomical variances of the triceps were detected. The patient had performed several strengthening exercises, thus the bulk of the triceps could be confirmed. Therefore, we considered that the bulk of the medial head of the triceps may have caused STS.

MRI or dynamic ultrasound can assist in the diagnosis of snapping triceps syndrome. Although MRI can enable accurate identification of anatomical structures of the elbow joint, there is limitation in identifying dislocation or

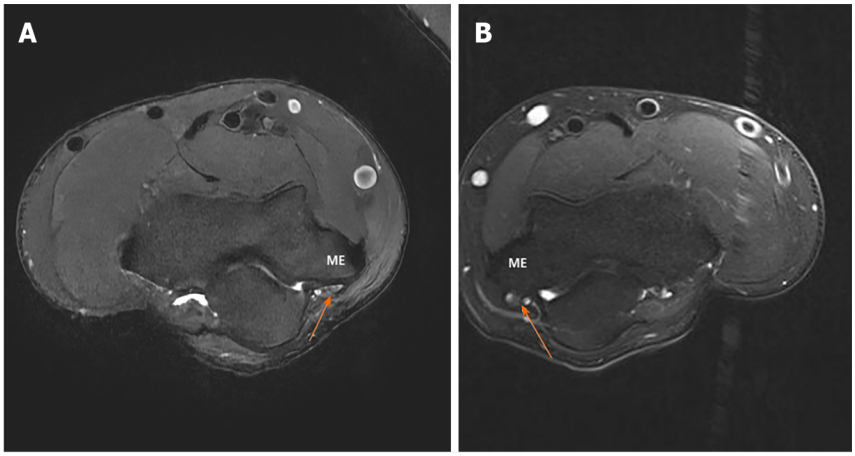

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Figure 1 Pre-operative axial T2-weighted magnetic resonance image shows the high signal change and swelling of the ulnar nerve. A: Rt. Elbow; B: Lt. Elbow. Arrow: Ulnar nerve, ME: Medial epicondyle.

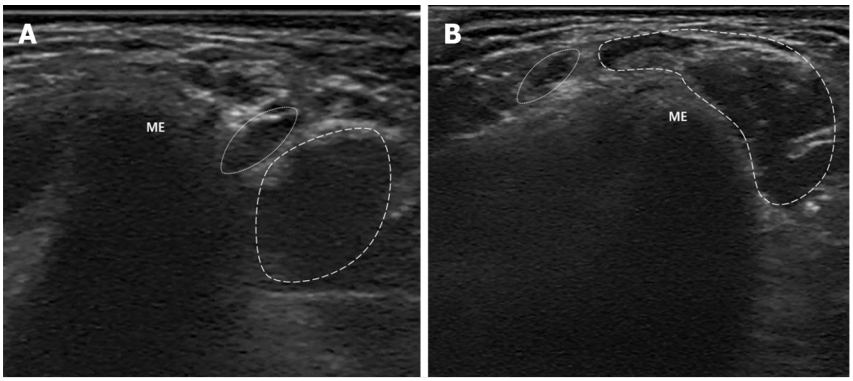

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Figure 2 Pre-operative transverse dynamic ultrasonography of the patient. A: In extension of the elbow, the ulnar nerve and medial head of the triceps are located posterior to the medial epicondyle; B: With flexion of the elbow by 100 degrees, the ulnar nerve and medial head of the triceps are dislocated anteriorly over the medial epicondyle. ME: Medial epicondyle, dotted circle: Ulnar nerve, dashed circle: Medial head of the triceps.

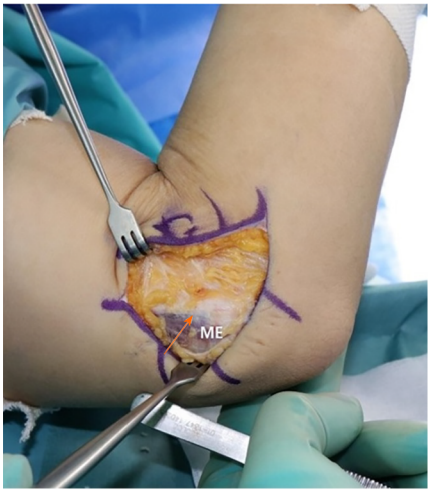

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Figure 3 Clinical photo of the left elbow. With flexion of the elbow by 90 degrees, the medial head of the triceps is dislocated anteriorly over the medial epicondyle. Arrow: ulnar nerve, ME: Medial epicondyle.

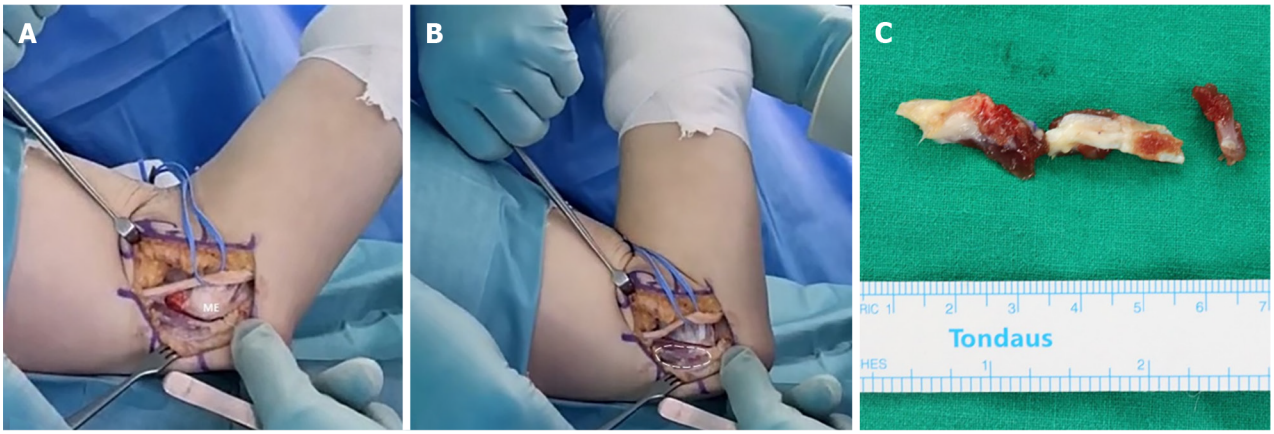

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Figure 4 Clinical photo after anterior transposition of the ulnar nerve. A: With flexion of the elbow by 80 degrees, the medial head of the triceps is located posterior to the medial epicondyle; B: With flexion of the elbow by 100 degrees, the medial head of the triceps is dislocated anteriorly over the medial epicondyle; C: Medial head of the triceps, located over the medial epicondyle, was resected. ME: Medial epicondyle, dashed circle: Dislocated medial head of the triceps.

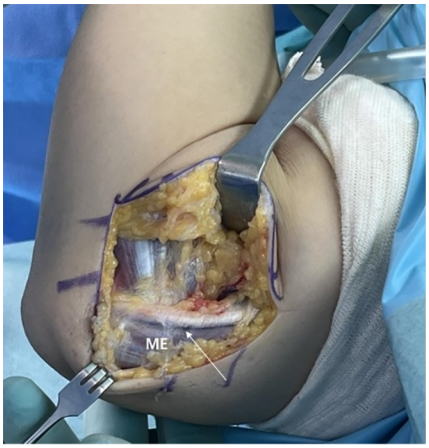

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Figure 5 Clinical photo of the right elbow. With flexion of the elbow by 90 degrees, the medial head of the triceps is dislocated anteriorly over the medial epicondyle. Arrow: Ulnar nerve, ME: Medial epicondyle.

subluxation of the ulnar nerve and triceps. Therefore, dynamic ultrasound is more useful for diagnosis of STS than MRI [7]. However, in cases where dislocation of the ulnar nerve and the medial head of the triceps occurs at a similar degree, diagnosis of snapping triceps syndrome may not be easy. Careful physical assessment is important during repetition of flexion and extension of the elbow in order to determine whether it is isolated dislocation of the ulnar nerve or STS. The ulnar nerve dislocated at 90 degrees and the medial head of the triceps dislocated at approximately 120 degrees[17].

Surgical options include partial resection of the snapping slip, centralization or lateralization of the medial triceps of the triceps, medial condylotomy or corrective osteotomy, addressing humeral malignment[18]. Centralization or lateralization involves detaching the tendon of the medial head of the olecranon and passing it under, interlacing it with the central tendon or lateral tendon. This procedure is typically chosen in cases where the segment of snapping triceps represents a significant bulk of the medial head[19]. Partial resection of a snapping slip is chosen in select cases with small dislocating segments and easier and more rapid recovery can be expected; most studies have reported excellent results [18]. In our case, the snapping slip was not large in size, therefore, partial triceps resection was selected. Care should be taken not to resect an excessive amount of tendon, with the aim of not compromising the triceps function.

A limitation of this case was that preoperative nerve conduction velocity-electromyography was not performed. Because, on the preoperative physical examination, two snapping sounds were detected during flexion of the elbow and only a tingling sensation of the ulnar side of the hand without weakness was observed.

CONCLUSION

STS should be included in the differential diagnosis for active young patients who present with painful snapping on the

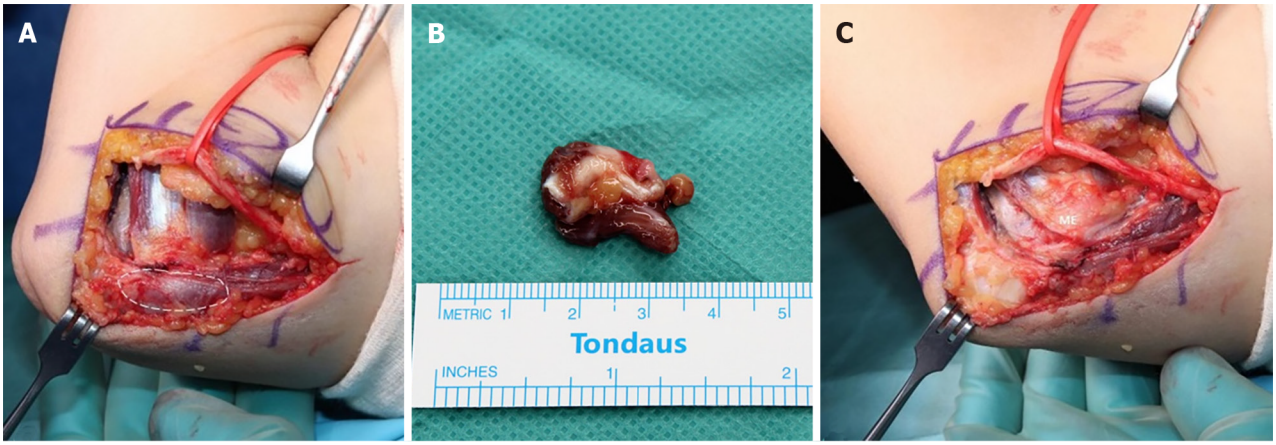

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Figure 6 Clinical photo after anterior transposition of the ulnar nerve. A: With flexion of the elbow by 100 degrees, the medial head of the triceps is dislocated anteriorly over the medial epicondyle; B: Medial head of the triceps, located over the medial epicondyle, was resected; C: After resection, it was confirmed that flexion of the elbow did not cause any dislocation of the triceps with flexion of the elbow by 100 degrees. ME: Medial epicondyle, dashed circle: Dislocated medial head of the triceps.

medial side of the elbow joint, particularly when dislocation of the ulnar nerve is detected. Dynamic sonography is used to assist in accurate diagnosis and differentiation between isolated dislocation of the ulnar nerve and STS.

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FOOTNOTES

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CASE REPORT

Management of post-liver transplantation biliary stricture inaccessible by endoscopic retrograde cholangiopancreatography: A case report

Yohan Lee, Chang Hwan Park, Eunae Cho, Ki-Hyun Kim

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Abstract

BACKGROUND

One challenging scenario in the treatment of biliary stricture is that post-liver transplantation (LT) biliary strictures cannot be accessed using endoscopic retrograde cholangiopancreatography (ERCP). Here, we report such a case that was successfully treated using a novel endoscopic technique.

CASE SUMMARY

A 60-year-old man presented with obstructive jaundice caused by a post-LT biliary stricture. He underwent LT for compensated alcoholic liver cirrhosis and hepatocellular carcinoma. Laboratory investigations unveiled a cholestatic pattern of abnormalities in liver function and a total bilirubin level of 16 mg/dL. Magnetic resonance cholangiopancreatography revealed a stricture extending from the right intrahepatic bile duct into the common hepatic duct. Severe postoperative deformities made accessing the ampulla of Vater with a side-viewing duodenoscope impossible. Percutaneous transhepatic biliary drainage (PTBD) was performed to treat biliary obstruction. Moreover, to resolve the stricture completely, a fully covered self-expandable metal stent (FC-SEMS) with a novel proximal retrievable string was deployed into the post-LT biliary stricture through the PTBD tract. Before inserting the stent through the PTBD tract, the stent with the distal string was manually inverted to ensure that the distal part with the string became the proximal part for later endoscopic removal. After 6 mo, the FC-SEMS was successfully removed without complications, as the string was pulled out using a forward-viewing gastroscope.

CONCLUSION

Deployment and endoscopic removal of an FC-SEMS with a novel proximal string through the PTBD tract may be a viable option for treating post-LT biliary

strictures that are inaccessible by ERCP.

Key Words: Jaundice; Obstructive; Percutaneous transhepatic cholangioscopy; Self-expandable metallic stents; Case report

Core Tip: Post-liver transplantation biliary stricture is complex and involves many variables. There is no established method for its evaluation and treatment, and various approaches are needed depending on patient factors. While a fully covered self-expandable metal stent shows good effectiveness, it is premised on endoscopic access. This case report presents a new solution through percutaneous stent insertion and endoscopic removal in cases where endoscopic retrograde cholangiopancreatography is not possible.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has become the standard treatment for benign biliary strictures (BBSs) associated with liver transplantation (LT) owing to the safety and efficacy of the technique[1,2]. However, a percutaneous transhepatic cholangioscopy (PTCS)-guided approach is sometimes required, particularly when ERCP is not feasible. The European Society of Gastrointestinal Endoscopy considers fully covered self-expandable metal stents (FC-SEMS) as the mainstay of BBS treatment[2]. Herein, we report a case of PTCS-guided insertion of an FC-SEMS with a proximal retrieval string in the treatment of a post-LT biliary stricture inaccessible by ERCP. This was followed by the successful endoscopic removal of the FC-SEMS.

CASE PRESENTATION

Chief complaints

A 60-year-old man presented with jaundice.

History of present illness

The patient denied the presence of any symptoms such as fever or abdominal pain.

History of past illness

In 2017, the patient underwent LT for compensated alcoholic liver cirrhosis with hepatocellular carcinoma.

Personal and family history

There was no other special personal or family history.

Physical examination

There were no unusual findings on physical examination.

Laboratory examinations

Laboratory investigations revealed a cholestatic pattern of abnormalities in the liver function with a total bilirubin level of 16 mg/dL.

Imaging examinations

Magnetic resonance cholangiopancreatography revealed a stricture extending from the right intrahepatic bile duct (IHBD) to the common hepatic duct (Figure 1). Therefore, ERCP was planned for the management of the post-LT biliary stricture. Although a forward-viewing gastroscope could reach the ampulla of Vater, a side-viewing duodenoscope was unable to reach the same extent due to severe postoperative deformities, including those at the gastric antrum and duodenal bulb. Percutaneous transhepatic biliary drainage (PTBD) was performed to achieve biliary decompression (Figure 2). During PTBD, it was impossible for the guidewires to pass through the post-LT biliary stricture.

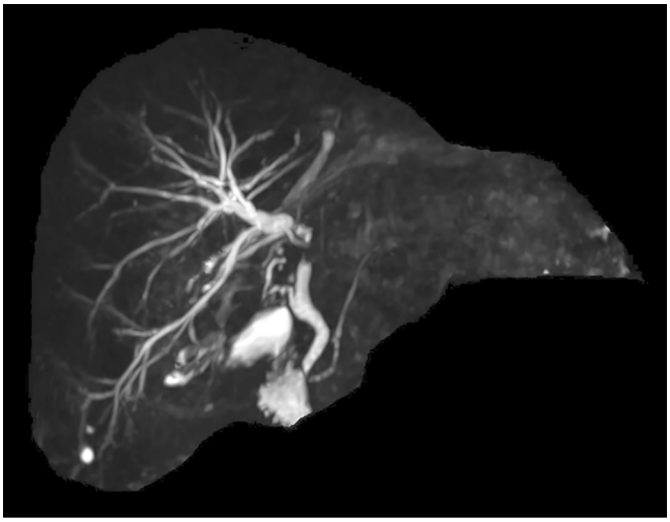

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Figure 1 Magnetic resonance cholangiopancreatography. A complete obstruction was observed from the right intrahepatic bile duct to the common hepatic duct segment with upstream dilatation of the biliary trees.

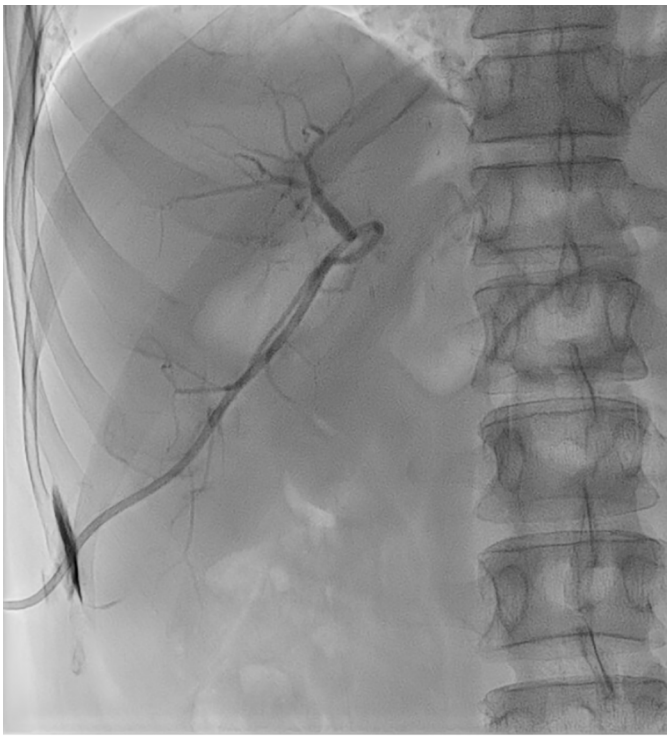

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Figure 2 Percutaneous transhepatic biliary drainage. An obstruction was observed at the confluence of the right intrahepatic bile duct (IHBD). However, the guidewire could not pass through the obstruction. An 8.5 Fr catheter was placed in the right IHBD.

FINAL DIAGNOSIS

PTCS is imperative for the accurate diagnosis of strictures and their resolution. After 1 wk, the PTBD tract was sequentially dilated using a Mustang balloon dilatation catheter (Boston Scientific, Marlborough, MA, United States), 8 mm in diameter. An 18 Fr PTCS catheter (Akita Sumitomo Bakelite Co. Ltd., Japan) was maintained *in situ* for 2 wk to facilitate tract maturation. A slit-like stricture opening was detected using PTCS (Figure 3A), and a guidewire was inserted through the opening into the common bile duct and duodenum. Additionally, an 18 Fr PTCS catheter was inserted after stricture dilation to resolve the stricture. Maintenance of the catheter in place for 3 mo was planned (Figure 3B). However, the catheter abruptly migrated into the right IHBD approximately 2 mo after insertion. Cholangioscopy revealed a near-complete obstruction of the previously dilated biliary stricture (Figure 4).

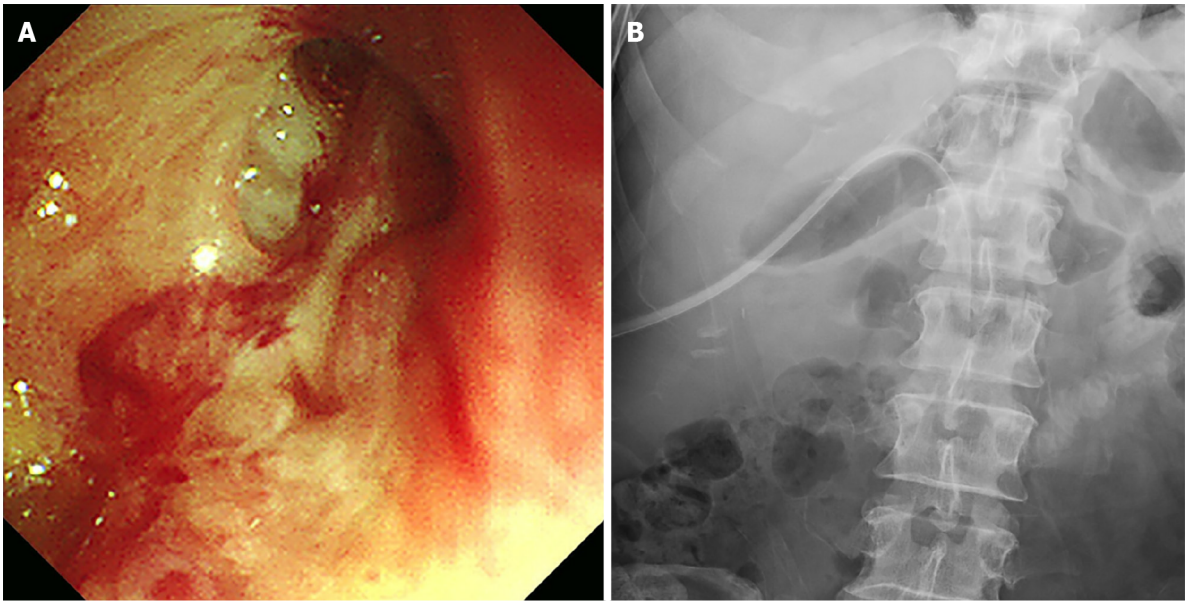

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Figure 3 Percutaneous transhepatic cholangioscopy. A: The slit-like orifice of the right intrahepatic bile duct stricture was detected using percutaneous transhepatic cholangioscopy (PTCS); B: An 18 Fr PTCS catheter was successfully inserted.

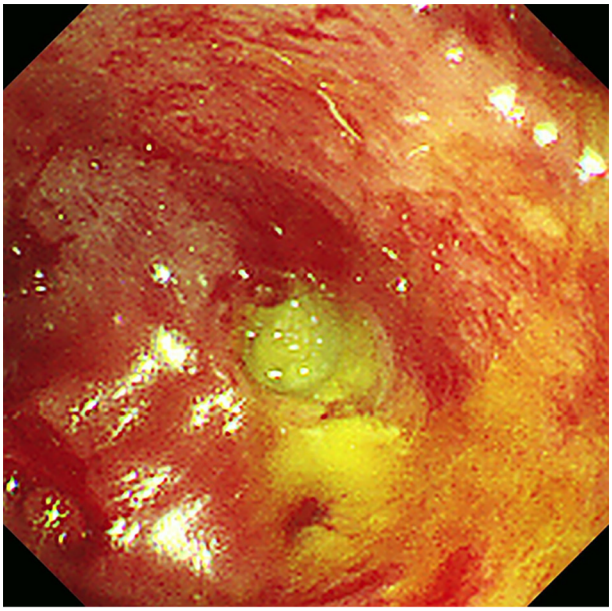

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Figure 4 Follow-up percutaneous transhepatic cholangioscopy. Subsequent cholangioscopy after catheter dislocation displayed almost complete occlusion of the stricture orifice.

TREATMENT

The insertion of a removable FC-SEMS through the PTBD tract was considered a definitive solution for post-LT biliary strictures with a low risk of recurrent PTCS catheter migration. The Kaffes stent (Taewoong Medical, South Korea) is a removable FC-SEMS with a radiopaque retrievable string as the distal attachment. For the endoscopic removal of the Kaffes stent inserted through the PTBD tract, the stent was manually inverted so that the distal part with a retrievable string became the proximal part before stent insertion. The stent was slowly deployed over the stricture under fluoroscopic guidance. Furthermore, the stent was initially inserted up to the third portion of the duodenum and slowly pulled back to the post-LT biliary stricture for the string to spontaneously change direction and be positioned correctly within the duodenal lumen (Figure 5A, Video 1). After the string was confirmed to be well-stretched in the duodenal lumen, the stent was positioned approximately over the stricture site and then deployed (Video 2). Subsequent cholangiography revealed that the stent had blocked the branches of the right proximal IHBD (Figure 5B). The proximal end of the stent

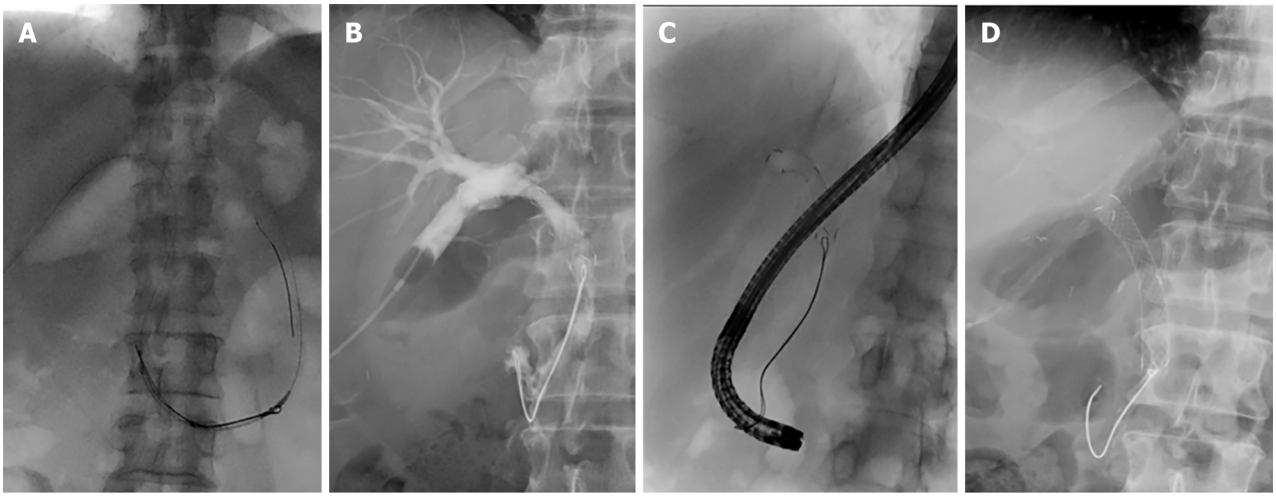

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Figure 5 Insertion process of an inverted metallic stent. A: An inverted metallic stent was pushed sufficiently to allow the string to spread well into the duodenal lumen; B: The first branches of the right intrahepatic bile duct were blocked by the stent end; C: The string was captured using a snare through a gastroscope and pulled carefully; D: Finally, the metallic stent was properly placed into the stricture without peripheral bile duct obstruction.

was adjusted to be distal to the right IHBD bifurcation to prevent obstruction of the branches of the right IHBD. Simultaneously, the string was carefully pulled using a forward-viewing gastroscope with a snare (Figure 5C and D).

OUTCOME AND FOLLOW-UP

After 6 mo, the Kaffes stent was removed without complications, as the string was pulled out following the same technique using a forward-viewing gastroscope (Figure 6).

DISCUSSION

Despite advances in endoscopic techniques, post-LT biliary strictures have recently been regarded as among the most difficult complications to address[3]. Post-LT biliary strictures are often complex, associated with recurrences, and inaccessible by ERCP. Numerous studies have demonstrated that the treatment of complex post-LT biliary strictures requires multiple modalities, including interventional radiologic and endoscopic techniques[4]. A recent meta-analysis displayed that multiple plastic stents and removable FC-SEMSs are equally effective and safe procedures for managing refractory biliary strictures or as primary treatment[5]. However, removable FC-SEMSs are favored over the aforementioned options[5].

When post-LT biliary strictures are inaccessible by ERCP, the resolution of the biliary strictures can be challenging. In this context, PTBD plays an important role as a salvage procedure in the treatment of acute cholangitis. However, long-term maintenance of PTBD is associated with significant patient distress and risk of various complications, including catheter dislodgement, bleeding, infection, and bile leakage[6]. A non-removable FC-SEMS may be inserted through the PTBD tract to prevent complications associated with the long-term maintenance of PTBD. However, long-term placement of a non-removable FC-SEMS could also lead to various serious complications such as stent occlusion, stone formation, secondary biliary cirrhosis, and death[7,8].

In the present case, an FC-SEMS with a novel proximal retrieval string was successfully deployed into a post-LT biliary stricture through the PTBD tract. After 6 mo, the FC-SEMS was removed without complications, by pulling out the string using a forward-viewing gastroscope with a snare. To the authors' knowledge, in the English literature, this was the first endoscopic removal of an FC-SEMS with a novel proximal string inserted through the PTBD tract for the treatment of post-LT biliary stricture[3-5]. An alternative approach to treating BBS involves the insertion of a removable FC-SEMS through a PTBD tract. In this method, the stent with a distal string is inserted in the conventional direction, and the string is fixed to the skin[9]. This carries a risk of peripheral stent migration along the string, infection through the string tract, and additional PTCS for stent removal[9].

The cause of BBS varies in patients, from post-LT biliary stricture to chronic inflammation[1]. Despite these various causes, a removable FC-SEMS is the preferred treatment for providing stricture resolution with sustained patency and reducing the number of endoscopic sessions[1]. In the present case, where a stricture was inaccessible by ERCP, either multiple plastic stents or an FC-SEMS would be considered to prolong patency. Regarding the number of PTBD sessions, a manually rearranged FC-SEMS attached to a proximal string was selected and deployed through the PTBD tract to facilitate stricture resolution in one session. This case demonstrates that the deployment of an FC-SEMS with a proximal string is a viable option for biliary strictures that are inaccessible by ERCP. Endoscopic ultrasonography (EUS)-guided

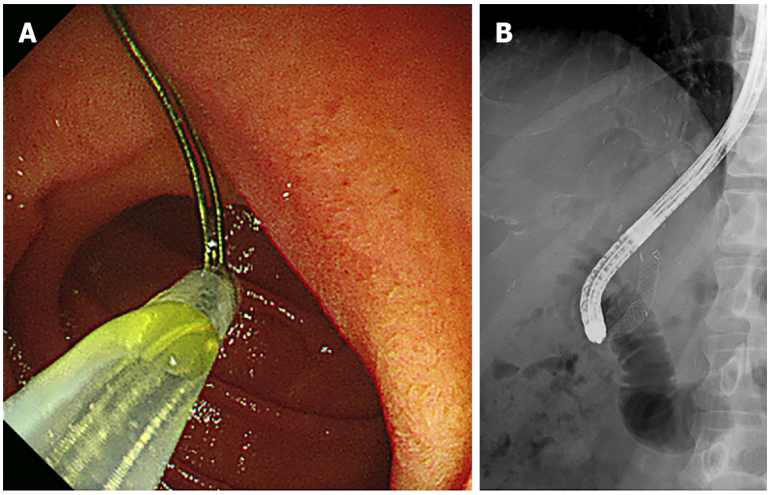

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Figure 6 Removal of the metallic stent. A: The retrieved string was captured through a forward-viewing gastroscope with a snare; B: And then, the stent was slowly pulled into the stricture site while the position and orientation of the string were maintained.

biliary drainage is also a salvage technique for strictures that are inaccessible by ERCP[1]. In this setting, FC-SEMS with a proximal string can help in EUS-guided antegrade biliary drainage for BBSs.

Traditionally, removable FC-SEMSs with distal strings have been inserted using ERCP. If an FC-SEMS inserted through the PTBD tract can be removed by pulling the string using endoscopy, the stent should be inverted so that the distal string becomes the proximal string before insertion through the tract. As this type of removable FC-SEMS was not available, rearrangement of the FC-SEMS was manually performed immediately before the procedure in the present case. No difficulties were encountered in rearranging the inverted FC-SEMS. Another technical point for consideration is the change in the string direction. During FC-SEMS insertion, the string was directed toward the liver. However, the direction of the string should be changed so that it faces the duodenum with the distal end positioned adjacent to the duodenum for endoscopic removal. To change direction, the FC-SEMS was initially inserted into the third portion of the duodenum and slowly pulled back into the post-LT biliary stricture. As the FC-SEMS was being pulled back, the string spontaneously changed direction.

CONCLUSION

In summary, a post-LT biliary stricture complicated by obstructive jaundice was treated by the placement of a removable FC-SEMS through a PTBD tract. Initially, PTBD played a central role as a salvage procedure for treating biliary obstruction in post-LT biliary strictures that were inaccessible by ERCP. A removable FC-SEMS inserted through the PTBD tract successfully resolved the stricture in one session. The endoscopic removal of an FC-SEMS with a novel proximal string through the PTBD tract may be a feasible option for the treatment of post-LT biliary strictures that are inaccessible by ERCP.

FOOTNOTES

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