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Contents

Thrice Monthly Volume 12 Number 9 March 26, 2024

EDITORIAL

ORIGINAL ARTICLE

Retrospective Study

Clinical Trials Study

Observational Study

Clinical and Translational Research

CASE REPORT

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 9 March 26, 2024

Contents

LETTER TO THE EDITOR

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 9 March 26, 2024

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Cases*, Luca Mezzetto, MD, Surgeon, Department of Vascular Surgery, University Hospital of Verona, Verona 37126, Italy. luca.mezzetto@aovr.veneto.it

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EDITORIAL

Multidisciplinary approach toward enhanced recovery after surgery for total knee arthroplasty improves outcomes

Deb Sanjay Nag, Amlan Swain, Seelora Sahu, Ayaskant Sahoo, Gunjan Wadhwa

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Deb Sanjay Nag, Amlan Swain, Seelora Sahu, Gunjan Wadhwa, Department of Anaesthesiology, Tata Main Hospital, Jamshedpur 831001, India

Ayaskant Sahoo, Department of Anaesthesiology, Manipal Tata Medical College, Jamshedpur 831001, India

Corresponding author: Deb Sanjay Nag, MBBS, MD, Doctor, Department of Anaesthesiology, Tata Main Hospital, C Road West, Northern Town, Bistupur, Jamshedpur 831001, India. ds.nag@tatasteel.com

Abstract

Knee osteoarthritis is a degenerative disorder of the knee, which leads to joint pain, stiffness, and inactivity and significantly affects the quality of life. With an increased prevalence of obesity and greater life expectancies, total knee arthroplasty (TKA) is now one of the major arthroplasty surgeries performed for knee osteoarthritis. When enhanced recovery after surgery (ERAS) was introduced in TKA, clinical outcomes were enhanced and the economic burden on the healthcare system was reduced. ERAS is an evidence-based scientific protocol aimed at ameliorating the surgical stress response. ERAS aims to enhance the recovery phase, which encompasses multidisciplinary strategies at every step of perioperative care, including the rehabilitation phase. Implementation of ERAS in TKA aids in reducing the length of hospital stay, improving pain management, reducing perioperative complications, and enhancing patient satisfaction. Multidisciplinary collaboration, integrating the expertise of anesthesiologists, orthopedic surgeons, nursing personnel, and other healthcare professionals, is the cornerstone of ERAS in patients undergoing TKA.

Key Words: Arthroplasty; Replacement; Knee; Recovery of function; Anesthesia; Care; Nursing

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Core Tip: Current evidence shows that a protocolized approach toward enhanced recovery after surgery with multidisciplinary collaboration improves outcomes following total knee arthroplasty (TKA). As healthcare professionals continue to refine and evolve enhanced recovery after surgery (ERAS) protocols in patients undergoing TKA, the integration of multidisciplinary teams in ERAS implementation is critical to achieving optimal patient outcomes.

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INTRODUCTION

Knee osteoarthritis is a degenerative disease affecting older adults with a significant effect on quality of life[1]. There is progressive articular cartilage loss that leads to debilitating pain with impairment of mobility. Increasing rates of obesity and longevity have indicated that knee osteoarthritis has resulted in public health crisis proportions[2].

Total knee arthroplasty (TKA) is a major surgical intervention that is effective in treating knee osteoarthritis and enhancing the quality of life for individuals with debilitating knee joint disorders[3]. Increased life expectancies and a rapidly growing geriatric population have indicated that a high number of people undergoing TKA have a strong need for an early return to daily activities[4].

The concept of enhanced recovery after surgery (ERAS) protocols was first proposed by Kehlet *et al*[5] in 1997 in colorectal surgery. The surgical stress response, which caused a multitude of systemic effects and resulted in increased convalescence time was targeted to enhance outcomes using this approach. The ERAS approach, with its significant advantages on health economics and improved patient outcomes, has been adopted and shown to be useful in diverse groups of surgical patient populations[6].

The ERAS approach necessitated a multidisciplinary (anesthetists, surgeons, nurses, and physiotherapists) collaboration to achieve early autonomy in the postoperative recovery period, resulting in a lower length of stay[7]. Multidisciplinary collaboration is the main goal of ERAS, integrating the expertise of surgeons, anesthetists, nurses, and various other healthcare professionals. This collaborative effort is crucial for evidence-based practice implementation and patient care optimization throughout the perioperative period. The synergy among team members contributes to a comprehensive and patient-centered approach, which aligns with ERAS principles[8,9].

The increased propagation of the ERAS approach has also included patients posted for orthopedic joint (hip and knee) replacements. The reasons for the increased use of ERAS in patients undergoing TKA are diverse-ranging from the increasing number of elderly people requiring knee surgery to the increased benefits of shorter hospital stays in such patients[10].

ERAS IN TKA PATIENTS

Similar to other surgical specialties, ERAS protocols for the TKA patient must be targeted to decrease the surgical stress response, which can be broadly divided into preoperative, intraoperative, and postoperative periods[11,12]. Various components during the perioperative period of implementation of ERAS protocols in patients undergoing TKA exist, which have been now summarized in recent consensus statements by the ERAS Society (Tables 1 and 2)[13,14].

Certain pertinent points of ERAS implementation in patients with TKA, which is specific to these patients, are as follows: (1) Preoperative education and physical therapy decrease anxiety and the cost of treatment[15,16]; (2) Anesthesia techniques must aim to use neuraxial/peripheral nerve block/local anesthesia infiltration techniques with the use of multimodal opioid-sparing regimens and hypobaric intrathecal solutions to promote early mobilization with adequate pain control[17-21]; (3) Urinary catheter placement and postoperative urinary retention: Spinal anesthesia and prostatism are contributory factors. Opioid-sparing spinal anesthetic is regarded to be the best choice[22,23]; (4) Use of tranexamic acid in the intraoperative period reduces blood loss and blood component therapy[24]; (5) Early mobilization should be encouraged[25]; and (6) Orthostatic intolerance is a notorious cause of failure of ERAS protocols in patients undergoing TKA and is frequently multifactorial[26].

ADVANTAGES OF ERAS IN TKA

Reduced length of hospital stay

Studies have consistently demonstrated that the implementation of ERAS protocols in TKA results in a significant reduction in the length of hospital stays. The study by Khan *et al*[27] highlighted the impact of ERAS on patient outcomes, indicating a shorter duration of hospitalization, which not only reduces healthcare costs but also facilitates a quicker return to normal activities.

Table 1 GRADE system for rating strength of recommendations and rating quality of evidence (Guyatt *et al*[15], 2008)

Recommendation strength	Definition
Strong	Desirable effects of intervention clearly outweigh the undesirable effects, or clearly do not
Weak	When trade-offs are less certain—either because of low-quality evidence or because evidence suggests desirable and undesirable effects are closely balanced
Evidence level	Definition
High quality	Further research unlikely to change confidence in estimate of effect
Moderate quality	Further research likely to have important impact on confidence in estimate of effect and may change the estimate
Low quality	Further research very likely to have important impact on confidence in estimate of effect and likely to change the estimate
Very low quality	Any estimate of effect is very uncertain

Improved pain management

Effective pain management is a fundamental component of ERAS, and its impact on nursing outcomes is shown by Urban *et al*[28] and Wei *et al*[29]. These authors validated the importance of multimodal analgesia and patient engagement in pain control strategies, resulting in improved postoperative pain management and enhanced patient comfort during the recovery phase.

Enhanced patient satisfaction

The patient experience is a vital aspect of healthcare, and ERAS, through its patient-centric approach, significantly influences patient satisfaction. Research by Aasvang *et al*[30] demonstrated that informed patients actively participating in their care decisions and early mobilization contribute to higher levels of satisfaction and overall positive experiences.

Early mobilization and functional recovery

Nurses play a pivotal role in encouraging early mobilization, which is a key component of ERAS associated with faster functional recovery. Riga *et al*[31] emphasized the importance of nursing interventions in facilitating early ambulation, resulting in improved joint function and overall recovery.

Reduced complications

ERAS implementation has been associated with a reduction in postoperative complications. Artz *et al*[32] highlighted the impact of ERAS concerning physiotherapy and exercise on minimizing complications and better functional outcomes. Nursing vigilance and prompt intervention play a crucial role in the identification and management of potential issues.

CONCLUSION

ERAS protocols are currently based on scientific evidence of a combination of multidisciplinary protocols to enhance outcomes, hasten recovery, and reduce costs during the perioperative period[33]. Even though ERAS has now scientifically established itself as the standard of care, future studies that focus on compliance with ERAS protocols would validate its utility and relationship with outcomes[34]. ERAS protocols continue to evolve as our learning in identifying therapeutic interventions targeting "modifiable risk factors" by modulating surgical stressors and ensuring perioperative homeostasis ensures improved outcomes[35].

Although ERAS protocols have been shown to decrease mortality, need for blood and blood component transfusion, complication rate, and length of stay, studies have identified at least 17 specific elements, and optimizing their usage in clinical scenarios would be guided by future studies[36]. These elements comprise preoperative components of (1) "preoperative information, education and counseling"; (2) "preoperative optimization of smoking, alcohol consumption and anemia"; and (3) optimum preoperative fasting[36]. The intraoperative components include: (1) A standardized anesthesia protocol; (2) local anesthetic infiltration and specific nerve blocks; (3) prevention of postoperative nausea and vomiting; (4) reducing perioperative blood loss with use of tranexamic acid; (5) perioperative analgesia including use of paracetamol; (6) ensuring normothermia; (7) optimum antibiotic prophylaxis; (8) perioperative fluid management; and (9) modulating surgical factors[36]. The postoperative interventions include: (1) Thromboprophylaxis; (2) postoperative nutrition; (3) early mobilization; (4) criteria-based discharge; and (5) continuous audit and improvement[36]. Recent studies also reveal the importance of a multidisciplinary approach in enhancing nursing outcomes[9].

The evidence from these studies highlights the positive impact of ERAS with multidisciplinary collaboration on overall outcomes following TKA. As healthcare professionals continue to refine and implement ERAS protocols in patients undergoing TKA, the integration of multidisciplinary expertise in ERAS implementation remains central to achieving optimal outcomes and ensuring a smoother recovery for these patients.

Table 2 Summary of recommended interventions for the perioperative care of knee replacement

		Recommendation	Recommendation grade	Level of evidence
Preoperative	Preoperative information, education and counselling	Preoperative patient education recommended	Strong	Low
Preadmission patient optimization	Smoking	Smoking cessation for 4 wk or more recommended before surgery	Strong	High
	Alcohol	Alcohol cessation recommended before surgery	Strong	Low
	Anemia	Anemia should be identified, investigated, and corrected prior to surgery	Strong	High
	Preoperative physio-therapy	Not recommended as an essential intervention	Strong	Moderate (for not recommending)
Perioperative	Preoperative fasting	Intake of clear fluids until 2 h before the induction of anesthesia, and a 6-h fast for solid food is recommended	Strong	Moderate
	Preoperative carbohydrate treatment	Not currently recommended as an essential routine Intervention	Strong	Moderate (for not recommending)
	Pre-anesthetic medication	routine administration of sedatives to reduce anxiety preoperatively is not recommended	Strong	Low
Standardized anesthetic protocol	General versus central neuraxial anesthesia	Both may be used as part of multimodal anesthetic regimes	Strong	Moderate (for both)
	Spinal (intrathecal) opioids	Not recommended for routine use	Strong	Moderate
	Epidurals	Not recommended for routine use	Strong	High (analgesic efficacy), moderate (negative safety and side-effect profile)
	Use of local anesthetics for nerve blocks and infiltration analgesia	LIA recommended for knee replacement Nerve blocks are therefore not recommended as an essential ERAS component	Strong	High (LIA in knee replacement)
Postoperative	Nausea and vomiting	screening for and multimodal PONV prophylaxis and treatment	Strong	Moderate
	Prevention of periop-erative blood loss-tranexamic acid	Recommended to reduce perioperative blood loss	Strong	High
Multimodal analgesia	Paracetamol	Recommended for routine use	Strong	Moderate
	Non-steroidal anti-inflammatory drugs (NSAIDs)	Routine use of NSAIDS recommended for patients without contraindications	Strong	High
	Gabapentinoids	Not recommended currently	Strong	Moderate (for not recommending)
	Supplemental opioid analgesia	ERAS programs seek to minimize the use of opioids. However, opioids such as oxycodone may be used when required as part of a multimodal approach	Strong	High
Perioperative factors	Maintaining normothermia	Normal body temperature should be maintained peri- and postoperatively through pre-warming and the active warming of patients intraoperatively	Strong	High
	Antimicrobial prophylaxis	Systemic antimicrobial prophylaxis recommended in accordance with local policy and availability	Strong	Moderate
	Antithrombotic prophylaxis treatment	Patients should be mobilized as soon as possible post-surgery and receive antithrombotic prophylaxis treatment in accordance with local policy	Strong	Moderate
Perioperative surgical factors	Surgical technique	No recommendation on surgical technique	Strong	High
	Use of tourniquet	Routine use not recommended	Strong	Moderate
	Surgical Drain	Routine use not recommended	Strong	Moderate

	Fluid management	Intravenous fluids – judicious use	Strong	Moderate
		Postoperative intravenous fluids – discouraged in favor of early oral intake		
	Urinary catheter	Routine use – not recommended	Strong	Moderate
		When used – should be removed as soon as the patient is able to void, ideally within 24 h of surgery		
		Recommended catheterization threshold – 800 mL		
	Nutritional care	Early return to normal diet recommended	Strong	Low
	Early mobilization	Patients should be mobilized as early as they are able to in order in order to facilitate early achievement of discharge criteria	Strong	Strong
	Criteria-based discharge	Objective discharge criteria should be used to facilitate patient discharge directly to their home	Strong	Low
Continuous improvement and audit		Routine internal and/or external audit of process measures, clinical outcomes, cost effectiveness, patient satisfaction/experience, and changes to the pathway is recommended	Strong	Low

FOOTNOTES

Author contributions: Nag DS, Swain A, Sahu S, Sahoo A, Wadhwa G contributed to this paper; Nag DS and Swain A designed the overall concept and outline of the manuscript; Sahu S, Sahoo A and Wadhwa G contributed to the discussion and design of the manuscript; Nag DS, Swain A, Sahu S, Sahoo A and Wadhwa G contributed to the writing, and editing the manuscript and review of literature.

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Country/Territory of origin: India

ORCID number: Deb Sanjay Nag 0000-0003-2200-9324; Amlan Swain 0000-0002-0810-7262.

Corresponding Author's Membership in Professional Societies: Indian Society of Anaesthesiology, S2863.

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EDITORIAL

Using clinical cases to guide healthcare

Michael Colwill, Samantha Baillie, Richard Pollok, Andrew Poullis

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Michael Colwill, Samantha Baillie, Richard Pollok, Andrew Poullis, Department of Gastroenterology, St George's University Hospital NHS Foundation Trust, London SW17 0QT, United Kingdom

Corresponding author: Michael Colwill, BSc, MBBS, MRCP, Doctor, Research Fellow, Department of Gastroenterology, St George's University Hospital NHS Foundation Trust, Blackshaw Road, London SW17 0QT, United Kingdom. michael.colwill@nhs.net

Abstract

Evidence-based practice (EBP) has been the gold standard in healthcare for nearly three centuries and aims to assist physicians in providing the safest and most effective healthcare for their patients. The well-established hierarchy of evidence lists systematic reviews and meta-analyses at the top however these methodologies are not always appropriate or possible and in these instances case-control studies, case series and case reports are utilised to support EBP. Case-control studies allow simultaneous study of multiple risk factors and can be performed rapidly and relatively cheaply. A recent example was during the Coronavirus pandemic where case-control studies were used to assess the efficacy of personal protective equipment for healthcare workers. Case series and case reports also play a role in EBP and are particularly useful to study rare diseases such as inflammatory bowel disease in transgender and gender non-conforming individuals. They are also vital in generating and disseminating early signals and encouraging further research. Whilst these methodologies have weaknesses, particularly with regards to bias and loss of patient confidentiality for rare pathologies, they have an important part to play in EBP and when appropriately utilised can significantly impact upon clinical practice.

Key Words: Evidence based medicine; Hierarchy of evidence; Case reports; Case series

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Core Tip: Evidence-based practice is used by physicians to select the optimum treatment for their patients. The hierarchy of evidence lists systematic reviews and meta-analyses as the highest quality of evidence however this is not always appropriate or possible which is when clinical cases, either as case-control studies or case reports, can be utilised. This paper will look at the strength and weaknesses of these methodologies and use recent examples to demonstrate the impact they can have on clinical practice.

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INTRODUCTION

James Lind, a Scottish physician in the 18th century, is considered to have conducted the first recorded clinical trial in the 1740s when he selected 12 sailors with scurvy and divided them into six cohorts of two to whom he administered various contemporary treatments and noted the greatest improvement in those given lemons and oranges[1]. Even though it took 50 years for the British navy to make lemon juice compulsory for sailor's diets because of the cost, the age of evidence-based medicine had begun.

Evidence-based practice (EBP) has dramatically changed since the 1700s and is now well recognised as key to providing the most effective and safe healthcare for patients[2,3]. A hierarchy of scientific evidence known as the evidence pyramid[4], has been developed in recognition of the fact that not all research is the same in terms of scientific significance and validity (Figure 1). At the top of this pyramid are the systematic review and meta-analysis, followed by double-blinded randomised-control trials, then cohort studies, case-control studies, case series, reports and expert opinion and all of these tiers have a role to play in EBP.

Whilst perhaps ideally all clinical decisions would have the backing of a meta-analysis or systematic review, there are many occasions where there simply is not the data available. For example when bringing a new therapy to market the most appropriate level of evidence is a randomised double-blinded placebo control trial (RCT) and this, whilst expensive and sometimes ethically problematic, provides the strongest evidence of a cause and effect relationship and is therefore the gold-standard for clinical trials and often a pre-requisite to achieve regulator approval. Similarly, in rare disease (sometimes called orphan diseases) there are not enough cases to be able to power a study, apply statistical analysis and determine the validity of a hypothesis. This is where case-control studies and case reports can be useful to allow healthcare professionals to perform EBP.

CASE-CONTROL STUDIES

These are retrospective observational studies which involve the identification of cases and researchers then constructing a control group with similar characteristics. Historical factors are then identified to see if these exposures are more frequently found in the case group rather than the controls. This study design allows for multiple risk factors to be examined at once and they can also be useful when disease outbreaks occur and potential links and exposures need to be identified.

Recent examples of the utility of these studies were during the initial phases of the coronavirus pandemic in 2020. A study in Thailand comparing 211 coronavirus infections with 839 controls aimed to assess the efficacy of personal protective equipment. The nature of their analysis meant they were able to examine multiple variables and identified that only with other measures, such as social distancing, was there a significant reduction in infections with personal protective equipment use[5]. Later in the pandemic, in response to rising concern regarding the rate of healthcare worker infection, further research was conducted into the factors putting them at risk. This suggested using a double-mask technique to reduce infection rates[6] but also identified other factors such as education and anxiety regarding infection which were found to be protective against infection outside the workplace.

Whilst there were some undoubted weaknesses in these studies, such as bias and lack of clear accounting for confounding variables, these examples demonstrate the utility of case-control studies particularly with regards to the speed at which they can be performed and the ability to react to a changing environment with new questions or concerns. However, these studies rely on a large pool of affected cases and it would not have been possible to do so for rarer diseases which is where case-series and case-reports can be used.

CASE REPORTS

Case reports and case series are descriptive studies which are used to present the clinical history and progress of patients in the 'real-world'. Case reports consist of 3 or fewer patients whilst case series tend to have multiple patients and offer further qualitative methodology. The observational nature of these studies means that they are cheap and relatively quick to perform but perhaps their greatest utility is in rare diseases or treatments[7] where the lack of available patients makes other research methodologies impossible.

An example is with regards to inflammatory bowel disease in trans-gender or gender non-conforming patients (IBD-TGNC). Research using census data has identified there are approximately 2000 IBD-TGNC patients in the United Kingdom[8]. Given the heterogenous and complex nature of this patient group as well as the low numbers, there is a lack of good quality evidence and the literature is largely made up of case reports and series. An example is the experience of a trans-gender woman, who had undergone previous vaginoplasty using her sigmoid colon 10 years previously, who later

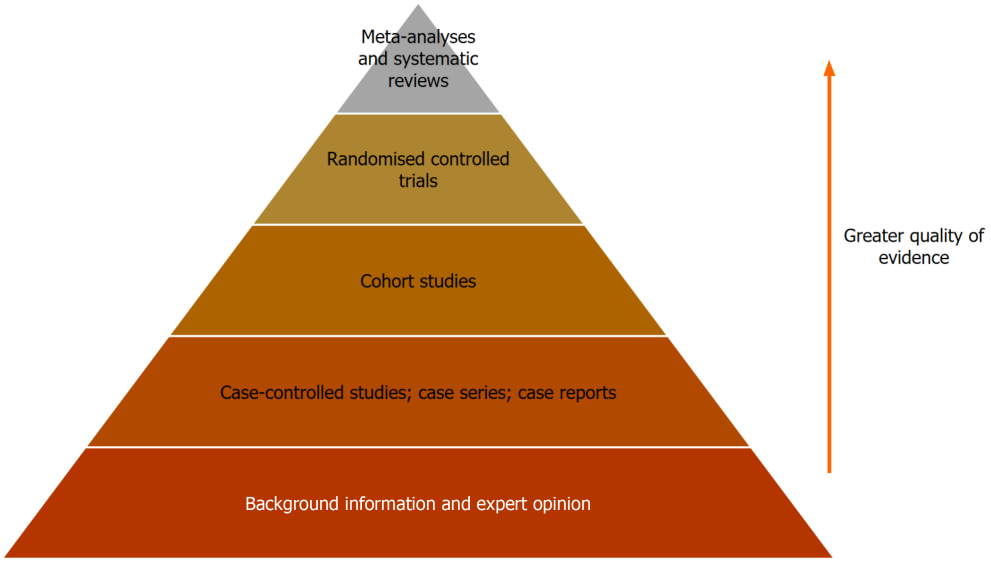

Figure 1 The hierarchy of evidence pyramid.

presented with diarrhoea, rectal bleeding and blood-stained vaginal discharge. Examination revealed histological changes consistent with ulcerative colitis within the neo-vagina, matching those from the colonic biopsies[9]. Whilst a rare occurrence this illustrates the educational utility of case reports.

Case reports can also be used to generate hypotheses which, once disseminated to the wider medical community, can be further tested and a body of evidence developed. One example of this, published in the Lancet in 1983, is that of an infant who required multiple blood transfusions but went on to die at 17 months of opportunistic infections and was found to have an acquired immunodeficiency. The authors hypothesised this may be due to a blood borne virus, later identified as the human immunodeficiency virus, and led to an unprecedented research effort which continues to this day.

Whilst advantageous in certain settings, one of the main areas of concern is regarding patient identity particularly in rare pathology. Even though the publication will anonymise some elements of the data, the description of very rare phenomena may be sufficient to de-anonymise individuals. Therefore, safeguarding measures should be in place as well as open communication with the patients described in these case reports to ensure explicit informed consent is gained and various institutions have published guidance regarding this[10].

Other disadvantages of these studies are that they are uncontrolled, suffer from selection bias and generally have an insufficient follow-up period. There can also be difficulty in using these studies for scientific research given that the cases described may not be easily generalisable to the wider population. However, whilst their value remains a matter for scientific debate[4], dismissing these studies as completely useless is incorrect and ignores their definite, if somewhat limited, strengths described above.

CASE SERIES

Case series were historically the backbone of medical literature and whilst their importance has become smaller, they continue to be an important part of research.

They are particularly useful for novel observations and publishing early signals can inform the medical community to be vigilant for similar cases. This was recently demonstrated in a series published in January 2020 regarding patients infected with coronavirus in Wuhan[11]. Case series can also be useful for testing novel treatments, demonstrated by an IBD study in 2018 which wanted to provide preliminary data on dual biologic therapy (DBT)[12]. Through a case series of four patients they were able to show safety and efficacy signals which led to larger studies and DBT is now considered an effective option for difficult to treat disease[13].

These series, similar to case reports, can also be useful for studying rarer pathology. A 2021 study by Phillips *et al*[14] used a case series of 15 patients across 8 different centres to investigate factors associated with intestinal lymphoma in the context of IBD, a rare pathology believed to be related to thiopurine and anti-TNF use. As well as helping to identify risk factors, such as male sex and thiopurine use in two-thirds of their cohort, the series also helped to address the challenging clinical conundrum regarding the safety of restarting immunosuppressive therapy in patients with a history of intestinal lymphoma.

Case series can be published quickly, a particular strength with regards to the coronavirus series described above, and are cheap to develop compared to other methodologies such as RCTs which can cost in excess of $100000 per patient enrolled[15]. However, their use as a research modality also suffers from similar disadvantages as described for case reports particularly a lack of control, selection bias and difficulty around generalising to the wider population. Nevertheless, as demonstrated, they certainly have utility in the correct setting.

CONCLUSION

Whilst they are the lowest ranked strata of research in EBP with clear disadvantages, case reports and case studies still represent an important and useful modality that are relatively quick and cost-effective to produce. When utilised in the appropriate context, these studies continue to have a significant impact upon clinical practice.

FOOTNOTES

Author contributions: Colwill M and Poullis A designed the research; Colwill M performed the literature review; Colwill M wrote the initial paper and Colwill M, Poullis A, Pollok R and Baillie S were all involved in manuscript review.

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Country/Territory of origin: United Kingdom

ORCID number: Michael Colwill 0000-0001-6925-8358; Samantha Baillie 0000-0003-3280-0347; Richard Pollok 0000-0001-6452-6763; Andrew Poullis 0000-0003-0703-0328.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of the causes of primary revision after unicompartmental knee arthroplasty: A case series

Jin-Long Zhao, Xiao Jin, He-Tao Huang, Wei-Yi Yang, Jia-Hui Li, Ming-Hui Luo, Jun Liu, Jian-Ke Pan

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Jin-Long Zhao, The Second Clinical Medical College, Guangzhou University of Chinese Medicine, Guangzhou 510405, Guangdong Province, China

Xiao Jin, Department of Chinese Medicine, The First Affiliated Hospital, Jinan University, Guangzhou 510630, Guangdong Province, China

He-Tao Huang, The Second School of Clinical Medical Sciences, Guangzhou University of Chinese Medicine, Guangdong Academy of Traditional Chinese Medicine, Guangzhou 510405, Guangdong Province, China

Wei-Yi Yang, Ming-Hui Luo, Jian-Ke Pan, The Second Affiliated Hospital, Guangzhou University of Chinese Medicine (Guangdong Provincial Hospital of Chinese Medicine), Guangzhou 510120, Guangdong Province, China

Jia-Hui Li, The Affiliated TCM Hospital, Guangzhou Medical University, Guangzhou 510405, Guangdong Province, China

Jun Liu, The Research Team on Bone and Joint Degeneration and Injury, Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou 510405, Guangdong Province, China

Corresponding author: Jian-Ke Pan, PhD, Chief Doctor, The Second Affiliated Hospital, Guangzhou University of Chinese Medicine (Guangdong Provincial Hospital of Chinese Medicine), No. 111 Dade Road, Yuexiu District, Guangzhou 510120, Guangdong Province, China. szypanjianke@yeah.net

Abstract

BACKGROUND

Unicompartmental knee arthroplasty (UKA) has great advantages in the treatment of unicompartmental knee osteoarthritis, but its revision rate is higher than that of total knee arthroplasty.

AIM

To summarize and analyse the causes of revision after UKA.

METHODS

This is a retrospective case series study in which the reasons for the first revision after UKA are summarized. We analysed the clinical symptoms, medical histories, laboratory test results, imaging examination results and treatment processes of the patients who underwent revision and summarized the reasons for primary

revision after UKA.

RESULTS

A total of 13 patients, including 3 males and 10 females, underwent revision surgery after UKA. The average age of the included patients was 67.62 years. The prosthesis was used for 3 d to 72 months. The main reasons for revision after UKA were improper suturing of the surgical opening (1 patient), osteophytes (2 patients), intra-articular loose bodies (2 patients), tibial prosthesis loosening (2 patients), rheumatoid arthritis (1 patient), gasket dislocation (3 patients), anterior cruciate ligament injury (1 patient), and medial collateral ligament injury with residual bone cement (1 patient).

CONCLUSION

The causes of primary revision after UKA were gasket dislocation, osteophytes, intra-articular loose bodies and tibial prosthesis loosening. Avoidance of these factors may greatly reduce the rate of revision after UKA, improve patient satisfaction and reduce medical burden.

Key Words: Unicompartmental knee arthroplasty; Total knee arthroplasty; Causes; Revision; Case series

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Core Tip: Despite the many advantages of unicompartmental knee arthroplasty (UKA), the long-term survival rate of implants and the rate of UKA revision remain controversial. Therefore, clarifying the reasons that may cause UKA revision can further reduce the revision rate of UKA surgery. We found that the main reasons for the initial revision of UKA were gasket dislocation, osteophytes, intra-articular loose bodies and tibial prosthesis loosening. Avoiding these factors may greatly reduce the revision rate after UKA surgery, improve patient satisfaction, and reduce medical burden.

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INTRODUCTION

Joint arthroplasty, such as total knee arthroplasty (TKA) or unicompartmental knee arthroplasty (UKA), is often used to treat end-stage unicompartmental knee osteoarthritis[1,2]. Compared with patients who undergo TKA, those who undergo UKA have smaller surgical wounds, recover faster postoperatively, have less blood loss, are more likely to have the anterior and posterior cruciate ligament preserved, as well as proprioception, a lower osteotomy rate, a shorter hospital stay, and lower costs[3-5]. Although UKA has many advantages, the long-term prosthesis survival rate and rate of revision after UKA are still controversial[6,7]. Many existing studies show that the rate of revision after UKA is much higher than that after TKA, and the main reason is aseptic loosening[8,9]. In this context, exploring and summarizing the causes that may lead to revision after UKA would be conducive to further reducing the UKA revision rate, which is highly valuable for orthopaedic surgeons and patients.

Although the rate of revision after UKA is higher than that after TKA, the total number of revisions after UKA is still relatively low; therefore, summarizing the causes of revision among UKA patients is necessary. By reviewing and analysing the causes of revision after UKA, we established references for the early detection of risk factors for revision in clinical practice and for formulating surgical strategies and rehabilitation programmes.

MATERIALS AND METHODS

Design and inclusion criteria

This was a retrospective case series study in which the reasons for primary revision after UKA were summarized. The inclusion criteria were as follows: (1) Indications for revision after UKA in the Department of Orthopaedics of Guangdong Provincial Hospital of Traditional Chinese Medicine from November 2016 to December 2020; and (2) First revision treatment after UKA (same side) (patients who underwent revision after the primary revision were not included). There were no restrictions regarding age, weight, race, activity or surgical materials used for UKA.

Data extraction and cause analysis

We used the electronic medical records system to extract and analyse the baseline data of the included patients, such as age, sex, surgical side and prosthesis use time. In addition, we comprehensively analysed the reasons for revision after

UKA among the included patients according to their medical histories, imaging data, physical and chemical test results, intraoperative conditions and pathological results. We also followed up on the recovery of the included patients after revision.

Data analysis

We used SPSS 25.0 software for the statistical analysis of the counts and descriptive statistics. The measurement data are expressed as the mean ± SD.

Ethical approval

This retrospective case series study was approved by the Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine, No. YE2021-370-01.

RESULTS

Characteristics of 13 patients

From November 2016 to December 2020, a total of 13 patients (13 knees), 3 males (23.08%) and 10 females (76.92%), underwent primary revision after UKA in our hospital (Table 1). The minimum age of the 13 patients included was 59 years, the maximum age was 76 years, and the average age was 67.62 years (standard deviation 5.88 years). There were 5 (38.46%) and 8 (61.54%) left and right knees, respectively, that underwent revision surgery after UKA. The prosthesis was used for 3 d to 72 months. The main causes of revision in 13 patients were improper suturing of the surgical opening (1 patient), osteophytes (2 patients), articular cavity free bodies (2 patients), tibial prosthesis loosening (2 patients), rheumatoid arthritis (RA) (1 patient), pad dislocation (3 patients), anterior cruciate ligament (ACL) injury (1 patient), and medial collateral ligament injury with residual bone cement (1 patient). As of February 2021, we have followed up all 13 patients who underwent revision surgery after UKA for at least half a year, and all patients have achieved good joint function.

Causes of revision after UKA in 13 patients

Improper suture: Patient 1, a 61-year-old female, underwent right-knee mobile-bearing UKA. She sought medical help because her right knee was red, swollen, hot and painful for 3 d. The lower part of the surgical opening of the right knee in Patient 1 was ulcerated and exuded, and the ulceration was round, measuring 0.5 cm × 0.5 cm. After the patient was admitted to the hospital, wound secretions and joint fluids were immediately collected for bacterial culture. No obvious abnormalities were found in the joint fluid test, and X-ray showed that the prosthesis was in a good position. Based on the above medical history and examination results, we ruled out intra-articular infection and decided to administer debridement treatment. During the operation, we found that the lower part of the original incision in the right knee had obvious inflammatory hyperplasia and subcutaneous soft tissue necrosis, and the wound was not connected to the joint cavity. Tissues near the surgical opening were sent for pathological examination. We thoroughly debrided- the necrotic incision during the operation. Postoperative pathology revealed hyperplasia of fibres and small vessels and infiltration of lymphocytes and neutrophils in the local area in the subcutaneous tissue of the right knee, which was consistent with inflammatory changes and multinuclear giant cell reactions. No bacteria were found in the preoperative wound secretion, joint fluid or intraoperative joint fluid culture. Based on the UKA surgical records of the patient and what we observed during the revision, we found that the original surgeon used bidirectional barbed suture, which is not suitable for suturing subcutaneous tissue. We believe that the application of knot-free sutures is the reason for the revision after UKA in Patient 1 (Figure 1).

Osteophytes: Patient 2, a 69-year-old male, underwent mobile-bearing UKA. He was admitted to the hospital because of pain in the upper lateral region of the right knee 4 months after UKA. Before revision, X-ray imaging revealed osteophytes on the lateral condyle of the right knee. We used a small incision to remove the osteophyte from the lateral condyle of the right knee. Postoperative X-ray showed that the osteophytes of the lateral condyle of the right knee had been removed (Supplementary Figure 1).

Patient 3, a 67-year-old male, underwent right-knee mobile-bearing UKA. He was admitted to the hospital due to postoperative pain in the right knee for 5 months. This patient underwent right-knee UKA at an external hospital 5 months prior and continued to experience medial anterior pain in the right knee after UKA. X-ray imaging showed that the tibial prosthesis was placed excessively inwards. Dual computed tomography (CT) showed osteophytes in front of the femoral prosthesis, and we confirmed this in the revision. During the knee joint activity test during revision, we found that the osteophyte collided with the tibial platform and that the bone cement at the lower front of the tibial platform prosthesis was broken, which seriously affected the stability of the tibial platform prosthesis. We cleaned the osteophytes, removed the tibial platform prosthesis, renovated it, and finally installed a new tibial platform prosthesis (Figure 2).

Intra-articular loose body: Two patients needed revision because of the presence of a free body in the joint cavity, and the clinical symptoms of both patients were obvious interlocking symptoms. We performed an arthroscopic downstream extracorporeal surgery.

Patient 4, a 59-year-old female, underwent mobile-bearing UKA of the left knee. She was hospitalized due to pain and locked symptoms for 1 month on the medial side of the left knee. After preoperative imaging and surgical exploration, we confirmed that the mass was free of residual bone cement.

Table 1 Characteristics of the 13 included patients

Case	Sex	Age (yr)	Side of knee	Year of revision	Duration of prosthesis	Cause for UKA revision	Outcome of UKA revision
Patient 1	Female	61	Right	2017	1 month	Improper suture	Cured
Patient 2	Male	69	Right	2018	4 months	Osteophyte	Cured
Patient 3	Male	67	Right	2017	5 months	Osteophyte	Cured
Patient 4	Female	59	Left	2018	20 months	Intra-articular loose body	Cured
Patient 5	Female	70	Left	2020	36 months	Intra-articular loose body	Cured
Patient 6	Male	75	Right	2018	8 months	Tibial prosthesis loosening	Cured
Patient 7	Female	70	Left	2018	23 months	Tibial prosthesis loosening	Cured
Patient 8	Female	76	Right	2017	72 months	Rheumatoid arthritis	Cured
Patient 9	Female	76	Right	2018	15 months	ACL injury	Cured
Patient 10	Female	63	Right	2019	7 months	Gasket dislocation	Cured
Patient 11	Female	63	Right	2016	48 months	Gasket dislocation	Cured
Patient 12	Female	69	Left	2018	10 months	Gasket dislocation	Cured
Patient 13	Female	61	Left	2018	3 d	Medial collateral ligament injury and bone cement residue	Cured

UKA: Unicompartmental knee arthroplasty.

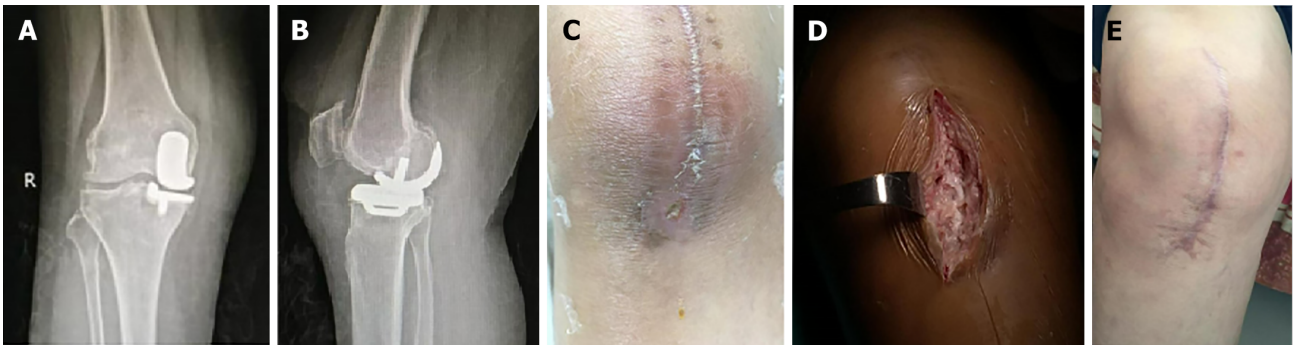

Figure 1 Treatment process (right knee) for Patient 1. A: Anteroposterior X-ray before revision; B: Lateral X-ray before revision; C: Surgical opening before revision; D: Incision for revision; E: The incision healed well after revision.

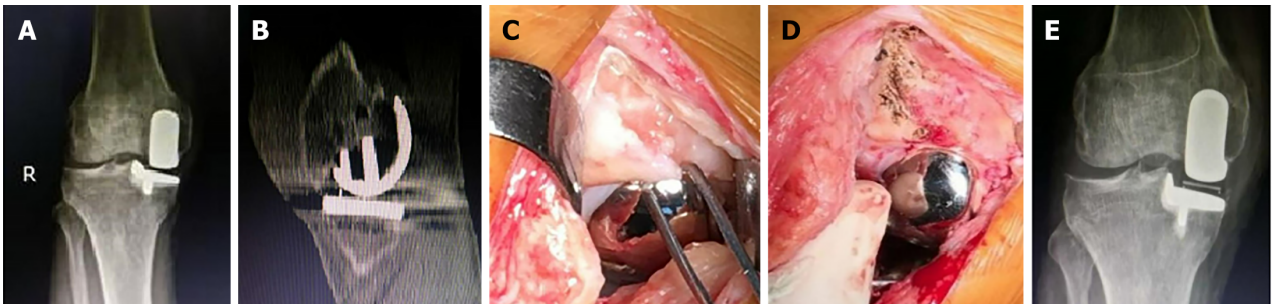

Figure 2 Treatment process (right knee) for Patient 3. A: Anteroposterior X-ray before revision; B: Dual computed tomography image showing osteophytes in front of the femoral prosthesis; C: Osteophytes in front of the femoral prosthesis; D: Excision of osteophytes; E: Anteroposterior X-ray after revision.

Patient 5, a 70-year-old female, underwent fixed-bearing UKA. The patient was hospitalized due to swelling and pain in the left knee for 2 years. Dual CT showed that there was a bone-free body between the tibial prosthesis and the femoral prosthesis (Figure 3).

Tibial prosthesis loosening: Two patients underwent fixed-bore UKA. The tibial platform prosthesis became loose, so we revised the operation to TKA.

Patient 6, a 75-year-old male, was admitted to the hospital due to walking pain for 8 months after right-knee UKA. X-ray imaging revealed an interface under the tibial platform prosthesis, and compared with the previous X-ray after UKA, we found a change in the tibial prosthesis position. The tibial plateau was easily removed with forceps during the operation (Figure 4).

Patient 7, a 70-year-old female, sought medical help because of weakness in the medial side of the left knee for 16 months. The X-ray and intraoperative conditions were similar to those of Patient 6.

RA: Patient 8, a 76-year-old female, underwent mobile-bearing UKA of the right knee. She sought medical help because of swelling and pain in the right knee and ankle for one year after UKA. The patient had undergone right-knee UKA 6 years prior and recovered well after the operation. Afterwards, she suffered from repeated swelling and pain in the right knee and ankle for one year. The rheumatoid antibody test confirmed RA, and a large amount of inflammatory synovium in the suprapatellar bursa and cartilage degeneration damage in the lateral compartment of the knee joint were observed during the revision. The prosthesis was easily and completely removed during the operation, and the knee joint was rebuilt during TKA (Figure 5).

ACL injury: Patient 9, a 76-year-old female, underwent fixed-bearing UKA of the right knee. She sought medical help because of postoperative pain in the right knee and limited mobility. Imaging before UKA indicated that the patient's right knee ACL was broken. X-ray imaging revealed that the right-knee tibia was moved forward, so fixed-bearing UKA was performed. Half a year after UKA, the patient developed instability of the knee joint and repeated pain, and the X-ray showed that the right-knee tibia had moved forward significantly. Following the patient's wishes, TKA was performed after conservative treatment failed (Figure 6).

Gasket dislocation: Three patients underwent mobile-bearing UKA.

Patient 10, a 63-year-old female, developed knee joint pain and limited activity 7 months after right-knee UKA. The X-ray image indicated that the gasket was dislocated forward. We performed knee flexion and extension tests with the original 3-mm pad. At the buckling position, the 3-mm gasket became loose, the 4-mm gasket was under proper tension, and the 5-mm gasket was too tight. The 3-mm gasket was in good condition, the 4-mm gasket was slightly tight, and the 5-mm gasket was very tight and straight. After the above tests, we replaced the gasket with a 4-mm gasket (Supplementary Figure 2).

Patient 11, a 63-year-old female, suffered from pain in the right knee and walking instability after UKA, which persisted for 4 months. The X-ray images indicated that the gasket was dislocated both backwards and downwards. We tested the range of motion of the knee joint and the position of the spacer during the revision, and the results showed that the uneven flexion extension space and poor placement of the femoral prosthesis led to a poor trajectory of the spacer. Finally, the case was revised to TKA (Supplementary Figure 3).

Patient 12, a 69-year-old female, underwent one-stage double-knee UKA at another hospital. She suffered from dislocation of the right knee pad half a year after UKA and returned to the external hospital for revision by TKA. Two months later, the patient had another anterior dislocation of the left knee pad. We compared the postoperative X-ray data of the patient with those of a patients whose prosthesis was placed in the Oxford Monocondyle Course[10] and found that the patient's bilateral femoral prostheses were close to the femur without overhang, which indicated residual osteophytes behind the femur and that the selected femoral prostheses were small. We found two problems at the same time during the operation: first, when the knee joint was in extreme flexion, the pad was moved forward, indicating that there was a rear impact; second, there were residual osteophytes of the femoral medial condyle, leading to the operator's incorrect assessment of the left and right diameters of the femoral medial condyle, and the femoral prosthesis being placed inwards, causing poor tracking of the spacer when the knee joint moved. We completely removed the osteophytes and placed the femoral prosthesis laterally. In addition, we replaced a larger femoral prosthesis and thickened pads (Figure 7).

Injury to the medial collateral ligament and residual bone cement: Patient 13, a 61-year-old female, underwent mobile-bearing UKA of her left knee. The patient was unable to walk and had pain in his left knee. Patient 13 underwent reoperation due to postoperative genu valgus with medial collateral ligament injury and residual bone cement. X-ray showed that the vertical osteotomy of the tibia was inwards, there was more medial suspension of the tibial prosthesis, and there was remaining bone cement. Physical examination revealed grade II damage to the medial collateral ligament. We performed bone cement cleaning+medial collateral ligament repair+shim (small 1) revision 3 d after UKA (Figure 8). This patients underwent revision due to the inexperience of the operator and technical failure.

DISCUSSION

In this study, we summarized the causes of 13 cases of revision after UKA, which we believe can provide a valuable reference for orthopaedic surgeons evaluating patient conditions and selecting surgical methods. Owing to the large advantages of UKA for the treatment of unicompartmental knee osteoarthritis, it is extremely important to reduce or even

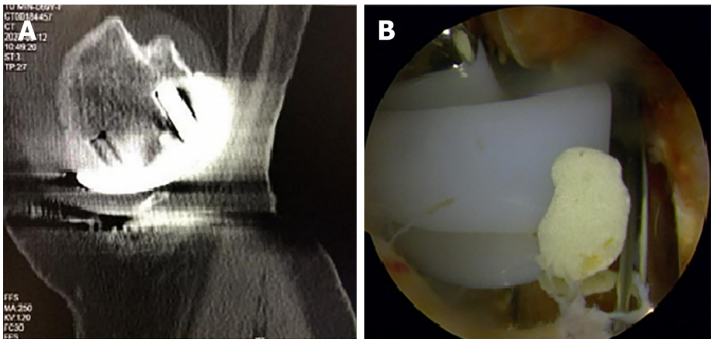

Figure 3 Treatment process (left knee) for Patient 5. A: Dual computed tomography image showing that there was a bone-free body between the tibial prosthesis and the femoral prosthesis; B: Residual bone cement was found during arthroscopic exploration.

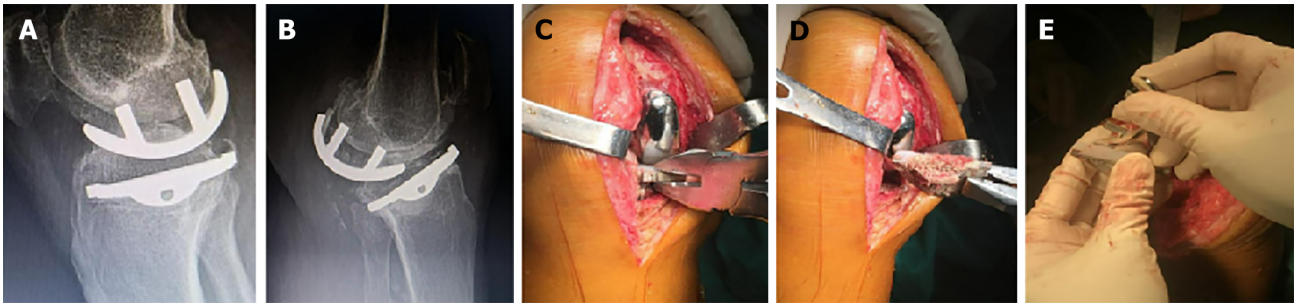

Figure 4 Treatment process (right knee) for Patient 6. A: Anteroposterior X-ray before revision; B: Lateral X-ray before revision; C: The tibial prosthesis was loose; D: The tibial prosthesis was easily removed during revision; E: The femoral prosthesis was removed and modified for total knee arthroplasty.

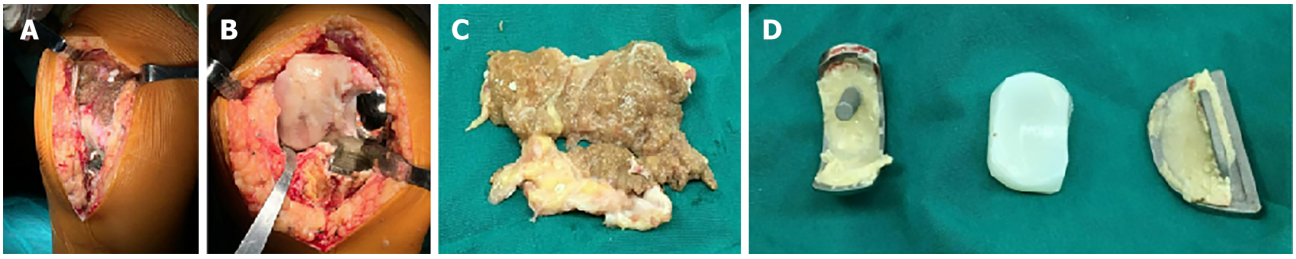

Figure 5 Treatment process (right knee) for Patient 8. A: A large amount of inflammatory synovium in the suprapatellar bursa was observed during revision; B: The lateral femoral condyle cartilage was injured; C: Synovial tissue; D: Oxford movable platform single condyle prosthesis.

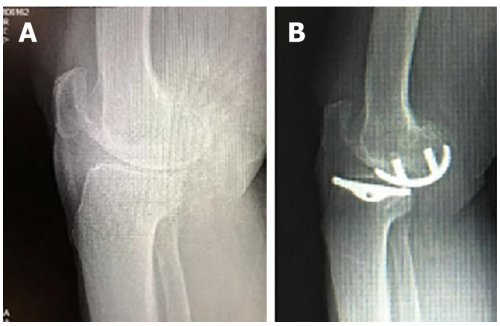

Figure 6 Treatment process (right knee) for Patient 9. A: Lateral X-ray before unicompartmental knee arthroplasty (UKA); B: Lateral X-ray in the weight-bearing position after UKA.

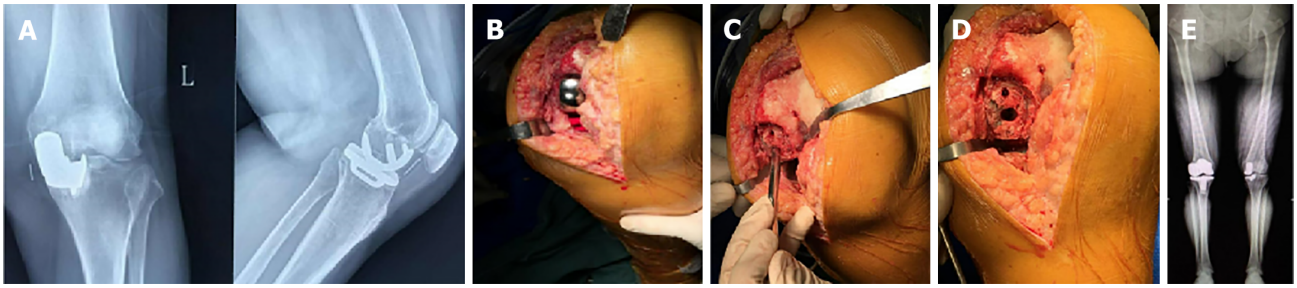

Figure 7 Treatment process (left knee) for Patient 12. A: Before revision, X-ray showed that the gasket was dislocated; B: The spacer was moved forward under extreme knee flexion; C: The centre of the femoral prosthesis was inwards; D: Prosthesis displacement; E: X-ray after revision.

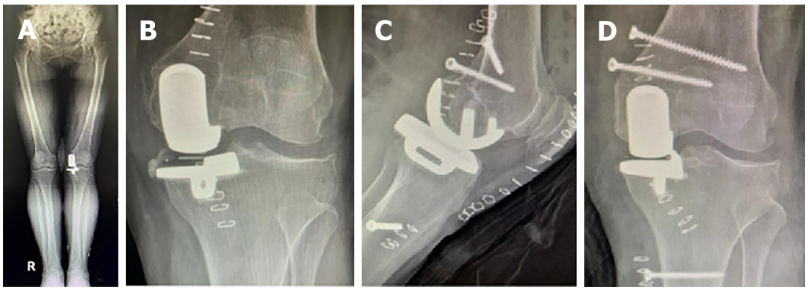

Figure 8 Treatment process (left knee) for Patient 13. A: X-ray image showing genu valgus after Unicompartmental knee arthroplasty (UKA); B: X-ray showing residual bone cement after UKA; C: Repair of the medial collateral ligament; D: X-ray anteroposterior films after revision.

eliminate the risk of revision after UKA. Circumventing the risk factors leading to revision after UKA summarized in this study may be beneficial for selecting UKA for the treatment of unicompartmental knee osteoarthritis and achieving better clinical outcomes.

In this study, gasket dislocation (3/13) was the main cause of revision after UKA. Compared with fixed-bearing prostheses, movable prostheses are more prone to dislocation. The 3 patients with spacer dislocation included in this study were all treated with mobile-bearing UKA. Pad dislocation occurs in 0.9% to 4.0% of cases[11], almost all of which occur in movable platform-type single condyle prostheses. We believe that the most common cause of iatrogenic gasket dislocation is insufficient gasket containment, which is often related to surgical errors. We believe that it is very important to fully evaluate and select the correct thickness of the shims and appropriate prostheses before or during UKA. For the treatment of dislocation of the pad after UKA, the operator needs to fully evaluate the position of the femoral and tibial prosthesis components, the balance of the knee joint space, and the state of the soft tissue and accurately determine the cause of dislocation to select the replacement pad model or revision. According to the results of the revision of Patient 12, we believe that the technical focus should be on the selection of a femoral prosthesis, which should be greater than or equal to the original prosthesis.

The proportion of UKA revisions caused by osteophytes, articular cavity free bodies and tibial prosthesis loosening was 15.35%. We believe that osteophytes, bone cement or bone residue caused by technical reasons should be considered by bone surgeons. The presence of osteophytes and an intra-articular loose body is likely to cause an impact between the prosthesis and the bone structure, which may lead to loosening of the prosthesis, fracture around the prosthesis, dislocation of the pad, degeneration or tearing of the cruciate ligament[12-14]. Therefore, the operator should be familiar with the technical needs of UKA. During the operation, the osteophyte and bone cement residue at risk of impact should be completely removed, and the hyperplastic synovium of the joint should be removed if necessary. When osteophytes or loose bodies in the joint cavity are found early after UKA without causing serious impact, we believe that cleaning up the hyperplastic osteophytes, synovium, and residual or fallen bone cement under arthroscopy is appropriate, which was also verified in our follow-up. If severe impact complications occur, orthopaedic surgeons should choose to perform pad replacement, single condylar prosthesis replacement or TKA revision according to the type of complication.

There were 1 case of improper suture, 1 case of RA, 1 case of ACL injury, and 1 case of medial collateral ligament injury with residual bone cement. Generally, UKA results in a smaller incision and less soft tissue damage, and the infection risk associated with UKA is lower than that associated with TKA. Therefore, UKA should be performed under strict aseptic conditions, and standardized surgical suturing procedures should be upheld. The medial collateral ligament and the ACL are important for maintaining joint stability and participating in flexion and extension activities, and their functional integrity is one of the necessary conditions for selecting UKA. Therefore, we carefully evaluated the function of the lateral collateral ligament and the ACL before the operation, especially the location and direction of the vertical osteotomy of the tibial plateau. The orthopaedic surgeon should focus on protecting the medial collateral ligament during horizontal osteotomy, which can reduce the risk of such complications. For patients with a family history of RA or who are considered susceptible patients, orthopaedic surgeons should fully communicate with patients before surgery and conduct corresponding RA screening tests, which may help reduce the rate of UKA revision due to RA. For elderly

patients and those who are at high risk of RA, we think that TKA may be a more suitable choice.

This was a retrospective case study. The main defects of this study design are memory bias and nonresponse bias. Second, because a small number of patients were included, the representativeness of the data was poor. Therefore, the conclusions of this study should be considered in light of the above limitations.

CONCLUSION

This study revealed that the causes of revision after UKA were mainly gasket dislocation, osteophytes, intra-articular loose bodies and tibial prosthesis loosening. Circumventing these factors may greatly reduce the rate of UKA revision, improve patient satisfaction and reduce medical burden. In addition, UKA is critical for comprehensively and objectively assessing the knee ligament status and RA risk of patients to subsequently select the appropriate surgical method (UKA or TKA).

ARTICLE HIGHLIGHTS

Research background

Unicompartmental knee arthroplasty (UKA) has great advantages in the treatment of unicompartmental knee osteoarthritis, but its revision rate is higher than that of total knee arthroplasty.

Research motivation

Providing a reference for orthopaedic surgeons to reduce the revision rate and improve patient satisfaction.

Research objectives

The study aims to summarize and analyse the causes of revision after UKA.

Research methods

This is a retrospective case series summarizing the reasons for the first revision after UKA in the Department of Orthopedics of Guangdong Provincial Hospital of Traditional Chinese Medicine from November 2016 to December 2020. We analysed data on the clinical symptoms, medical history, laboratory tests, imaging examinations and treatment process of the revision cases and summarized the reasons for primary revision after UKA among all cases.

Research results

Thirteen patients, including 3 males and 10 females, underwent revision surgery after UKA. The average age of the included patients was 67.62 years. The main reasons for revision after UKA were improper suturing of the surgical opening, osteophytes, intra-articular loose bodies, tibial prosthesis loosening, rheumatoid arthritis, gasket dislocation, anterior cruciate ligament injury, and medial collateral ligament injury with residual bone cement.

Research conclusions

The causes of primary revision after UKA were gasket dislocation, osteophytes, intra-articular loose bodies and tibial prosthesis loosening.

Research perspectives

Avoidance of these factors found in this study may greatly reduce the rate of revision after UKA, improve patient satisfaction and reduce medical burden.

FOOTNOTES

Co-first authors: Jin-Long Zhao and Xiao Jin.

Co-corresponding authors: Jun Liu and Jian-Ke Pan.

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Country/Territory of origin: China

ORCID number: Wei-Yi Yang 0000-0001-8657-2269; Ming-Hui Luo 0000-0001-6831-6317; Jun Liu 0000-0002-1943-3880; Jian-Ke Pan 0000-0002-4596-6111.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of minimally invasive laparoscopic surgery under general anesthesia for ovarian cancer

Xian Qin, Chen Chen, Yang Liu, Xian-Hong Hua, Jia-Yi Li, Meng-Jie Liang, Fang Wu

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Xian Qin, Chen Chen, Yang Liu, Xian-Hong Hua, Department of Anesthesiology, The First People's Hospital of Jiangxia District, Wuhan 430200, Hubei Province, China

Jia-Yi Li, Meng-Jie Liang, Fang Wu, Department of Obstetrics and Gynecology, The First People's Hospital of Jiangxia District, Wuhan 430200, Hubei Province, China

Corresponding author: Fang Wu, MBChB, Department of Obstetrics and Gynecology, The First People's Hospital of Jiangxia District, No. 1 Zhifang Cultural Avenue, Jiangxia District, Wuhan 430200, Hubei Province, China. wufang771025@163.com

Abstract

BACKGROUND

Ovarian cancer is one of the most common malignant tumors in female reproductive system in the world, and the choice of its treatment is very important for the survival rate and prognosis of patients. Traditional open surgery is the main treatment for ovarian cancer, but it has the disadvantages of big trauma and slow recovery. With the continuous development of minimally invasive technology, minimally invasive laparoscopic surgery under general anesthesia has been gradually applied to the treatment of ovarian cancer because of its advantages of less trauma and quick recovery. However, the efficacy and safety of minimally invasive laparoscopic surgery under general anesthesia in the treatment of ovarian cancer are still controversial.

AIM

To explore the efficacy and safety of general anesthesia minimally invasive surgery in the treatment of ovarian cancer.

METHODS

The clinical data of 90 patients with early ovarian cancer in our hospital were analyzed retrospectively. According to the different surgical treatment methods, patients were divided into study group and control group (45 cases in each group). The study group received minimally invasive laparoscopic surgery under general anesthesia for ovarian cancer, while the control group received traditional open surgery for ovarian cancer. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), clinical efficacy and safety of the two groups were compared.

RESULTS

The intraoperative blood loss, length of hospital stay, postoperative gas evacuation time, and postoperative EORTC QLQ-C30 score of the study group were significantly better than those of the control group ($P < 0.05$). The incidence of postoperative complications in the study group was significantly lower than in the control group ($P < 0.05$). The two groups had no significant differences in the preoperative adrenocorticotropic hormone (ACTH), androstenedione (AD), cortisol (Cor), cluster of differentiation 3 positive (CD3+), and cluster of differentiation 4 positive (CD4+) indexes ($P > 0.05$). In contrast, postoperatively, the study group's ACTH, AD, and Cor indexes were lower, and the CD3+ and CD4+ indexes were higher than those in the control group ($P < 0.05$).

CONCLUSION

Minimally invasive laparoscopic surgery under general anesthesia in patients with early ovarian cancer can significantly improve the efficacy and safety, improve the short-term prognosis and quality of life of patients, and is worth popularizing.

Key Words: Early-stage ovarian cancer; Efficacy; Minimally invasive; Laparoscopy; Safety; Surgery

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Core Tip: This study found that compared with traditional open surgery, minimally invasive laparoscopic surgery under general anesthesia has better curative effect, faster recovery speed, lower risk of complications and less impact on immune function in the treatment of patients with early ovarian cancer. Therefore, minimally invasive laparoscopic surgery under general anesthesia can be the first choice for patients with early ovarian cancer.

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INTRODUCTION

Ovarian cancer is one of the malignant tumors of the female reproductive system. It is mainly characterized by lower abdominal masses and abdominal effusion as clinical manifestations. According to reports, the mortality rate of ovarian cancer ranks first among gynecological malignancies. Most cases originate from the ovarian epithelium and during the course of the disease, local infiltration and distant metastasis are common[1]. Ovarian cancer accounts for 2.5% of female malignancies, and the 5-year survival rate for early-stage ovarian cancer is as high as 93%. However, early-stage ovarian cancer usually presents no characteristic symptoms, making diagnosis relatively difficult. Approximately 70% of ovarian cancer patients are diagnosed in the late stage, resulting in a poor prognosis with a 5-year survival rate of less than 30%[2-4]. Therefore, early and accurate diagnosis as well as standardized treatment can better improve the prognosis of ovarian cancer patients[5]. Currently, surgery remains the main treatment for early-stage ovarian cancer. However, traditional surgical procedures, primarily open surgeries, have many drawbacks including large trauma and slow patient recovery. With the continuous development of laparoscopic techniques, their application in the treatment of early-stage ovarian cancer has become more widespread[6,7].

Compared to the issues of large incision and slow recovery associated with open surgery, laparoscopic techniques have the following advantages: smaller trauma[8], simultaneous diagnosis and treatment, faster recovery[9], shorter hospitalization time[10], better abdominal cosmetic effect, and easy preservation of imaging data. In the diagnosis and treatment of ovarian cancer, laparoscopic techniques can complement open surgeries. In clinical practice, laparoscopic exploration is performed for suspected pelvic masses, and if intraoperative frozen pathology confirms ovarian cancer, the procedure can be converted to open surgery for comprehensive staging, thus avoiding the need for a second surgery[11,12]. For patients with advanced ovarian cancer, laparoscopic exploration can be performed. If evaluated as suitable for primary tumor debulking, the procedure can be directly converted to open surgery for tumor debulking[13,14].

Therefore, this study focuses on early-stage ovarian cancer patients and evaluates the application value of open surgery and minimally invasive laparoscopic surgery under general anesthesia in this population, aiming to provide clinical reference for the optimal selection of surgical approaches in the treatment of early-stage ovarian cancer.

MATERIALS AND METHODS

General information

A retrospective analysis was conducted on the clinical data of 90 early-stage ovarian cancer patients admitted to our department from January 2022 to January 2023. According to different surgical treatment methods, the patients were

divided into a study group and a control group, with 45 cases in each group. The study group underwent laparoscopic ovarian cancer surgery, while the control group underwent open abdominal ovarian cancer surgery. Pathological examination was performed on all tumors, including all histological types of ovarian cancer. After comprehensive staging, epithelial ovarian cancer was defined as stage I or II disease according to the International Federation of Gynecology and Obstetrics (FIGO) classification, excluding patients with stage III or IV disease.

Inclusion criteria

Inclusion criteria: (1) Confirmed diagnosis of ovarian cancer through imaging and cytology examination; (2) Diagnosed with early-stage ovarian cancer according to the FIGO criteria; (3) Suitable for surgical intervention; and (4) No tumor metastasis.

Exclusion criteria: (1) Presence of other tumors; (2) Organ failure; (3) Inability to tolerate surgery; or (4) Allergy to anesthesia drugs.

Data collection

Retrospective review of electronic medical records of all included patients was conducted to collect demographic and clinical characteristics, preoperative assessment, surgical description (duration, amount of bleeding, tumor rupture, and intraoperative complications), postoperative complications and their occurrence time, tolerance to oral intake and activity, and length of hospital stay.

Study methods

Study group: Study group (Laparoscopy group) performed laparoscopic lymph node dissection for treatment. The patient received general anesthesia and was placed in the lithotomy position with bladder lithotomy. After disinfection, aseptic drapes were placed and a uterine elevator was inserted through the vagina. A puncture needle was inserted about 3 cm above the umbilicus, and pneumoperitoneum was established with an insufflation pressure of 12-14 mmHg. After the procedure was completed, a laparoscope was inserted, and the patient's position was adjusted to a high hip and low head position under the monitoring of the laparoscope. Cannulation was performed under laparoscopic guidance at the lower abdomen on both sides, with 2 or 3 5-mm Trocar ports. The abdominal and pelvic cavities were thoroughly explored, and approximately 200 mL of 0.9% saline solution was used for irrigation of the abdominal and pelvic cavities. The irrigation fluid was then collected and sent for examination. Based on intraoperative exploration, ovarian tumors and adnexa were removed, and rapid frozen sections were performed to examine the tumor lesions. Bilateral adnexectomy, hysterectomy, pelvic lymph node dissection, and abdominal aorta lymph node dissection were performed according to the pathological results. The excised tissues were placed in specimen bags.

Control group: In the control group (open surgery group), under general anesthesia, the patient was placed in a supine position. After routine disinfection and draping, the midline of the abdomen was used as the surgical incision. The abdomen was opened layer by layer to expose the lesion site, and the same tumor cell reduction technique as the laparoscopy group was performed. Postoperatively, all patients received chemotherapy when conditions allowed.

Observation indicators

Perioperative indicators: Operation time, intraoperative bleeding volume, number of lymph nodes cleaned, postoperative anal exhaust time, time to get out of bed, and length of hospital stay.

Occurrence of complications: Incision infection, pulmonary infection, urinary retention, venous thrombosis, and intestinal obstruction, *etc.*

Quality of life: The quality of life of patients was evaluated before surgery, 1 month after surgery, and 3 months after surgery using the Chinese version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. It includes 30 items with a total score of 126 points. A higher score indicates a better quality of life[15].

Stress response: 5 mL of fasting morning venous blood was taken before surgery and 1 d after surgery, centrifuged at 3000 rpm for 10 min to separate serum, and enzyme-linked immunosorbent assay was used to detect adrenocorticotropic hormone (ACTH), androstenedione (AD), and cortisol (Cor).

Immune function: 5 mL of fasting morning venous blood was collected before surgery and 1 day after surgery, and the supernatant was taken after centrifugation for flow cytometry to detect cluster of differentiation cluster of differentiation 3 positive (CD3+) and CD4+ levels.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 statistical software. Continuous variables were expressed as mean ± SD and compared using *t*-test or *F*-test. Categorical variables were expressed as percentages [*n* (%)] and compared using χ^2 test. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Comparison of baseline characteristics between the two patient groups

Study group (using laparoscopic ovarian cancer surgery) patients aged 35 to 66 years, with an average age of 55.0 ± 17.1 years; Body mass index (BMI) score of 24.1 ± 3.9 kg/m^2; tumor average diameter 6.84 ± 2.15 cm; FIGO clinical stage: stage I in 21 cases, accounting for 46.67%, stage II in 24 cases, accounting for 53.33%; pathological classification: mucinous carcinoma in 20 cases, accounting for 44.44%, serous adenocarcinoma in 16 cases, accounting for 35.56%, endometrioid carcinoma in 6 cases, accounting for 13.33%, clear cell carcinoma in 3 cases, accounting for 6.67%; control group (using open abdominal ovarian cancer surgery) patients aged 34 to 65 years, with an average age of 55.8 ± 18.8 years; BMI score of 24.7 ± 4.2 kg/m^2; tumor average diameter 6.92 ± 2.21 cm; FIGO clinical stage: stage I in 23 cases, accounting for 51.11%, stage II in 22 cases, accounting for 48.89%; pathological classification: mucinous carcinoma in 21 cases, accounting for 46.67%, serous adenocarcinoma in 15 cases, accounting for 33.33%, endometrioid carcinoma in 5 cases, accounting for 11.11%, clear cell carcinoma in 4 cases, accounting for 8.89%. The general clinical data of the research group and the control group were compared, and there was no statistically significant difference ($P > 0.05$), indicating comparability, as shown in Table 1.

Comparison of perioperative conditions between two groups of patients

The research group had significantly less intraoperative bleeding compared to the control group. The postoperative anal exhaust time, time to get out of bed, and length of hospital stay were significantly shorter in the research group compared to the control group. The differences between the two groups were statistically significant ($P < 0.05$). There was no statistically significant difference in surgical time and number of lymph node dissections compared to the control group ($P > 0.05$), as shown in Table 2.

Comparison of incidence of complications between the two groups

The incidence of complications in the study group was significantly lower than that in the control group, with a statistically significant difference ($\chi^2 = 7.688$, $P < 0.05$), as shown in Table 3.

Comparison of quality of life between the two groups of patients

There was no statistically significant difference in preoperative quality of life scores between the study group and control group ($P > 0.05$); however, the postoperative 1-month and 3-month quality of life scores in the study group were significantly higher than those in the control group ($P < 0.05$), as shown in Table 4.

Comparison of stress response between the two groups

There was no difference in the preoperative levels of ACTH, AD, and Cor between the two groups ($P > 0.05$). However, after the surgery, all these indicators in the study group were significantly lower than those in the control group ($P < 0.05$), as shown in Table 5.

Comparison of immune function between the two groups

There was no difference in preoperative CD3+ and CD4+ levels between the two groups ($P > 0.05$). However, after the surgery, these indicators in the study group were higher than those in the control group ($P < 0.05$), as shown in Table 6.

DISCUSSION

Ovarian cancer is a common clinical condition. Early ovarian cancer refers to stage I and II Ovarian cancer. Due to its deep anatomical location, early ovarian cancer may have no typical clinical manifestations. It is often diagnosed when patients present with menstrual disorders, lower abdominal pain or discomfort, or palpable masses. Most patients are already in the advanced stage when diagnosed, and the treatment results are poor. Moreover, this disease has a high incidence and mortality rate. Surgery is one of the main treatment methods for early ovarian cancer. Open surgery is the traditional treatment method for early ovarian cancer, aiming to remove tumor tissue as much as possible to achieve a macroscopically tumor-free effect. However, this surgical approach has limitations such as large incisions and slow postoperative recovery[16]. In recent years, minimally invasive laparoscopic surgery under general anesthesia has been applied in the treatment of various diseases due to its minimally invasive advantages. Under laparoscopic visualization, it can fully utilize its advantages of minimally invasiveness and magnified vision, making the surgical procedure smoother[17]. With the further development of minimally invasive laparoscopic surgery under general anesthesia, adopting minimally invasive laparoscopic surgery under general anesthesia to treat early ovarian cancer will become a new standard procedure.

This study shows that the research group has lower blood loss and higher number of lymph node clearances compared to the control group. The postoperative exhaust time and length of stay in the hospital are both shorter, indicating that minimally invasive laparoscopic surgery under general anesthesia can significantly reduce intraoperative blood loss, improve the number of lymph node clearances, accelerate postoperative exhaust time, and shorten hospital stay. The analysis suggests that laparoscopy can enlarge the surgical field of view, better distinguish anatomical levels, and provide a more comprehensive clearance of pelvic lymph nodes and para-aortic lymph nodes[18]. In addition, laparoscopic instruments are more delicate and can cut tissues closely, reducing damage to surrounding organs and minimizing

Table 1 Basal characteristics of patients included in the study, according to surgical approach, *n* (%)

Index	Study group (*n* = 45)	Control group (*n* = 45)	*t*/χ^2 value	*P* value
Age (yr)	55.0 ± 17.1	55.8 ± 18.8	0.211	> 0.05
BMI (kg/m^2)	24.1 ± 3.9	24.7 ± 4.2	0.702	> 0.05
Tumor diameter (cm)	6.84 ± 2.15	6.92 ± 2.21	0.174	> 0.05
FIGO			0.178	> 0.05
I	21 (46.67)	23 (51.11)		
II	24 (53.33)	22 (48.89)		
Type of pathology			0.645	> 0.05
Mucinous cancer	20 (44.44)	21 (46.67)		
Serous carcinoma	16 (35.56)	15 (33.33)		
Endometrioid cancer	6 (13.33)	5 (11.11)		
Clear cell carcinoma	3 (6.67)	4 (8.89)		

BMI: Body mass index; FIGO: International Federation of Gynecology and Obstetrics.

Table 2 Perioperative comparison between study and control groups (mean ± SD)

Index	Study group (*n* = 45)	Control group (*n* = 45)	*t* value	*P* value
Duration of surgery (min)	257.41 ± 28.16	255.23 ± 28.37	0.366	> 0.05
Intraoperative bleeding quantity (min)	323.76 ± 40.25	387.44 ± 43.23	7.232	< 0.05
Lymph node clearance number of sweeps (pcs)	25.78 ± 3.35	26.04 ± 3.17	0.378	> 0.05
Postoperative anus exhaust time (d)	1.96 ± 0.42	2.61 ± 0.54	6.374	< 0.05
Get out of bed after surgery time (d)	2.85 ± 0.53	3.92 ± 0.64	8.638	< 0.05
Postoperative hospitalization time (d)	13.29 ± 2.11	16.66 ± 2.24	7.346	< 0.05

Table 3 Comparison of complications between study and control groups, *n* (%)

Index	Study group (*n* = 45)	Control group (*n* = 45)	χ^2 value	*P* value
Incision infection	1 (2.22)	2 (4.44)		
Lung infections	1 (2.22)	3 (6.67)		
Urinary retention	1 (2.22)	2 (4.44)		
Venous thrombosis	0 (0.00)	1 (2.22)		
Ileus	0 (0.00)	1 (2.22)		
Total	5 (6.67)	9 (20.00)	7.688	< 0.05

intraoperative blood loss. On the other hand, open surgery has limited visual range and more restrictions on surgical instruments, resulting in fewer lymph node clearances and more blood loss during the procedure. Therefore, open surgery requires a longer recovery time and extended length of hospital stay compared to minimally invasive laparoscopic surgery under general anesthesia[19].

Surgical safety has always been an important concern in clinical practice. Studies have shown that the incidence and recurrence rates of complications were significantly lower in the study group compared to the control group, indicating that minimally invasive laparoscopic surgery under general anesthesia can significantly reduce postoperative complications and have a high level of safety. The reasons for this analysis are that minimally invasive laparoscopic surgery under general anesthesia causes less tissue damage, reduces the risk of postoperative infections and other complications, and promotes milder reflex spasms of the anal sphincter due to smaller incisions and less postoperative pain. As a result, the risks of postoperative urinary retention and urinary incontinence are lower[20,21]. At the same time, performing surgical treatment under laparoscopy allows physicians to clearly explore the diseased tissue and its surrounding tissues. With the magnification function of laparoscopy, physicians can more thoroughly remove tumor tissues, thereby reducing

Table 4 Quality of life scores comparison between study and control groups (mean ± SD, points)

Index	Study group (*n* = 45)	Control group (*n* = 45)	*t* value	*P* value
Preoperatively	65.62 ± 9.58	66.12 ± 10.26	0.239	> 0.05
One month after surgery	66.25 ± 8.95	60.42 ± 8.53	3.163	< 0.05
Three months after surgery	78.95 ± 12.39	66.84 ± 11.34	4.837	< 0.05
F value	23.467	5.447		
P value	< 0.05	< 0.05		

Table 5 Comparison of the two sets of stress responses (mean ± SD)

Index	Group	Study group (*n* = 45)	Control group (*n* = 45)	*t* value	*P* value
ATCH (pmol/L)	Before surgery	11.22 ± 5.35	11. 64 ± 5.51	0.367	> 0.05
	After surgery	14.21 ± 12.03	20. 35 ± 12.37	2.387	< 0.05
AD (pmol/L)	Before surgery	30.35 ± 7.49	31. 22 ± 7.48	0.551	> 0.05
	After surgery	39.69 ± 8.71	46. 86 ± 7.36	4.218	< 0.05
Cor (nmol/L)	Before surgery	230.51 ± 8.92	231. 64 ± 8.76	0.606	> 0.05
	After surgery	299.13 ± 9.42	312. 02 ± 9.64	6.4150	< 0.05

ATCH: Adrenocorticotropic hormone; AD: Androstenedione; Cor: Cortisol.

Table 6 Comparison of the two groups of immune function (mean ± SD)

Index	Group	Study group (*n* = 45)	Control group (*n* = 45)	*t* value	*P* value
CD3+	Before surgery	53.54 ± 5.07	55.56 ± 5.12	1.881	> 0.05
	After surgery	50.85 ± 5.16	43.12 ± 5.82	6.667	< 0.05
CD4+	Before surgery	35.32 ± 4.95	33.91 ± 5.53	1.274	> 0.05
	After surgery	32.64 ± 3.06	27.61 ± 3.24	7.571	< 0.05

CD3+: Cluster of differentiation 3 positive; CD4+: Cluster of differentiation 4 positive.

the postoperative recurrence rate and improving the prognosis of ovarian cancer patients[22].

Stress response mainly refers to the changes in various neuroendocrine systems in the body after trauma caused by surgery or anesthesia, which is closely related to the trauma of surgery[3]. ACTH is secreted by the pituitary gland and has the function of promoting the secretion of corticosteroids by the adrenal cortex. When the body is stimulated by trauma such as surgery, it can cause pituitary-adrenal axis excitation, which in turn triggers a series of neuroendocrine responses, belonging to the body's adaptive stress response[23]. Some studies have pointed out that the higher the level of Cor, the more severe the trauma in patients. Sustained high levels of serum Cor can lead to patient death. Therefore, dynamic monitoring of serum Cor levels can serve as a sensitive indicator to evaluate the body's stress response, which helps in assessing the patient's stress status[24]. AD belongs to adrenal medullary hormones, which are rapidly metabolized in the body. Testing AD can help assess medullary function, maintain sympathetic nervous system activity, and promote normal heart rhythm. It is reported that the postoperative research group had lower levels of ACTH, AD, and Cor compared to the reference group, indicating that minimally invasive laparoscopic surgery under general anesthesia treatment for early-stage ovarian cancer patients had a smaller impact on the body's stress response. This may be related to the minimally invasive nature of minimally invasive laparoscopic surgery under general anesthesia, smaller surgical incisions, less damage to the abdominal-pelvic tissues, timely and reasonable hemostasis, and less trauma to the body, which can help reduce the body's stress response and promote postoperative recovery.

CD3+ is an antigen found on the surface of T lymphocytes, mainly mature T cells, and it represents the immune function of the body. CD4+ cells play an important role in the immune system, mainly expressed by helper T cells, and they are receptors for TCR recognition of antigens. Abnormal levels of T lymphocytes can lead to a decrease in physiological functions in the body[25,26]. The study concluded that the CD3+ and CD4+ markers in the postoperative research group were higher compared to the reference group, indicating that minimally invasive laparoscopic surgery under general anesthesia for early ovarian cancer has minimal impact on the immune function of patients. This may be

due to the advantages of minimally invasive laparoscopic surgery under general anesthesia, such as minimally invasive and high safety, which can avoid damage to normal organ tissues of patients during surgery, thereby reducing damage to the body and minimizing the impact on immune function. At the same time, early ovarian cancer itself has a reduced immune function due to the influence of malignant tumors. Compared to open surgery, minimally invasive laparoscopic surgery under general anesthesia can accurately and effectively remove tumors, contributing to the recovery of immune function. This further confirms the effectiveness and feasibility of minimally invasive laparoscopic surgery under general anesthesia for early ovarian cancer.

Limitations

As a retrospective study, this study also has limitations, such as the relatively small number of patients in the study, which may affect the universality of the results. Because the study is a retrospective collection of patients' clinical data, the potential confounding factors cannot be completely ruled out, which may have an impact on the rigor of the results. In the future, a large sample prospective study will be further carried out to further verify the accuracy of the results.

CONCLUSION

In summary, minimally invasive laparoscopic surgery under general anesthesia for early-stage ovarian cancer patients can further improve treatment efficacy, promote quick postoperative recovery, and have minimal impact on the body's stress response and immune function. The risk of postoperative complications is low.

ARTICLE HIGHLIGHTS

Research background

The background of this study mainly focuses on patients with early ovarian cancer, and evaluates the application value of open surgery and minimally invasive laparoscopic surgery under general anesthesia in this population, aiming at providing clinical reference for the choice of the best surgical method for early ovarian cancer.

Research motivation

The research motivation of this study is to evaluate the application value of open surgery and endoscopic surgery for patients with early ovarian cancer, aiming at providing clinical reference for the best choice of surgical methods in the treatment of early ovarian cancer.

Research objectives

The objectives of this study is to evaluate the application value of open surgery and minimally invasive laparoscopic surgery under general anesthesia in patients with early ovarian cancer, so as to improve the therapeutic effect, promote postoperative recovery, and reduce the risk of postoperative complications, and provide reference for clinical treatment.

Research methods

According to the different surgical methods of patients, this study was randomly divided into study group (laparoscopic group) and control group (open surgery group). The study group received minimally invasive laparoscopic surgery under general anesthesia, while the control group received traditional open surgery. All patients received chemotherapy after operation.

Research results

This study evaluates the application value of open surgery and minimally invasive laparoscopic surgery under general anesthesia in the treatment of early ovarian cancer. The results show that minimally invasive laparoscopic surgery under general anesthesia can further improve the therapeutic effect of early ovarian cancer patients, promote rapid postoperative recovery, reduce the stress response and immune function of patients, and the incidence of postoperative complications is low.

Research conclusions

Minimally invasive minimally invasive laparoscopic surgery under general anesthesia is safe and effective in the treatment of early ovarian cancer, which can significantly reduce the stress response and immune function of patients, promote patients' rapid recovery after surgery and reduce the risk of postoperative complications.

Research perspectives

This study focuses on patients with early ovarian cancer and evaluates the application value of open surgery and minimally invasive minimally invasive laparoscopic surgery under general anesthesia in this population, aiming at providing clinical reference for the choice of surgical methods for early ovarian cancer. The results show that minimally invasive laparoscopic surgery under general anesthesia can further improve the therapeutic effect, promote patients' rapid recovery after operation, and have minimal impact on patients' stress response and immune function.

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FOOTNOTES

Co-first authors: Xian Qin and Chen Chen.

Author contributions: Qin Xand Chen C designed the research; Liu Y, Hua XH, Li JY and Liang MJ contributed new reagents/analytic tools; Qin X and Chen C analyzed the data; Wu F, Qin X and Chen C wrote the paper; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript; Qin X and Chen C contributed equally to this work as co-first authors equally to this work. The reasons for designating Qin X and Chen C as co-first authors are threefold. First, Data analysis: All two authors analyzed or explained the data of the article; second, Design and implementation of the experiment: All two authors participated in the design and implementation of the experiment; third, Data interpretation: All two authors have made important contributions to data interpretation.

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Xian-Da Chai, Huan Jiang, Ling-Ling Tang, Jing Zhang, Department of Oral and Maxillofacial Surgery, People's Hospital of Anshun, Anshun 561000, Guizhou Province, China

Long-Fei Yue, Department of General Practice, People's Hospital of Anshun, Anshun 561000, Guizhou Province, China

Corresponding author: Long-Fei Yue, MD, Chief Doctor, Department of General Practice, People's Hospital of Anshun, No. 140 Huangguoshu Street, Anshun 561000, Guizhou Province, China. longfei_yue@163.com

Abstract

BACKGROUND

Frey syndrome, also known as ototemporal nerve syndrome or gustatory sweating syndrome, is one of the most common complications of parotid gland surgery. This condition is characterized by abnormal sensations in the facial skin accompanied by episodes of flushing and sweating triggered by cognitive processes, visual stimuli, or eating.

AIM

To investigate the preventive effect of acellular dermal matrix (ADM) on Frey syndrome after parotid tumor resection and analyzed the effects of Frey syndrome across various surgical methods and other factors involved in parotid tumor resection.

METHODS

Retrospective data from 82 patients were analyzed to assess the correlation between sex, age, resection sample size, operation time, operation mode, ADM usage, and occurrence of postoperative Frey syndrome.

RESULTS

Among the 82 patients, the incidence of Frey syndrome was 56.1%. There were no significant differences in sex, age, or operation time between the two groups ($P > 0.05$). However, there was a significant difference between ADM implantation and occurrence of Frey syndrome ($P < 0.05$). ADM application could reduce the variation in the incidence of Frey syndrome across different operation modes.

CONCLUSION

ADM can effectively prevent Frey syndrome and delay its onset.

Key Words: Parotid gland tumor; Frey syndrome; Acellular dermal matrix; Acellular allogenic dermal matrix

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Core Tip: The use of acellular dermal matrix in parotid tumor surgery can reduce the incidence of Frey syndrome, especially when the diameter of the surgically removed parotid tissue is greater than 4 cm.

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INTRODUCTION

Frey syndrome, also known as ototemporal nerve syndrome or gustatory sweating syndrome, is one of the most common complications of parotid gland surgery. This condition is characterized by abnormal sensations in the facial skin accompanied by episodes of flushing and sweating triggered by cognitive processes, visual stimuli, or eating[1]. This syndrome was first described by Lucie Frey in 1923; however, its precise pathogenesis remains unclear. The incidence rate of Frey syndrome varies greatly, ranging from 4% to 96%[2,3], attributed, in part, to differences in the diagnostic criteria for Frey syndrome[4] and differences in methods[5] and techniques used in parotid gland surgery. The primary therapeutic approach is managing associated symptoms. Notably, some researchers have diagnosed Frey syndrome using a minor test and evaluated its severity. Unfortunately, this diagnostic method only assesses subclinical patients without overt clinical symptoms. This inclusion has inadvertently increased the recorded incidence of Frey syndrome[6-8]. This retrospective study investigated the factors influencing the acellular dermal matrix (ADM) in the prevention of Frey syndrome in patients who have undergone parotid surgery.

MATERIALS AND METHODS

Research methods

In this retrospective analysis of clinical data from 126 patients who underwent parotid gland surgery in the Department of Oral and Maxillofacial Surgery at Anshun People's Hospital between January 2018 and December 2020, a total of 82 patients were deemed eligible for the study. Patients with parotid gland inflammation, patients who had undergone lymph node dissection, and patients who had undergone periparotid gland surgery during the same period were excluded. All patients provided informed consent for both computed tomography examinations and surgeries. Before the use of ADM, patients were informed regarding the manufacturer, safety, cost, and surgical benefits of ADM. The ADM used was the Hiao B-type oral repair membrane produced by Yantai Zhenghai Biological Technology (registration number: 20153460386).

Surgical method

A modified "S" incision[9] was made in the conventional parotid area. The platysma muscle under the skin was incised, the parotid gland envelope was opened, and the envelope was preserved for tumors that did not invade it. The facial nerve was dissected retrogradely, and any tumor-invading segments of the facial nerve were resected. Partial parotid resection or total parotid lobectomy was performed, depending on the size and location of the tumor. The surgical method randomly categorized the patients into either the partial parotid resection group or the total parotid lobectomy group. The patients were randomly divided into a tissue patch implantation group and a control group according to their preoperative informed consent and willingness to undergo tissue patch implantation. After surgery, all patients underwent negative pressure ball drainage; for patients with an implanted tissue patch, the drainage tube was placed above the patch according to the product guidelines (Figure 1). Pressure was applied routinely for 14 d after surgery.

Diagnostic criteria for Frey syndrome

Patients were contacted by phone each month after surgery, during which they were questioned regarding symptoms, such as facial flushing, facial paresthesia, and facial sweating during eating. These responses were used to assess Frey syndrome using a subjective questionnaire. Positive Frey syndrome was defined as the presence of any of the four indicators.

Statistical analysis

Data analysis was performed using SPSS (version 25.0) to assess the correlations between age, sex, surgical method, size

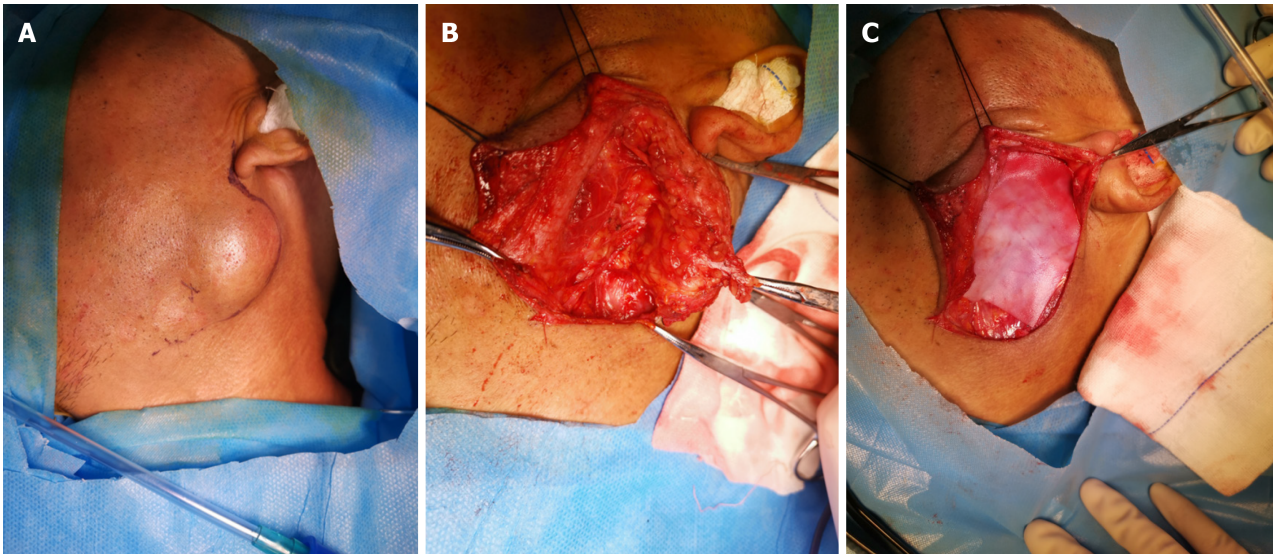

Figure 1 The drainage tube was placed above the patch according to the product guidelines for patients with an implanted tissue patch.
A: Diagram B of the surgical incision; B: For superficial parotid lobectomy behind nerve exposure; C: Acellular dermal matrix after implantation.

of surgically removed samples, time of occurrence of postoperative Frey syndrome, and intraoperative application of ADM for the prevention of Frey syndrome. A logistic regression model was established to analyze the risk factors associated with Frey syndrome. Additionally, a receiver operating characteristic (ROC) curve was constructed to predict the diagnostic value of certain risk factors for Frey syndrome. The significance level for the tests was set at $\alpha = 0.05$.

RESULTS

Data of patients with Frey syndrome

A total of 82 patients were included in this study, 46 of whom developed Frey syndrome, an incidence rate of 56.1%. Among them, 43 (52.4%) experienced facial paresthesia after eating, 29 (35.4%) experienced facial flushing after eating, 13 (15.9%) exhibited facial sweating after eating, and 4 (4.9%) reported that these symptoms seriously affected their daily lives (Table 1).

Analysis of related Frey syndrome factors

The 82 patients were categorized into the Frey and non-Frey groups (Table 2). No significant differences were observed in terms of sex, age, or operation time between the two groups. However, a significant difference was noted in the occurrence of Frey symptoms between patients with and without ADM implantation ($P = 0.027$ and $P < 0.05$, respectively). Regarding the surgical methods, no significant difference was observed between the Frey and non-Frey groups ($P = 0.295$); however, there were significant differences in the various surgical approaches without ADM implantation ($P = 0.006$ and $P < 0.05$). All 82 patients were followed up for 16 months postoperatively. In the group with ADM implantation, the median time for Frey symptoms onset was 7.54 ± 3.2 months, whereas in the group without ADM implantation, it was 3.43 ± 2.33 months; these differences were significant ($P = 0.001$ and $P < 0.05$, respectively).

ROC curve analysis was performed to assess the relationship between the maximum diameter of the surgically resected sample and the occurrence of symptoms of Frey syndrome. The results indicated that the larger the diameter of the resected sample, the higher the probability of Frey syndrome occurrence, with an area under the curve (AUC) of 0.661 (Figure 2).

ROC curve analysis comparing the timing of ADM implantation with the timing of the occurrence of symptoms of Frey syndrome revealed that ADM could significantly delay the occurrence of Frey syndrome, with an AUC of 0.842 (Figure 3).

DISCUSSION

Frey syndrome is now commonly believed to be most likely caused by parotid gland surgery or injury. Destruction of parotid gland cyst integrity exposes the parasympathetic branch, which controls the parotid gland acinar secretion in the auriculotemporal nerve issued by the trigeminal nerve within the parotid gland and leads to its misplacement with the sympathetic nerve, which controls the skin sweat glands. Consequently, upon seeing or eating food, an individual's parasympathetic branch is stimulated, resulting in secretion from skin sweat glands, leading to facial paresthesia, flushing, or sweating[10]. Frey syndrome occurred in 56.1% of the patients in this study, a rate similar to that reported in

Table 1 Number and proportion of patients with different symptoms in the Frey symptoms group, *n* (%)

Symptoms	Number and proportion of cases, *n* = 82
Facial paresthesia after eating	43 (52.4)
Flushed cheeks after eating	29 (35.4)
Facial sweating after eating	13 (15.9)
Feeling that life is severely affected after surgery	4 (4.9)

Table 2 Baseline characteristics of patients after parotidectomy

Clinical features	Frey group (*n* = 46)	Non-Frey group (*n* = 36)	*P* value
Sex (male)	26 (56.52%)	20 (55.56%)	0.93
Age (yr)	48.09 ± 14.95	47.08 ± 16.31	0.97
Surgically removed sample size (maximum diameter, cm)	3.40 ± 0.97	2.878 ± 0.79	0.029[1]
Method of surgery			
ADM implants			
Partial removal of parotid gland	8	9	0.295
Complete removal of parotid gland	3	8	
No-implant ADM			
Partial removal of parotid gland	21	18	0.006[1]
Complete removal of parotid gland	14	1	
Procedure time (min)	198.54 ± 43.87	185.97 ± 57.75	0.92
Implanted ADM			
Yes	11	17	0.027[1]
No	35	19	
Time of Frey sign occurrence (months)			
Implant ADM	7.54 ± 3.2	0	0.001[1]
Non-implant ADM	3.43 ± 2.33	0	

[1]Comparison of the time when Frey signs occurred with and without acellular dermal matrix implantation.
ADM: Acellular dermal matrix.

most studies[11]. ROC analysis of the tumor sample diameter demonstrated that a resected sample with a larger area was correlated with a higher probability of Frey syndrome occurrence (AUC = 0.661). This finding was consistent with the results presented by Lin *et al*[12]. Therefore, it was concluded that the probability of Frey syndrome increased when the resected tumor diameter exceeded 4 cm[12,13]. ADM can effectively prevent the occurrence of Frey syndrome after resection. Favorable outcomes have been achieved using sternocleidomastoid flap[14] and superficial muscle aponeurotic system flap[15]. For the prevention of Frey syndrome. However, it is important to note that the flap preparation process inevitably prolongs the operation time. In this study, there was no significant difference in operation time between the ADM and non-ADM groups, indicating that this method did not extend the operation time in the context of Frey syndrome prevention. Significant differences in the incidence of Frey syndrome were evident among different surgical methods without ADM. Total parotid excision was more likely to result in Frey syndrome, likely because of the removal of excessive parotid tissue that could potentially damage more ototemporal nerve endings[16]. This can contribute to more dislocation-related complications during nerve injury reconstruction. The use of ADM reduced the variability in the occurrence of Frey syndrome between surgical methods. According to the currently available parotid surgery guidelines [17] for benign tumors, preference is given to extracapsular resection or endoscopic minimally invasive surgery[18,19] to reduce the risk of Frey syndrome. However, in cases of tumors > 4 cm in diameter or located deeper within the parotid gland, total parotid excision combined with ADM[20] to decrease postoperative recurrence and prevent Frey syndrome is recommended.

Regarding the timing of Frey syndrome occurrence, non-implantation of ADM resulted in Frey syndrome occurring approximately 3 months after the operation, consistent with the neural reconstruction theory that the occurrence time for the middle auriculotemporal nerve is abnormal[16]. After ADM implantation, the onset of Frey syndrome was delayed by

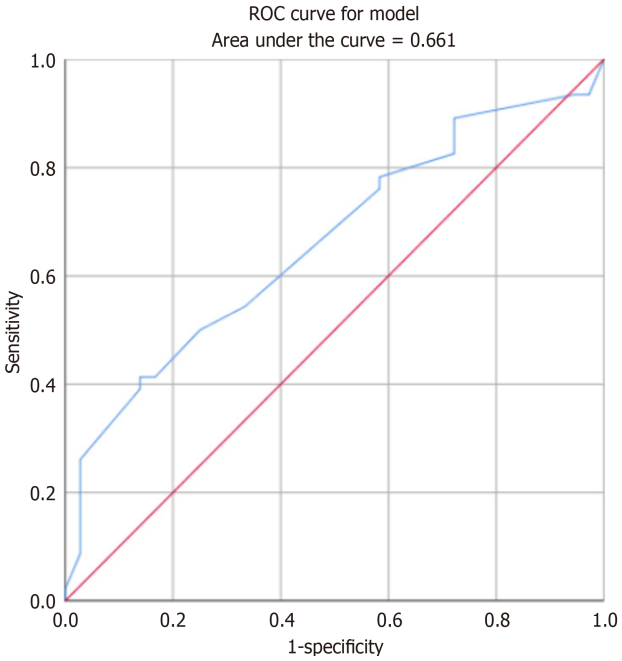

Figure 2 Diameter of surgically resected sample and receiver operating characteristic curve with Frey sign. ROC: Receiver operating characteristic.

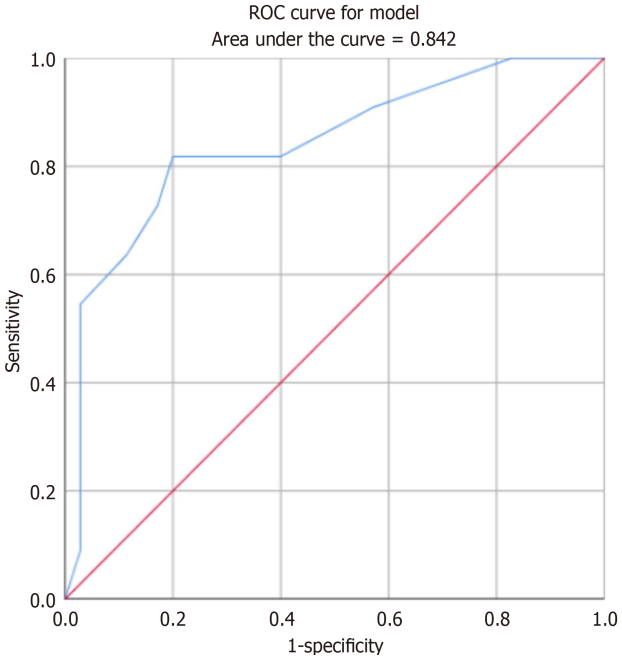

Figure 3 Frey sign occurrence time and receiver operating characteristic curve after acellular dermal matrix implantation. ROC: Receiver operating characteristic.

approximately three months. This delay might be attributed to the severity of the auriculotemporal nerve injury and the absorption timeframe of the ADM.

CONCLUSION

In conclusion, the application of ADM affects Frey syndrome prevention. However, it is important to note that ADM degrades within approximately six months, and Frey syndrome may still occur after this degradation. Nonetheless, because of the limited number of Frey syndrome cases following ADM implantation in this study, the results may be biased. Additionally, controlling the diameter of the excised samples can help prevent the occurrence of Frey syndrome.

ARTICLE HIGHLIGHTS

Research background

Frey syndrome, also known as ototemporal nerve syndrome or guest-sweating syndrome, is one of the most common complications of parotid gland surgery. It is characterized by abnormal facial skin sensations, flushing, or sweating when the patient thinks, sees, or eats.

Research motivation

This inclusion has inadvertently increased the recorded incidence of Frey syndrome. This retrospective study investigated the factors influencing the acellular dermal matrix (ADM) in the prevention of Frey syndrome in patients who have undergone parotid surgery.

Research objectives

Because of the effects of frey syndrome, there was a need to find a way to reduce its incidence

Research methods

The data of 82 patients were retrospectively analyzed using SPSS 25.0, and the correlations between sex, age, resection sample size, operation time, operation mode, ADM use, and postoperative Frey syndrome were analyzed.

Research results

The incidence of Frey syndrome was 56.1% among the 82 patients. There were no significant differences in sex, age, or operation time between the two groups ($P > 0.05$). There was a significant difference between ADM implantation and the onset of symptoms of Frey syndrome ($P < 0.05$). ADM can reduce the variation in Frey syndrome onset. ADM can delay the onset of Frey signs.

Research conclusions

the application of ADM affects Frey syndrome prevention. However, it is important to note that ADM degrades within approximately six months, and Frey syndrome may still occur after this degradation. Additionally, controlling the diameter of the excised samples can help prevent the occurrence of Frey syndrome.

Research perspectives

The incidence of Frey syndrome was reduced by surgery and the implantation of ADM.

FOOTNOTES

Author contributions: Chai XD and Yue LF designed the study, analyzed the data and prepared the manuscript; Jiang H, Tang LL and Zhang J collected the data; Chai XD interpreted the data; All authors have read and approved the manuscript.

Institutional review board statement: The study was reviewed and approved by the Anshun People's Hospital Ethics Committee (Approval No. 3).

Informed consent statement: The patient provided informed written consent prior to study enrollment.

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

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at email lonhfei_yue@163.com. Participants gave informed consent for data.

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Country/Territory of origin: China

ORCID number: Xian-Da Chai 0009-0002-2896-8921; Long-Fei Yue 0000-0001-5086-7866.

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ORIGINAL ARTICLE

Clinical Trials Study

Allogeneic mesenchymal stem cells may be a viable treatment modality in cerebral palsy

Osman Boyalı, Serdar Kabatas, Erdinç Civelek, Omer Ozdemir, Yeliz Bahar-Ozdemir, Necati Kaplan, Eyüp Can Savrunlu, Erdal Karaöz

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Osman Boyalı, Serdar Kabatas, Erdinç Civelek, Omer Ozdemir, Department of Neurosurgery, University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Istanbul 34360, Turkey

Serdar Kabatas, Center for Stem Cell & Gene Therapy Research and Practice, University of Health Sciences Turkey, Istanbul 34360, Turkey

Yeliz Bahar-Ozdemir, Department of Physical Medicine and Rehabilitation, Health Sciences University Sultan Abdulhamid Han Training and Research Hospital, Istanbul 34668, Turkey

Necati Kaplan, Department of Neurosurgery, Istanbul Rumeli University, Çorlu Reyap Hospital, Tekirdağ 59860, Turkey

Eyüp Can Savrunlu, Department of Neurosurgery, Nevşehir State Hospital, Nevşehir 50300, Turkey

Erdal Karaöz, Center for Regenerative Medicine and Stem Cell Research & Manufacturing (LivMedCell), Liv Hospital, Istanbul 34340, Turkey

Erdal Karaöz, Department of Histology and Embryology, Istinye University, Faculty of Medicine, İstanbul 34010, Turkey

Erdal Karaöz, Center for Stem Cell and Tissue Engineering Research and Practice, Istinye University, Istanbul 34340, Turkey

Corresponding author: Osman Boyalı, MD, Neurosurgeon, Department of Neurosurgery, University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Karayolları Mahallesi, Osmanbey Caddesi 616. Sokak No. 10 Gaziosmanpaşa, Istanbul 34360, Turkey. drosmanboyali@gmail.com

Abstract

BACKGROUND

Cerebral palsy (CP) describes a group of disorders affecting movement, balance, and posture. Disturbances in motor functions constitute the main body of CP symptoms. These symptoms surface in early childhood and patients are affected for the rest of their lives. Currently, treatment involves various pharmacotherapies for different types of CP, including antiepileptics for epilepsy and Botox A

for focal spasticity. However, none of these methods can provide full symptom relief. This has prompted researchers to look for new treatment modalities, one of which is mesenchymal stem cell therapy (MSCT). Despite being a promising tool and offering a wide array of possibilities, mesenchymal stem cells (MSCs) still need to be investigated for their efficacy and safety.

AIM

To analyze the efficacy and safety of MSCT in CP patients.

METHODS

Our sample consists of four CP patients who cannot stand or walk without external support. All of these cases received allogeneic MSCT six times as 1×10^6/kg intrathecally, intravenously, and intramuscularly using umbilical cord-derived MSCs (UC-MSC). We monitored and assessed the patients pre- and post-treatment using the Wee Functional Independence Measure (WeeFIM), Gross Motor Function Classification System (GMFCS), and Manual Ability Classification Scale (MACS) instruments. We utilized the Modified Ashworth Scale (MAS) to measure spasticity.

RESULTS

We found significant improvements in MAS scores after the intervention on both sides. Two months: Right χ^2 = 4000, P = 0.046, left χ^2 = 4000, P = 0.046; four months: Right χ^2 = 4000, P = 0.046, left χ^2 = 4000, P = 0.046; 12 months: Right χ^2 = 4000, P = 0.046, left χ^2 = 4000, P = 0.046. However, there was no significant difference in motor functions based on WeeFIM results (P > 0.05). GMFCS and MACS scores differed significantly at 12 months after the intervention (P = 0.046, P = 0.046). Finally, there was no significant change in cognitive functions (P > 0.05).

CONCLUSION

In light of our findings, we believe that UC-MSC therapy has a positive effect on spasticity, and it partially improves motor functions.

Key Words: Cerebral palsy; Mesenchymal stem cell; Transplantation; Wharton's jelly; Muscle spasticity

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Core Tip: Cerebral palsy (CP) describes a group of non-progressive disorders affecting movement, balance, posture, and motor function. Research suggests that stem cell therapy may be a new treatment option in CP. We monitored four CP patients who underwent mesenchymal stem cell therapy (MSCT) for 12 months and analyzed treatment efficacy. MSCT resulted in significantly improved Modified Ashworth Scale, Gross Motor Function Classification System, and Manual Ability Classification System scores.

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INTRODUCTION

Cerebral palsy (CP) describes a group of disorders affecting movement, balance, posture, and motor functions. These symptoms surface in early childhood and patients are affected for the rest of their lives[1,2]. While motor dysfunctions constitute the main body of CP symptoms, patients often suffer from other pathologies such as epilepsy, musculoskeletal diseases, and cognitive, perceptive, communicative, sensory, and behavioral disorders[3]. Research reports the incidence rate of CP as 0.15%-0.25% in developed countries[4]. Given the complex etiology (perinatal stroke, gestational age, low birth weight, birth complications, *etc*.) and symptom variations, CP comprises a wide spectrum[5,6]. This has led researchers to try various treatment modalities[1,7]. Currently, treatment involves physical therapy and comprehensive rehabilitation (neurodevelopmental and reflex locomotion treatment), as well as various pharmacotherapies for different types of CP (baclofen, diazepam, *etc*. for generalized spasticity; Botox A for focal spasticity; antiepileptics for epilepsy)[1,8]. However, known treatment methods can provide partial symptom relief at best, prompting a continuous search for new treatment modalities[9].

Stem cell therapy (SCT) is a novel treatment option that has been researched in over 250 studies involving a wide variety of disorders. Accordingly, SCT boasts significant potential and versatility and is promising for ameliorating CP symptoms[10-12].

The therapeutic efficacy of mesenchymal SCT (MSCT) is evaluated based on its anti-inflammatory effects, neuroregeneration, and neural protection. According to early studies, the mechanism of action of MSCT involves stem cells migrating to the stroke area, differentiating into functional cells, and interacting with cells in the penumbra, providing regeneration of the damaged area. Recent research has focused on other effects, including paracrine interactions, mitochondrial transfer, and extracellular vesicle secretion[13]. The paracrine interactions occur through a variety of different mechanisms associated with mesenchymal stem cells (MSCs), including their cytoprotective, provasculogenic, anti-inflammatory, and metabolic effects[14].

One study focused on the neuroprotective activity of MSCs and reported a lower count of apoptotic neurons after intravenous treatment in a stroke model created in female rats. The stem cells migrated to the injury site, increased the expression of basic fibroblast growth factor (bFGF), and promoted endogenous proliferation, providing functional recovery and showcasing their anti-apoptotic activities[15]. Another study on rats using a stroke model reported reduced infarct area and improved function after using human-derived MSCs. The authors observed higher expressions of numerous neurotrophic factors in the experimental group of rats after MSC transplantation, even in rat-derived neurotrophic factors such as vascular endothelial growth factor (VEGF), epidermal growth factor, and bFGF[16].

Many researchers have reported the anti-inflammatory activity of MSCs through paracrine mechanisms. Huang *et al* [17] found that interleukin (IL)-6 and VEGF had an important role in the anti-inflammatory activity of MSCs *in vitro*. The anti-inflammatory activity of IL-6 occurs through its inhibitory effect on tumor necrosis factor α and IL-1[17]. The roles of IL-6 in this mechanism have been supported by other studies. MSC implantation increases IL-6 production through resident neuronal stem cells NFkB activation, independent of the PI3/Akt pathway, thus reducing apoptosis and providing neuroprotection[18]. Jung *et al*[19] observed that IL-6 injection increased phosphorylated STAT-3 and Mn-SOD levels and protected cells from oxidative stress[19].

Given this variety of mechanisms of action, MSCT offers a new treatment perspective not only in CP, but also in many central nervous system disorders such as hypoxic ischemic encephalopathy, Alzheimer's disease, stroke, Parkinson's disease, multiple sclerosis, and spinal cord injury[20,21].

Lee *et al*[22] examined a murine model of Alzheimer's disease and found that human umbilical cord-derived MSCs (UC-MSC) inhibited the release of pro-inflammatory cytokines from microglia and reduced apoptosis and amyloid plaques, contributing to functional recovery[22]. Kim *et al*[23] conducted a phase I clinical trial with Alzheimer's disease patients where they administered MSCs by stereotactic brain infusion at two different doses in a single round (3×10^6 cells/60 μL and 6×10^6 cells/60 μL). The authors encountered no serious side effects at either dose. However, their results include limitations of not including a sham group and being an open label trial[23].

One study used the experimental autoimmune encephalitis (EAE) model, which is the most common model in animal research on multiple sclerosis; the authors found that treatment reduced inflammatory infiltrates and demyelination[12]. Other clinical trials on EAE have also shown some clinical improvements and have deemed EAE as a safe and effective model[24].

In 2012, Lalu *et al*[25] published a meta-analysis on the possible risks of MSCT and highlighted that no statistically significant side effects were involved other than transient fever[25]. Similarly, another meta-analysis published in 2021 revealed that, despite the expanding patient population in the intervening years, the only side effect that could be associated with MSCT was transient fever. Transient fever is more common in women and less common in the North American population. Despite the tumorigenic potential of MSCs, only one malignancy was detected in the entire population and it was not associated with stem cell application. This meta-analysis also shed light on some trials that reported other side effects such as vascular disorders, urticaria/dermatitis, dizziness/headache, diarrhea, infection, death, anemia, metabolic and nutritional disorders, nausea, seizure, and vomiting. However, none of these side effects was significantly correlated with MSCT[26].

In the present research, we monitored four CP patients who underwent MSCT for 12 months and analyzed treatment efficacy.

MATERIALS AND METHODS

This was a multi-center, longitudinal, open-label phase I trial. Our sample included four CP patients with severe disability (inability to mobilize without assistance), aged between one and nine years, under home nursing care and assistance. None of these patients could stand or walk without external support. Table 1 summarizes the demographic data of these patients. Our inclusion criteria were as follows: Being under 18 years of age, having no chronic disease (*i.e.*, cancer, kidney, heart/hepatic failure), having an estimated life expectancy of > 12 months, and showing no significant change in neurological or functional status despite three months of conservative treatment (*e.g.*, physical rehabilitation and botulinum toxin injection). The exclusion criteria were as follows: Being recently diagnosed with severe infection (meningitis, *etc.*), liver/kidney/heart failure, sepsis, or skin infection at the IV infusion site, or hepatitis B/C/HIV, having a history of uncontrolled seizure disorder, presenting certain laboratory results (white blood cell count ≥ 15000/μL, platelet count ≤ 100000/μL, serum aspartate aminotransferase and serum alanine aminotransferase > 3 × upper limit of normal, creatinine > 1.5 × upper limit of normal), or having participated in an another stem cell trial.

The study protocol was approved by the local Ethics Committee. We obtained the informed consent of each participant and/or their caregivers in written form. The trial was conducted in accordance with the principles of the Declaration of Helsinki.

Table 1 Patient characteristics

		Frequency	%
Age, yr	1	1	25.0
	4	1	25.0
	9	2	50.0
Sex	Female	1	25.0
	Male	3	75.0
Etiology of cerebral palsy	Hypoxia during birth	2	50.0
	Hypoxia with bleeding in the surgical field after tonsillectomy operation	1	25.0
	Cardiac arrest	1	25.0
Comorbidity	None	4	100.0
Cerebral palsy duration and first transplantation	1 year	1	25.0
	13 months	1	25.0
	7 years	1	25.0
	9 years	1	25.0

Intervention procedure

Ethical information and donor consent: The present study was approved by the medical ethics committee of the authors' institution (protocol No. 56733164-203-E.3178). Umbilical Cords (UCs) were obtained from the Good Manufacturing Practices facility of LivMedCell (Istanbul, Turkey). In accordance with the approval of an institutional regulatory board (LivMedCell); the donors donated UCs after being informed of the aim of the current study and gave their informed consent in written form.

Processing and quality control of UCs: The UCs were washed with phosphate-buffered saline (Invitrogen/Gibco, Paisley, United Kingdom). Before removing blood vessels, the tissue samples were cut into 5-10 mm^3 pieces as explants. These explants were placed in dishes and cultured under humanized culture conditions at 37 °C with 5% CO_2 until the cells displaced. The resulting cells were collected when they reached 70% to 80% confluence and subjected to characterization tests at Passage 3[27]. Quality control and assurance was performed by the Pharmaceuticals and Medical Devices Agency.

Determination of UC-MSCs by flow cytometry: Expressed surface antigens were analyzed by flow cytometry, which revealed that cells were consistently positive for CD44, CD73, CD90, and CD105 and negative for hematopoietic lineage markers of CD34, CD45, and human leukocyte antigen DR2 (Figure 1). Telomerase activity was stable in culture conditions with a large and flat cellular morphology[27].

Cell differentiation and karyotyping: We identified some stem cell expressions and the differentiation markers of TERT, SOX2, POU5F1, CD44, ZFP42, VIM, ICAM1, THY1, VCAM1, BMP2, RUNX-1, and NES. Differentiation analyses confirmed that these cells had a trilineage (chondrocytes, osteoblasts, and adipocytes) differentiation capacity[27]. Karyotyping studies revealed no numerical or structural chromosomal abnormalities.

***In vitro* adipogenic differentiation and oil red O staining:** To induce adipogenic differentiation, cells from Passage 3 (3000 cells/cm^2) were seeded onto coated type I collagen coverslips (BD Biosciences) in 6-well plates. The adipogenic medium Dulbecco's Modified Eagle's Medium, Low Glucose (DMEM-LG, Invitrogen) was supplemented with 10% FBS (Invitrogen/Gibco), 0.5 mmol/L isobutyl-methylxanthine (IBMX-Sigma-Aldrich), 10^{-6} M dexamethasone (Sigma-Aldrich, Fluka Chemie AG, Buchs, Switzerland), 0.02% insulin (Invitrogen/Gibco), 200 µM indomethacin (Sigma-Aldrich), and 1% penicillin-streptomycin (Invitrogen/Gibco) for three weeks. The medium was replaced twice a week. Intracellular lipid droplets indicating adipogenic differentiation were confirmed by oil red O (Sigma-Aldrich) staining with 0.5% oil red O in methanol. The cells were then allowed to dry completely and mounted in a mounting medium.

***In vitro* osteogenic differentiation and Alizarin red S staining:** Cells from Passage 3 (3000 cells/cm^2) were seeded onto type I collagen-coated coverslips (BD Biosciences) in 6-well plates. The osteogenic medium DMEM-LG (Invitrogen) was supplemented with 10^{-8} M dexamethasone (Sigma-Aldrich), 50 µg/mL ascorbate-2- phosphate (Wako Chemicals, Richmond, VA, United States), 10 mmol/L b-glycerophosphate (Sigma-Aldrich), 1% penicillin-streptomycin, and 10% FBS (Invitrogen/Gibco) for three weeks. The medium was replaced twice a week. At the end of the third week, osteogenic differentiation was assessed by staining with Alizarin Red (Sigma-Aldrich, Fluka Chemie AG, Buchs, Switzerland). The medium was discarded and the cells were washed with PBS. Cells were incubated with ethanol for 5 min at room temperature and then allowed to dry completely. Cells were washed with distilled water and stained with alizarin red solution comprising 2% alizarin red S for one minute. Stained cells were dehydrated in acetone (20 dips), fixed in

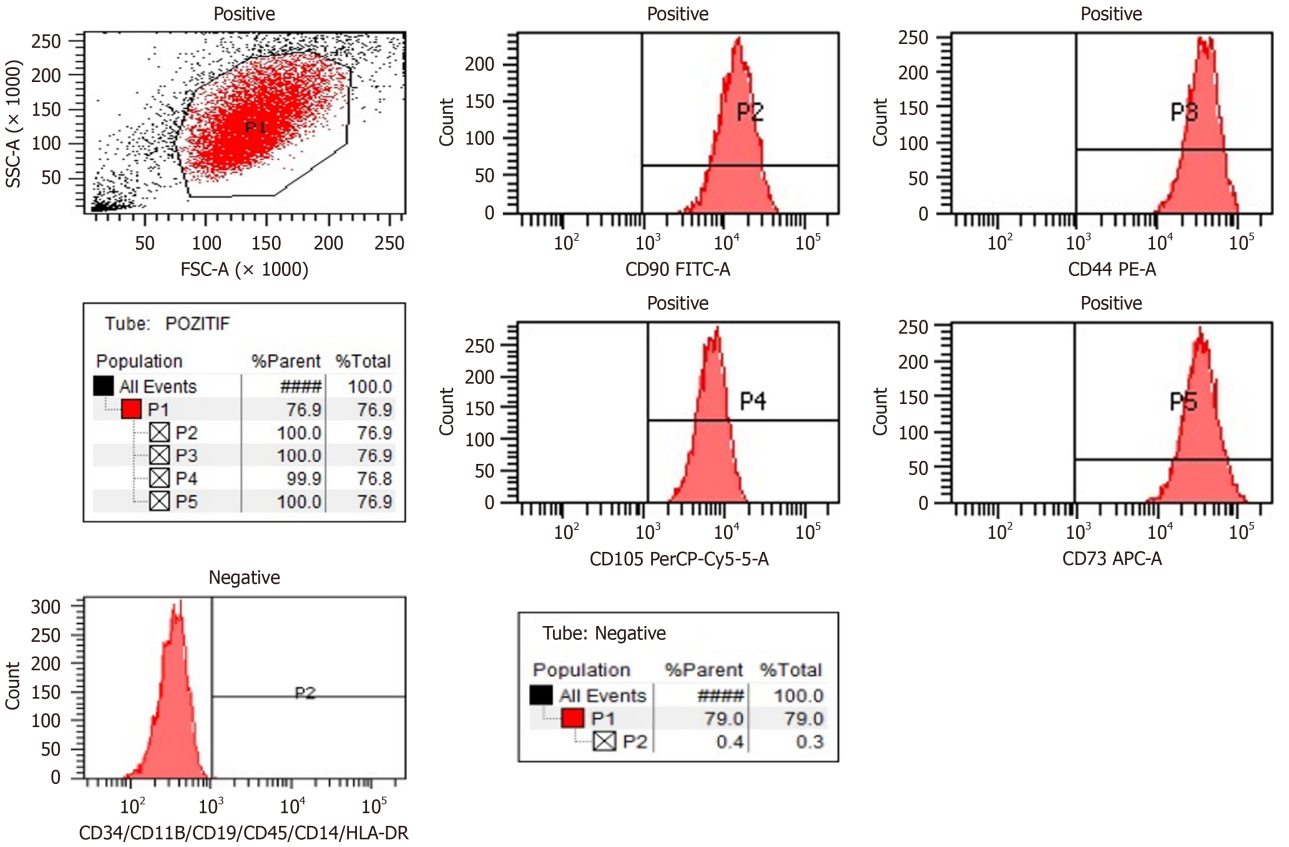

Figure 1 Wharton's Jelly–derived mesenchymal stem cell flow cytometry, positive marker values (CD90, CD105, CD73 and CD44) are above 95%. Negative marker values (CD45, CD34, CD19, CD11B, human leukocyte antigen-DR and CD14) are below 2%. HLA: Human leukocyte antigen.

acetone–xylene (1:1) solution (20 dips), cleared with xylene (20 dips), and then allowed to dry completely and mounted in a mounting medium.

***In vitro* chondrogenic differentiation and Alcian blue staining:** In the chondrogenesis mechanism, high cell density and cell-cell interaction play an important role. Therefore, for chondrogenic differentiation, cells were seeded as droplets onto type I collagen-coated coverslips (BD Biosciences) in 6-well plates. The medium was added after the cells adhered to the coverslips. The cells were incubated in chondrogenic medium Dulbecco's Modified Eagle's Medium, High (4.5 g/L) Glucose (DMEM-HG, Invitrogen) supplemented with 100 nM dexamethasone (Sigma-Aldrich), 50 µg/mL ascorbate-2-phosphate (Wako Chemicals, Richmond, VA, United States), 10 ng/mL transforming growth factor-beta 1 (TGF-β1, Peprotech, Rocky Hill, NJ, United States), 1% sodium pyruvate (Invitrogen), 50 mg/mL ITS (Sigma-Aldrich), 40 µg/mL proline (Sigma-Aldrich), 1% penicillin-streptomycin, and 10% FBS (Invitrogen/Gibco) for three weeks. The medium was replaced twice a week. Cells were fixed with formaldehyde for 10 min at room temperature, washed with distilled water, and then allowed to dry completely. Chondrogenic differentiation was confirmed by Alcian Blue (Abcam) staining. The cells were allowed to dry completely and mounted in a mounting medium (Figure 2).

Pre-transfer process: Final UC-MSCs preparations before implantation were collected from Passage 3 and maintained in normal saline at final concentrations of 1×10^6 in 3 mL, 1×10^6 in 20 mL, and 1×10^6 in 30 mL.

Transfer of UC-MSCs and operational procedures: Before starting the treatment, we performed a multidisciplinary approach with a team of pediatricians, pediatric neurologists, neurosurgeons, anesthesia and reanimation specialists, and physical medicine and rehabilitation specialists. Prior to implantation, we evaluated the patients for contraindications to sedoanalgesia or general anesthesia[13]. Intrathecal (IT) administration was performed with a 22-gauge spinal needle through the lumbar 3/4 vertebra. For intravenous (IV) administration, 1×10^6 cells/kg were administered with 250 cc isotonic slow infusion in 60 min intramuscularly (IM) and the patients stayed in the hospital for one day. After these applications, movement restrictions were applied for two days, and the patients' relatives were warned to avoid water contact around the injection sites.

Rehabilitation procedure

On the third day of application, we initiated an intense physiotherapy and exercise program. A rehabilitation session included warm-up, neck-trunk stabilization, and postural control exercises. Exercises were performed in a pool three days a week; stretching exercises were practiced for a longer time for extremities with severe spasticity. We also included exercises to improve fine motor skills[8,28].

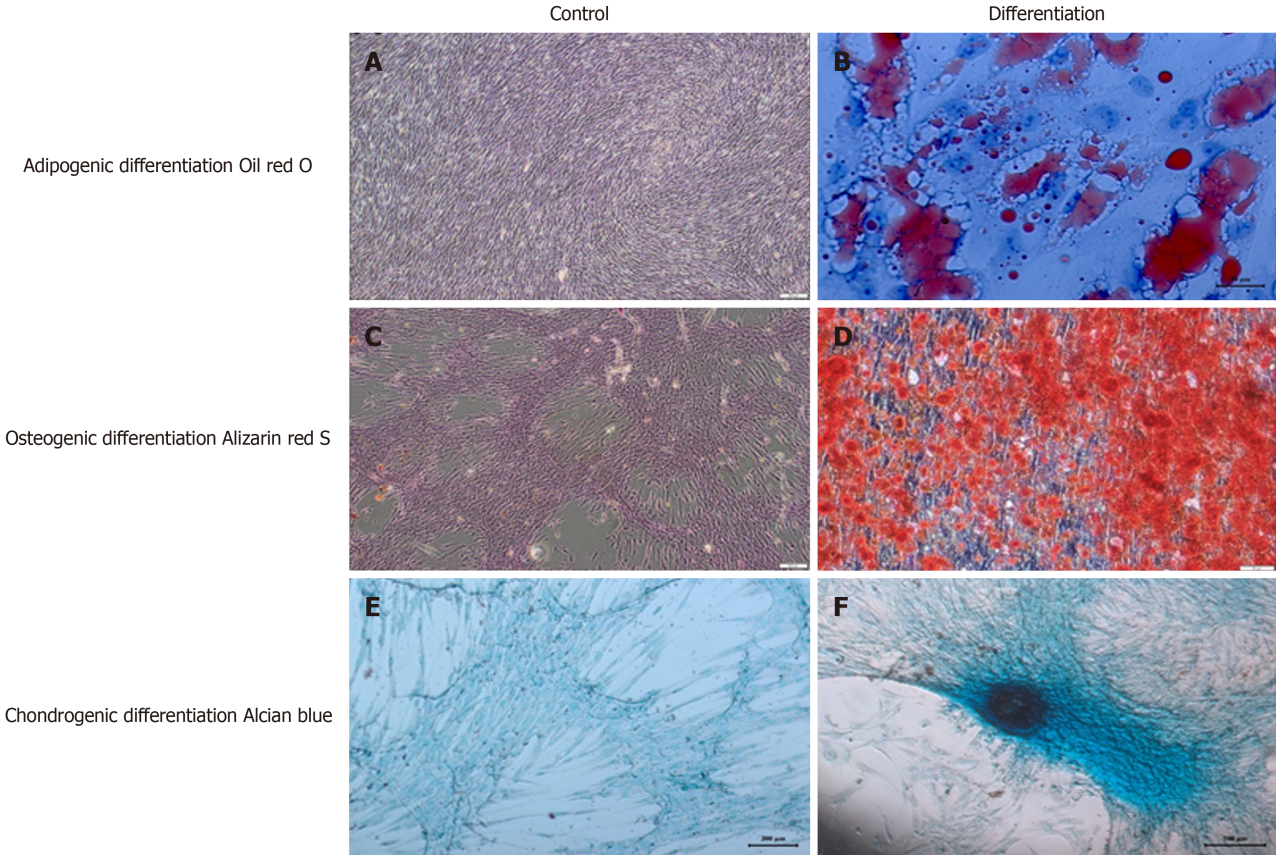

Figure 2 Detection of the differentiation potential of Wharton's Jelly–derived-mesenchymal stem cells. A and B: Wharton's Jelly Derived-mesenchymal stem cells (WJ-MSCs) were cultured without adipogenic induction and cultured for 3 wk in adipogenic differentiation medium. Adipogenic differentiation was evidenced by the formation of lipid vacuoles with oil red O staining; C and D: WJ-MSCs were cultured without osteogenic induction and cultured for 3 wk in osteogenic differentiation medium. Osteogenic differentiation was evidenced by the detection of calcium deposits with Alizarin red staining; E and F: WJ-MSCs were cultured without chondrogenic induction and cultured for 3 wk in chondrogenic differentiation medium. Chondrogenic differentiation was evidenced with Alcian blue staining.

Patient assessment: We categorized the patients according to their functional levels using the Gross Motor Function Classification System (GMFCS) and the Manual Ability Classification System (MACS). MACS describes how children with CP use their hands during daily activities. We used the Modified Ashworth Scale (MAS) to evaluate spasticity and the Wee Functional Independence Measure (WeeFIM) scale to assess quality of life in terms of independence in daily activities[27].

Patient assessment took place preoperatively and postoperatively (one week, one month, two months, four months, and 12 months). Postoperative improvement in neurological and functional evaluations based on GMFSC, MAS, and WeeFIM scores was accepted as treatment success.

Statistical analysis: We used the Friedman Test to measure the changes in WeeFIM, MAS, GMFCS, and MACS scores after the intervention. We chose this nonparametric test as the number of obtained data was not sufficient for parametric tests. All analyses were carried out using SPSS 22 (IBM Corp., Armonk, NY, United States).

RESULTS

Case series presentation

Case 1: The first case was a one-year-old female diagnosed with CP due to hypoxia at birth. Before treatment, case 1 had a WeeFIM score of 18, a MAS score of 14 (both sides), a GMFCS score of five, and a MACS score of five. The patient received allogeneic MSCT six times as 1×10^6/kg IT, IV, and IM using UC-MSCs. Four months after the treatment, her WeeFIM cognitive score increased by one and her MAS score (both sides) decreased by one. Moreover, her GMFCS and MACS scores went down to three. The patient showed no side effects after the second and third applications, except subfebrile fever, which lasted approximately 12 h and regressed with cold application.

Case 2: The second case was a four-year-old male diagnosed with CP due to hypoxia that developed secondary to bleeding during tonsillectomy approximately one year before our trial. Before treatment, the patient had a WeeFIM score of 18, a MAS score of 21 (both sides), a GMFCS score of five, and a MACS score of five. This case had severe spasticity. He

Table 2 The change in the pre- and post-transplantation mean scores of the modified Ashworth scale

		n	Mean	SD	Mean rank	χ^2	*df*	*P* value
Right	Preoperative	4	20.00	6.06	5.50	17.414	5	0.004
	Postoperative 1-wk	4	19.75	6.02	5.13			
	Postoperative 1-month	4	19.00	5.48	3.88			
	Postoperative 2-month	4	18.25	5.74	2.75			
	Postoperative 4-month	4	17.75	5.25	1.88			
	Postoperative 1-year	4	17.75	5.25	1.88			
Left	Preoperative	4	20.00	6.06	5.38	17.368	5	0.004
	Postoperative 1-wk	4	19.75	6.02	5.00			
	Postoperative 1-month	4	19.50	6.35	4.25			
	Postoperative 2-month	4	18.25	5.74	2.63			
	Postoperative 4-month	4	17.75	5.25	1.88			
	Postoperative 1-year	4	17.75	5.25	1.88			

received allogeneic MSCT six times as 1 × 10^6/kg IT, IV, and IM using UC-MSCs. His WeeFIM score did not change after the intervention, but his MAS score started to decrease from the first postoperative week, eventually reaching 18 on both sides. His GMFCS and MACS scores decreased to three. This patient showed no side effects during the entire follow-up period.

Case 3: This was a nine-year-old male diagnosed with CP due to cardiac arrest of unknown cause 11 months after birth. Before treatment, this case had a WeeFIM score of 18, a MAS score of 28 (both sides), a GMFCS score of five, and a MACS score of five. Aside from limb spasticity, the patient demonstrated significant truncal spasticity and had an extensor posture. He received allogeneic MSCT six times as 1 × 10^6/kg IT, IV, and IM using UC-MSCs. His WeeFIM score did not change after the intervention, but his MAS score went down by three points (both sides) at four months. The patient showed no improvement in GMFCS and MACS scores. Similarly, this case did not experience any side effects after three applications, other than subfebrile fever, which regressed within approximately 12 h with cold application.

Case 4: The final case was a nine-year-old male diagnosed with CP that developed due to hypoxia during birth. Before treatment, he had a WeeFIM score of 48, a MAS score of 17 (both sides), a GMFCS score of four, and a MACS score of four. He underwent allogeneic MSCT six times as 1 × 10^6/kg IT, IV, and IM using UC-MSCs. This patient showed a significant increase of 32 points in his WeeFIM motor score and a decrease of two points in his MAS score (both sides) starting from the second month. Also, his GMFCS and MACS scores went down to two points after the intervention. Regarding side effects, the patient only suffered temporary pain in the injection sites after the application.

Wee functional independence measure

Figure 3A shows the changes in WeeFIM motor and cognitive subtests at different times. Accordingly, these scores did not show a statistically significant change between preoperative and postoperative periods (P = 0.42).

Modified Ashworth scale

Table 2 lists the changes in the patients' mean MAS scores at different times. Accordingly, MAS scores for both sides decreased significantly after the intervention (two months: Right χ^2 = 4000, P = 0.046, left χ^2 = 4000, P = 0.046; four months: Right χ^2 = 4000, P = 0.046, left χ^2 = 4000, P = 0.046; 12 months: Right χ^2 = 4000, P = 0.046, left χ^2 = 4000, P = 0.046).

Gross motor function classification system and manual ability classification system

Figure 3B presents our patients' GMFCS and MACS scores at different times. Accordingly, there were some statistically significant changes in these scores between preoperative and postoperative measurements. To determine the cut-off times for significant improvement, we compared the preoperative results with each follow-up period individually. For GMFCS, preoperative and postoperative first week scores were the same for all cases. While GMFCS scores showed some decrease after the first week, these changes were not statistically significant compared to the baseline measurements (one month: χ^2 = 2000, P = 0.157; two months: χ^2 = 3000, P = 0.083; four months: χ^2 = 3000, P = 0.083). However, GMFCS scores at 12 months were significantly lower than baseline (χ^2 = 4000, P = 0.046). In other words, the GMFCS scores of our cases continued to decrease after the first week of intervention, but this improvement was only statistically significant at 12 months. MACS scores followed a similar trend. There was no difference between preoperative and postoperative first week measurements. Then, there were insignificant improvements up to the fourth month (one month: χ^2 = 2000, P = 0.157; two months: χ^2 = 3000, P = 0.083; four months: χ^2 = 3000, P = 0.083). Again, MACS scores at 12 months were significantly lower than baseline (χ^2 = 4000, P = 0.046). Thus, the MACS scores of our cases continued to go down after the

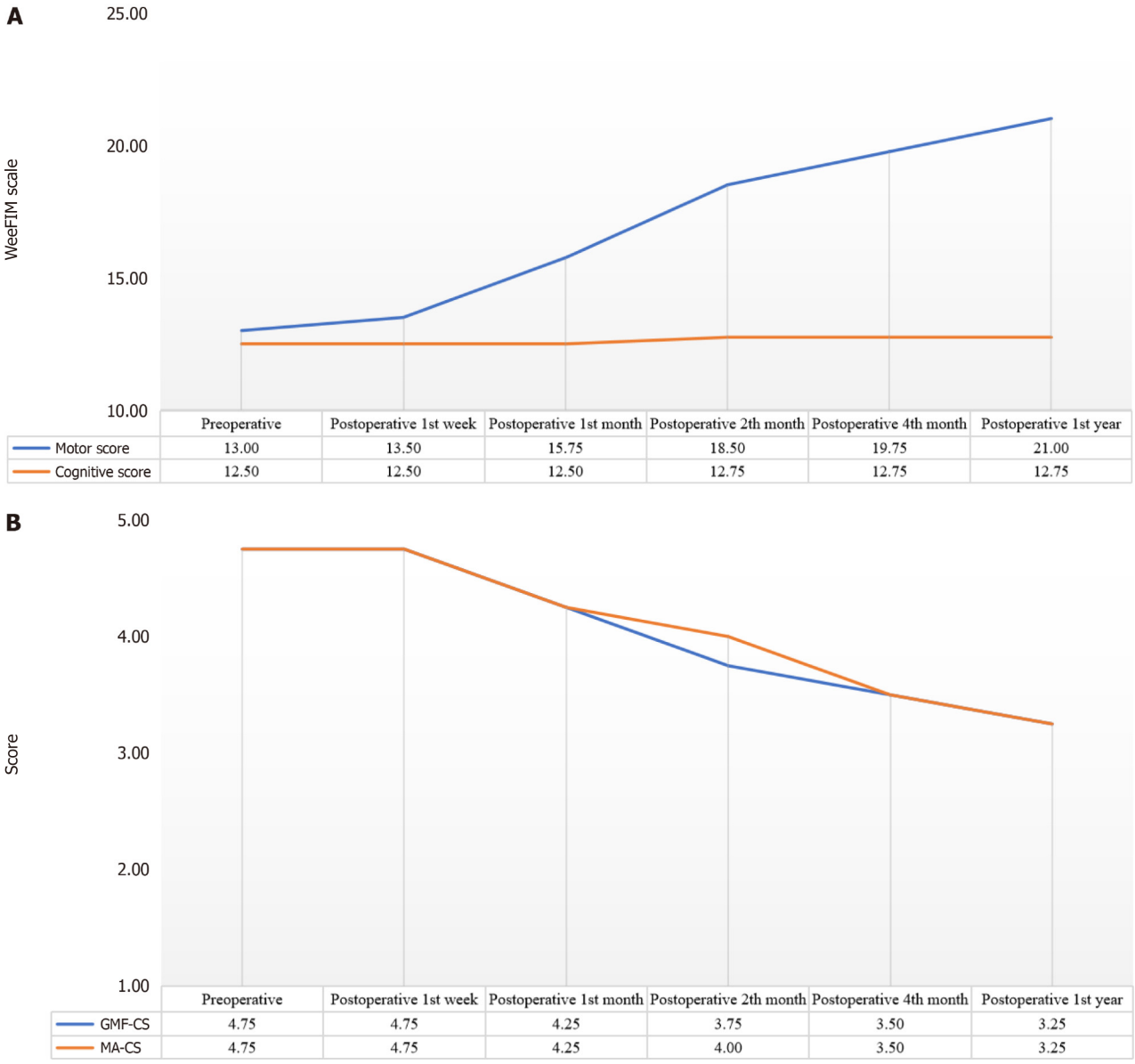

Figure 3 Change observed in the pre-test and post-test averages. A: Change observed in the pre-test and post-test averages of the patients' Wee functional independence measure motor score and cognitive score values; B: Change observed in the pre-test and post-test averages of the patients' Gross motor function classification system and manual ability classification system values. WeeFIM: Wee functional independence measure motor; GMF-CS: Gross motor function classification system; MA-CS: Manual ability classification system.

first week of treatment, but this change was only statistically significant at the one-year mark after the intervention.

DISCUSSION

CP is a group of disorders affecting movement, balance, and posture. UC-MSCs have been researched for CP treatment, albeit with limited or inconclusive clinical evidence regarding their benefits. One randomized study investigated the safety and efficacy of UC-MSC transplantation in CP patients and observed improvement in gross motor and functions after treatment combined with rehabilitation[14]. Other researchers have emphasized that the recovery of cerebral metabolic activity may be crucial for the development of brain functions in CP patients and the therapeutic window, transfusion route, and dosage are key for reference in clinical practice[29]. We believe that our findings can constitute a similar reference.

One trial focused on motor functions after treatment with allogeneic umbilical cord blood (AlloCB) in 91 children diagnosed with CP due to hypoxic-ischemic encephalopathy, stroke, or periventricular leukomalacia[30]. The authors used the Gross Motor Function Measure-66 and Peabody Developmental Motor Scale, Second Edition to measure motor functions. Accordingly, treatment with AlloCB and UC-MSC proved safe. They observed no significant change in motor functions at six months after treatment and AlloCB was associated with greater increases in Gross Motor Function Measure-66 scores at the one year mark[30].

We performed neurological and functional evaluations using GMFSC, MAS, and WeeFIM at different times up to 12 months after treatment. Based on WeeFIM scores, we observed a significant improvement in spasticity ($P = 0.046$) but no significant difference in motor functions ($P > 0.05$). GMFSC scores revealed improvement ($P = 0.046$), but there was no significant change in cognitive functions ($P > 0.05$).

UC-MSCs are a new and promising treatment modality for CP[8]. We observed no complications in any of our cases during one year of monitoring after six applications. Similarly, previous research reported no serious side effects[16-18]. Symptoms such as lower back pain and a mild increase in temperature were observed as minor side effects due to IT applications[31-33]. UC-MSCs release neurotrophic factors and increase muscle mass, displaying neuroprotective and neuro-regenerative activities on cognitive functions[8,34,35]. UC-MSCs have facilitated neuron regeneration in Parkinson's disease and stroke models in animals[36]. In addition, UC-MSCs have demonstrated positive effects on central and peripheral nervous systems[37]. Some clinical trials applied rehabilitation in their control groups to measure the therapeutic efficacy of SCT combined with rehabilitation. In these studies, patients who received SCT showed significant improvement compared to those who received rehabilitation only[38]. However, further research is warranted to clarify whether the combination of SCT and rehabilitation can yield better therapeutic effects than SCT alone. Previous studies also made use of MAS to measure muscle tone, one of the key symptoms of CP. Accordingly, researchers reported serious improvement after UC-MSC transplantation[39,40]. Only a few clinical studies noted improvement in fine motor movements such as pinching small objects and hand-eye coordination after using fetal brain-derived neural progenitor cells [8,41,42].

According to a systematic review that listed all findings after cell therapy in CP and the measurement tools used, 2066 participants have undergone various cell therapy interventions in 54 trials[43]. Movement and posture were the most frequently reported outcome categories, followed by safety, although quality of life and various common comorbidities and complications associated with CP have rarely been reported[43].

We observed significant improvements in spasticity and motor functions in our sample, which is compatible with some studies in the relevant literature[44-46] and conflicting with others[8]. Our patients displayed no difference in cognitive functions after therapy, but Vaquero *et al*[44] reported a significant improvement in the cognitive skills of patients with spinal cord injury after treatment. We associate this conflicting result with the low number of cases in our sample[44].

One of the limitations in the current study was the small group of subjects of the same race and of a wide age range. Also, we did not include a control group of volunteer CP patients who did not receive UC-MSC therapy. However, we believe that our data can make notable contributions to the existing literature.

CONCLUSION

In conclusion, UC-MSC transplantation yielded improvements in spasticity and motor functions at 12 months after treatment in CP patients. No clear improvement was gained in cognitive skills. Future randomized controlled trials with larger samples can illuminate the advantages and limitations of UC-MSC therapy.

ARTICLE HIGHLIGHTS

Cerebral palsy (CP) describes a group of nonprogressive disorders affecting movement, posture, and motor functions. It occurs in early childhood and persists until the end of life. Currently, the treatment of CP involves numerous modalities, such as various surgical treatments (selective dorsal rhizotomy, selective peripheral neurotomy, *etc.*), pharmacotherapies for generalized spasticity, Botox A for focal spasticity, and antiepileptics for epilepsy.

Research motivation

Current modalities can only provide partial symptom relief, which warrants research into new methods. One novel option for treating CP is mesenchymal stem cell therapy.

Research objectives

We aimed to investigate the efficacy and safety of mesenchymal stem cell therapy in CP cases.

Research methods

Our sample consisted of four patients who were unable to stand or walk without external support. All cases received allogeneic mesenchymal stem cell therapy six times as 1×10^6/kg intrathecally, intravenously, and intramuscularly using umbilical cord-derived mesenchymal stem cells. We monitored the patients before and after the treatment using the Wee Functional Independence Measure, the Gross Motor Function Classification System, the Manual Ability Classification Scale, and the Modified Ashworth Scale.

Research results

Spasticity measures showed significant improvement in both sides after the intervention. There was no significant change in motor functions or cognitive functions. Gross motor function and manual ability measures differed statistically significantly at 12 months after treatment compared to baseline values.

Research conclusions

In light of our findings, umbilical cord-derived mesenchymal stem cell therapy shows positive effects on spasticity and partial improvement in motor functions.

Research perspectives

In this study, we demonstrated that allogeneic mesenchymal stem cell application *via* intrathecal, intramuscular and intravenous routes is safe and effective in cerebral palsy patients. The effectiveness of this treatment protocol should be evaluated at a higher level of evidence by conducting randomized, double-blind, case-control studies with a high number of participants in the future.

FOOTNOTES

Author contributions: Boyali O, Civelek E, and Kabatas S contributed to concept; Osman Boyali, Kabatas S, and Savrunlu EC contributed to design; Boyali O, Kabatas S, and Karaoz E contributed to supervision; Civelek E, Kabatas S, Savrunlu EC, and Kaplan N contributed to analysis and/or interpretation; Boyali O, Kabatas S, Civelek E, Savrunlu EC, Ozdemir O, and Ozdemir YB contributed to literature search; Boyali O, Civelek E, Kabatas S, Kaplan N, Savrunlu EC, Ozdemir YB, and Karaoz E contributed to writing; Boyali O, Civelek E, Kabatas S, and Ozdemir O contributed to critical reviews.

Institutional review board statement: The present study was approved by the medical ethics committee of the authors' institution, No. 56733164-203-E.3178.

Clinical trial registration statement: Due to local legal restrictions, separate permission was obtained from the Turkish Ministry of Health for each patient included in the study, and therefore clinical trial registration could not be obtained.

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

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

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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Country/Territory of origin: Turkey

ORCID number: Osman Boyalı 0000-0002-2500-1718; Serdar Kabatas 0000-0003-2691-6861; Erdinç Civelek 0000-0002-3988-4064; Omer Ozdemir 0000-0003-3783-0203; Necati Kaplan 0000-0001-5672-0566; Eyüp Can Savrunlu 0000-0001-9022-200X; Erdal Karaöz 0000-0002-9992-833X.

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ORIGINAL ARTICLE

Observational Study

Clinical characteristics of acute non-varicose upper gastrointestinal bleeding and the effect of endoscopic hemostasis

Xiao-Juan Wang, Yu-Peng Shi, Li Wang, Ya-Ni Li, Li-Juan Xu, Yue Zhang, Shuang Han

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Xiao-Juan Wang, Yu-Peng Shi, Li Wang, Ya-Ni Li, Li-Juan Xu, Yue Zhang, Shuang Han, Department of Gastroenterology, Honghui Hospital Affiliated to Medicine College of Xi'an Jiaotong University, Xi'an 710054, Shaanxi Province, China

Corresponding author: Shuang Han, PhD, Professor, Department of Gastroenterology, Honghui Hospital Affiliated to Medicine College of Xi'an Jiaotong University, No. 555 Youyi East Road, Xi'an 710054, Shaanxi Province, China. shuanghamy@163.com

Abstract

BACKGROUND

Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) constitutes a prevalent emergency within Gastroenterology, encompassing 80%-90% of all gastrointestinal hemorrhage incidents. This condition is distinguished by its abrupt onset, swift progression, and notably elevated mortality rate.

AIM

To gather clinical data from patients with ANVUGIB at our hospital in order to elucidate the clinical characteristics specific to our institution and analyze the therapeutic effectiveness of endoscopic hemostasis.

METHODS

We retrospectively retrieved the records of 532 patients diagnosed with ANVUGIB by endoscopy at our hospital between March 2021 and March 2023, utilizing our medical record system. Data pertaining to general patient information, etiological factors, disease outcomes, and other relevant variables were meticulously collected and analyzed.

RESULTS

Among the 532 patients diagnosed with ANVUGIB, the male-to-female ratio was 2.91:1, with a higher prevalence among males. Notably, 43.6% of patients presented with black stool as their primary complaint, while 27.4% had hematemesis as their initial symptom. Upon admission, 17% of patients exhibited both hematemesis and black stool, while most ANVUGIB patients primarily complained of overt gastrointestinal bleeding. Urgent routine blood examinations at admission revealed that 75.8% of patients had anemia, with 63.4% experiencing moderate to severe anemia, and 1.5% having extremely severe anemia (hemoglobin < 30 g/L). With regard to etiology, 53.2% of patients experienced bleeding without a definitive trigger, 24.2% had a history of using gastric mucosa-irritating medications,

24.2% developed bleeding after alcohol consumption, 2.8% attributed it to improper diet, 1.7% to emotional excitement, and 2.3% to fatigue preceding the bleeding episode. Drug-induced ANVUGIB was more prevalent in the elderly than middle-aged and young individuals, while bleeding due to alcohol consumption showed the opposite trend. Additionally, diet-related bleeding was more common among the young age group compared to the middle-aged group. Gastrointestinal endoscopy identified peptic ulcers as the most frequent cause of ANVUGIB (73.3%), followed by gastrointestinal malignancies (10.9%), acute gastric mucous lesions (9.8%), and androgenic upper gastrointestinal bleeding (1.5%) among inpatients with ANVUGIB. Of the 532 patients with gastrointestinal bleeding, 68 underwent endoscopic hemostasis, resulting in an endoscopic treatment rate of 12.8%, with a high immediate hemostasis success rate of 94.1%.

CONCLUSION

ANVUGIB patients exhibit diverse characteristics across different age groups, and endoscopic hemostatic treatments have demonstrated remarkable efficacy.

Key Words: Acute non-varicose upper gastrointestinal bleeding; Clinical characteristics; Cause of disease; Endoscopic homeostatic therapy

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Core Tip: This retrospective study analyzed the data of patients diagnosed with acute non-varicose upper gastrointestinal bleeding (ANVUGIB) through endoscopic examinations at our hospital. The results revealed distinct characteristics among patients of different age groups with ANVUGIB. Although this study was conducted at a single center, the age and gender distribution of the patients in this study were similar to those reported in previous multicenter studies in China. The study also assessed the therapeutic effectiveness of endoscopic hemostatic treatment, and indicated that it is an effective approach for treating ANVUGIB, improving efficacy, and deserves wider application.

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INTRODUCTION

Non-variceal upper gastrointestinal bleeding (NVUGIB) is characterized as gastrointestinal hemorrhage that originates proximal to the ligament of Treitz in the duodenum. Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) represents a common emergency in the field of Gastroenterology, accounting for 80%-90% of all cases of gastrointestinal bleeding[1]. It is characterized by its sudden onset, rapid progression, and high mortality rate[2]. The primary cause of NVUGIB is typically gastroduodenal peptic ulcers, succeeded by gastroduodenal erosions. Other prevalent causes include peptic esophageal lesions (esophagitis or esophageal ulcers), vascular anomalies such as Dieulafoy lesions (a medical condition characterized by an abnormal, tortuous arteriole penetrating the gastrointestinal mucosa), and vascular ectasias such as angiodysplasia (a minor vascular malformation in the gut). Additionally, Mallory–Weiss tears (mucosal lacerations at the gastroesophageal junction, often associated with recurrent vomiting, particularly following excessive alcohol consumption or a large meal) and, to a lesser extent, neoplastic lesions, are also notable causes of NVUGIB[3,4]. Significant advancements in medicine over the past two decades have influenced both the incidence and outcomes of NVUGIB. On the one hand, the introduction of potent acid-suppressing medications, recognition of *Helicobacter pylori* as a key etiological factor in peptic ulcers leading to targeted eradication therapy, advancements in diagnostic and therapeutic endoscopy, implementation of restrictive blood transfusion policies, and enhanced management of critically ill patients are pivotal factors that have decreased the risk of developing NVUGIB and improved its management and outcomes. On the other hand, certain risk factors are becoming increasingly prevalent. These include an aging population, which contributes to a higher prevalence of cardiovascular diseases and other comorbidities that escalate the mortality risk associated with NVUGIB, and the growing use of low-dose aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and other antiplatelet and anticoagulant agents[5-7]. The etiological landscape seems to be changing over time, but the overall incidence of hospitalizations remains high. During the initial stages of this condition, patients frequently present symptoms such as hematemesis and melena, and in severe cases, peripheral circulatory failure may develop. In clinical practice, traditional medical treatments are often employed to manage ANVUGIB, but their effectiveness in controlling acute active bleeding is frequently unsatisfactory. The advent of endoscopic techniques and innovative endoscopic accessories has significantly enhanced the efficiency of hemostasis[8-10].

This study entails a retrospective analysis involving the retrieval of medical records pertaining to 532 patients who received a diagnosis of ANVUGIB through endoscopic examination at our hospital between March 2021 and March 2023.

Data encompassing general patient information, etiological factors, and disease outcomes were systematically collected to gain insights into the clinical characteristics of ANVUGIB within our hospital. Furthermore, the study aims to enhance the understanding of ANVUGIB among our clinical practitioners and improve the standards of diagnosis and treatment. Additionally, the research assesses the efficacy of endoscopic hemostasis in patients who underwent this procedure.

MATERIALS AND METHODS

Patient data

The data of 532 patients diagnosed with ANVUGIB through endoscopic examinations at our hospital between March 2021 and March 2023 were retrieved from the hospital's medical records system. General patient information, etiological factors, and disease outcomes were meticulously gathered and refined. Data from patients who underwent endoscopic hemostasis treatment were specifically chosen to evaluate the effectiveness of this therapeutic approach.

Research methods

A retrospective analysis of patient data was undertaken, including age, gender, chief complaint upon admission, hemoglobin (Hb) levels, precipitating factors, etiology, treatment outcomes, and the effectiveness of endoscopic treatment. Moreover, an additional analysis examined the interplay between precipitating factors, etiology, and age groups by categorizing patients into the following groups: the young group (age < 40 years), middle-aged group (age < 60 but ≥ 40 years), and elderly group (age ≥ 60 years).

Statistical analysis

In this study, initial data collection was accomplished through Excel spreadsheets. All data underwent statistical analysis using SPSS 26.0 software. Frequency and percentage (%) were used to present count data, while measurement data were presented as means with standard deviations (mean ± SD). The comparison of count data was performed using the Pearson chi-square test or the continuity correction test, with statistical significance set at $P < 0.05$ to indicate significant differences.

RESULTS

General situation

A total of 532 patients diagnosed with ANVUGIB were treated at our center between March 2021 and March 2023, presenting with symptoms such as hematemesis, melena, and other upper gastrointestinal bleeding (Table 1). Among them, there were 396 males (74.44%) and 136 females (25.56%), resulting in a male-to-female ratio of 2.91:1. The age of the patients ranged from 18 to 94 years, with an average age of 53.34 ± 18.92 years and an average hospital stay of 7.6 ± 4.56 d.

Chief complaint and hemoglobin levels on admission

After collecting and analyzing the chief complaints of patients upon admission, it was observed that the majority of ANVUGIB patients presented with a primary complaint related to gastrointestinal bleeding. Among these patients, 232 cases (43.6%) reported melena as their primary complaint, representing the highest proportion. Additionally, 146 cases (27.4%) cited hematemesis as their primary complaint, while 90 cases (17.0%) reported both hematemesis and melena. Abdominal pain was the primary complaint in 32 cases (6.0%), while 32 cases (6.0%) had atypical complaints such as dizziness and weakness, with ANVUGIB confirmed after further examination.

Urgent routine blood tests conducted upon admission revealed that 75.8% of the patients were anemic. Among them, 8 cases (1.5%) had severe anemia (Hb ≤ 30 g/L), 58 cases (10.9%) had moderate anemia (Hb 30-60 g/L), 203 cases (38.2%) had mild to moderate anemia (Hb 60-90 g/L), 134 cases (25.2%) had mild anemia (Hb 90-120 g/L), and 129 cases (24.2%) did not exhibit anemia (Hb ≥ 120 g/L).

Precipitating factor of ANVUGIB

Upon reviewing the admission records and the medical course, it was observed that 53.2% of the patients did not have an evident precipitating factor before experiencing bleeding, while nearly half of the patients had relatively clear triggers preceding the bleeding episode. Among this group, 129 cases (24.2%) had used aspirin, NSAIDs, glucocorticoids, chemotherapy, and molecular targeted drugs known to stimulate and damage the gastric mucosa. Additionally, some patients were taking anticoagulant drugs such as warfarin and rivaroxaban, which impacted their coagulation function. Eighty-four (15.8%) patients had a history of alcohol consumption before bleeding occurred. Improper diet was a contributing factor in 15 cases (2.8%), emotional excitement was noted in 9 cases (1.7%), and physical exertion was a factor in 12 cases (2.3%). Given the relatively low frequency of physical exertion and emotional excitement as precipitating factors, these will be collectively referred to as psychological factors in the subsequent text.

Relationship between etiology of ANVUGIB and age groups

The patients were stratified into three age groups: the young group (age < 40 years), the middle-aged group (age < 60 but ≥ 40 years), and the elderly group (age ≥ 60 years), with 139 patients in the young group, 221 patients in the middle-aged

Table 1 Clinical characteristics of the included patients

Items		Number	Percentage
Sex	Men	396	74.44
	Women	136	25.56
Age (yr)	Young group (age < 40)	139	26.13
	Middle-aged group (age < 60 but ≥ 40)	221	41.54
	Elderly group (age ≥ 60)	172	32.33
Chief complaint	Melena	232	43.60
	Hematemesis	146	27.40
	Both hematemesis and melena	90	17.00
	Abdominal pain	32	6.00
	Atypical complaints (dizziness, weakness)	32	6.00
Hemoglobin levels	Hb ≤ 30 g/L	8	1.50
	Hb 30-60 g/L	58	10.90
	Hb 60-90 g/L	203	38.20
	Hb 90-120 g/L	134	25.20
	Hb ≥ 120 g/L	129	24.20
Precipitating factor	Drugs	129	24.20
	Alcohol	84	15.80
	Diet	15	2.80
	Psychological factors	21	4.00
	No precipitating factor	283	53.20

group, and 172 patients in the elderly group. Among the 249 patients for whom bleeding triggers were recorded, there were 65 cases in the young group, 103 cases in the middle-aged group, and 81 cases in the elderly group. Statistical analysis revealed differences in ANVUGIB triggered by drugs and alcohol among patients in various age groups, while no significant differences were observed in ANVUGIB induced by dietary and psychological factors among patients in different age groups (Table 2).

Various causes of ANVUGIB

Upon completion of gastrointestinal endoscopy, it was evident that peptic ulcer disease constituted the vast majority of ANVUGIB cases, accounting for 73.3% (390 cases). Gastrointestinal malignancies comprised 10.9% (58 cases), while acute gastric mucosal lesions represented 9.8% (52 cases). Other contributing factors included duodenal diseases, angiodysplasia, esophageal ulcers, and anastomotic ulcers, collectively amounting to 4.5% (24 cases). Iatrogenic upper gastrointestinal bleeding accounted for 1.5% (8 cases), encompassing post-endoscopic submucosal dissection (ESD)/endoscopic mucosal resection (EMR) bleeding, post-EST bleeding at the duodenal papilla, and post-polypectomy bleeding in the upper gastrointestinal tract.

Among the 390 diagnosed cases of gastrointestinal ulcer bleeding, 213 were attributed to duodenal ulcers, 116 to gastric ulcers, and 53 to compound ulcers involving both gastric and duodenal ulcers. Given the relatively low theoretical frequency, variance analysis based on the age of onset was not conducted for upper gastrointestinal bleeding patients caused by esophageal ulcers, anastomotic ulcers, duodenal diseases, upper gastrointestinal vascular malformations, and iatrogenic factors.

Relationship between causes of ANVUGIB and age of onset

A total of 532 patients with ANVUGIB underwent complete gastrointestinal endoscopy to determine the cause of bleeding. Among them, 139 cases were in the young age group, 221 cases were in the middle-aged group, and 172 cases were in the elderly group. Statistical analysis revealed differences in the causes of gastrointestinal bleeding among the different age groups (Table 3). Further pairwise comparisons using chi-square analysis showed that the comparison of bleeding caused by duodenal ulcers between the young and middle-aged groups was not statistically significant (χ^2 = 3.841, P = 0.05). However, the incidence rate in both the young and middle-aged groups was higher than that in the elderly group, with significant differences (P < 0.05).

The comparison of gastric ulcer bleeding between the middle-aged and elderly groups was not statistically significant (χ^2 = 0.041, P = 0.840), but the incidence rate in both the middle-aged and elderly groups was higher than that in the

Table 2 Relationship between acute non-varicose upper digestive hemorrhage pathogenesis and age group

Age group	Drugs	Alcohol	Diet	Psychological factors
Young group	6	51	7	7
Middle-aged group	36	28	3	9
Elderly group	86	6	5	5
χ^2	76.563	35.741	1.600	1.143
P value	0.000	0.000	0.449	0.565

Table 3 Relationship between acute non-varicose upper digestive hemorrhage etiology and age group

Age group	Duodenal ulcer	Gastric ulcer	Complex ulcer	Cancer	Acute gastric mucosal lesions
Young group	75	18	20	2	23
Middle-aged group	101	48	27	8	25
Elderly group	37	50	6	48	5
χ^2	29.183	16.621	12.943	64.690	13.736
P value	0.000	0.000	0.002	0.000	0.001

young group, with significant differences (χ^2 = 13.363, P < 0.001, χ^2 = 15.059, P < 0.001). The incidence rate of compound ulcer bleeding was not statistically significant between the young and middle-aged groups (χ^2 = 1.043, P = 0.307), but it was higher than that in the elderly group, with significant differences (P < 0.05).

The comparison of bleeding caused by upper gastrointestinal malignancies between the young and middle-aged groups was not statistically significant (χ^2 = 3.600, P = 0.773), but it was significantly lower than that in the elderly group (P < 0.05). Among patients admitted with a diagnosis of acute gastric mucosal lesions, there was no statistical difference between the young and middle-aged groups (χ^2 = 0.083, P = 0.058), but both were higher than those in the elderly group (P < 0.05).

Therefore, it can be concluded that acute gastric mucosal lesions, duodenal ulcers, and compound ulcers are more common in the middle-aged and young age groups, while gastric ulcers are more common in the middle-aged and elderly groups. The incidence rate of upper gastrointestinal malignancies was significantly higher in the elderly population compared to the middle-aged and young age groups.

Treatment and outcome

Of the 532 patients with gastrointestinal bleeding, a total of 464 patients were diagnosed by endoscopy. These patients either received conservative drug therapy or were promptly referred to other departments for surgery or interventional treatment. Among them, 68 patients who were hemodynamically stable or stabilized after volume expansion underwent endoscopic hemostatic treatment, representing an endoscopic treatment rate of 12.8%. Of the 68 patients who underwent endoscopic hemostasis during gastroscopy, four patients encountered challenges during the procedure for various reasons. Among these, three patients required embolization therapy for hemostasis, while one patient underwent surgical intervention for hemostasis. The remaining 64 bleeding patients achieved immediate hemostasis through endoscopic treatment, resulting in an immediate endoscopic hemostasis rate of 94.1% (Table 4).

DISCUSSION

ANVUGIB represents a grave condition characterized by a high incidence, rebleeding rate, and mortality rate. It has consistently remained a subject of great concern for gastroenterologists and emergency physicians. This study undertook a retrospective analysis of patients diagnosed with ANVUGIB through endoscopic examinations conducted between March 2021 and March 2023 at our hospital. The findings revealed a significantly higher number of male patients compared to female patients, with a male-to-female ratio of 2.91:1. The age of patients ranged from 18 to 94 years, with an average age of 53.34 ± 18.92 years and an average hospital stay of 7.6 ± 4.56 days. In line with previous studies conducted by Yan-Xia Zhang and Rong Han, gender emerged as one of the influencing factors for the occurrence of gastrointestinal bleeding[11,12]. Simplified statistics concerning admission complaints indicated that 43.6% of patients presented with melena as their primary complaint upon admission, while 27.4% presented with hematemesis. Additionally, 17% of patients exhibited both hematemesis and melena upon admission. The majority of ANVUGIB patients sought medical attention with clear complaints of gastrointestinal bleeding, underscoring the importance of vigilance for patients with atypical gastrointestinal bleeding complaints during the clinical assessment. Routine blood examination results at admission revealed that 75.8% of patients exhibited anemia, with 63.4% of them classified as having moderate or more

Table 4 Statistics of rebleeding after acute non-varicose upper digestive hemorrhage endoscopic hemostasis

	Number	Percentage
Rebleeding was recorded within 72 h after endoscopic treatment	7	10.9
Rebleeding was recorded 72 h after endoscopic treatment	4	6.3
No further bleeding after endoscopic treatment	53	82.8

severe anemia. A minority of patients (1.5%) presented with extremely severe anemia (Hb < 30 g/L). The initial routine blood examination upon admission played a crucial role in determining whether patients required immediate blood transfusion therapy. Patients with Hb levels below 70 g/L were considered primary candidates for transfusion therapy [5].

In recent years, there has been a notable surge in drug-related acute gastric mucosal lesions and bleeding, specifically associated with medications such as aspirin and heparin. This trend can be attributed to the aging population and the heightened prevalence of cardiovascular and cerebrovascular diseases among the elderly. Cai *et al*[13] conducted a study involving 253 patients with acute gastric mucosal lesions, where 153 cases (60.47%) were linked to NSAIDs and anticoagulant drugs. Notably, the incidence ratio between the first five years and the last five years exhibited statistical significance ($P < 0.05$). In this investigation, upon categorizing the patients into different age groups, it was revealed that 53.2% of the patients experienced bleeding without any apparent triggers beforehand, while nearly half of the patients had identifiable triggers preceding the bleeding episode. Among this latter group, 24.2% of the patients were using aspirin, NSAIDs, corticosteroids, chemotherapy drugs, and molecularly targeted drugs known to stimulate and damage the gastric mucosa, along with patients taking anticoagulant medications such as warfarin and rivaroxaban, which impact coagulation function. These individuals were primarily middle-aged and elderly, further reinforcing the aforementioned findings. Moreover, patients with a history of alcohol consumption accounted for 15.8% of cases before the onset of bleeding. Subsequent subgroup analysis indicated that the rise in the proportion of ANVUGIB in the younger age group was primarily linked to digestive ulcers and acute gastric mucosal lesions caused by alcohol consumption in this demographic.

Further research conducted among the different age groups revealed variations in the etiology of gastrointestinal bleeding. When comparing bleeding caused by duodenal ulcers between the young and middle-aged groups, no statistically significant difference was observed ($\chi^2 = 3.841$, $P = 0.05$). However, the incidence rates were higher in both the young and middle-aged groups when compared to the elderly group, and these differences were statistically significant ($P < 0.05$). Similarly, when examining gastric ulcer bleeding between the middle-aged and elderly groups, no statistical significance was found ($\chi^2 = 0.041$, $P = 0.840$). Nevertheless, the incidence rates of gastric ulcer bleeding were notably higher in both the middle-aged and elderly groups in comparison to the young group, and these disparities were statistically significant ($\chi^2 = 13.363$, $P < 0.001$, $\chi^2 = 15.059$, $P < 0.001$). The incidence rate of combined ulcer bleeding showed no statistical significance between the young and middle-aged groups ($\chi^2 = 1.043$, $P = 0.307$), but it was significantly elevated in both of these groups when compared to the elderly group, with statistically significant differences ($P < 0.05$). Furthermore, when comparing patients with upper gastrointestinal malignant tumors causing bleeding between the young and middle-aged groups, no statistical significance was observed ($\chi^2 = 3.600$, $P = 0.773$). However, both of these groups exhibited significantly lower incidence rates when compared to the elderly group, with statistically significant differences ($P < 0.05$). In conclusion, it can be deduced that acute gastric mucosal lesions, duodenal ulcers, and combined ulcers are more prevalent in the middle-aged and young groups, while gastric ulcers are more common in the middle-aged and elderly groups. Additionally, the incidence rate of upper gastrointestinal malignant tumors is notably higher among the elderly population as compared to the middle-aged and young groups.

Furthermore, as endoscopic technology continues to advance and the number of endoscopic procedures performed rises, iatrogenic gastrointestinal bleeding has been increasingly identified as a notable complication during and after surgeries. In this retrospective analysis, iatrogenic upper gastrointestinal bleeding constituted 1.5% of cases (8 instances), encompassing post-ESD/EMR bleeding, bleeding following EST procedures in the duodenal papilla, and post-endoscopic polypectomy bleeding in the upper gastrointestinal tract. A comprehensive literature review disclosed noteworthy discrepancies in the incidence of intraoperative and postoperative bleeding associated with ESD/EMR across different medical centers[14-17]. This analysis suggests that the substantial variations in occurrence rates might be attributed to various factors, such as differing definitions of bleeding complications employed by different physicians, the extent of submucosal dissection, and the extent of electrocoagulation applied to the wound surface after dissection.

Several previous studies[18-22] have affirmed the therapeutic efficacy of gastrointestinal endoscopy in the management of ANVUGIB. It has been shown to significantly enhance treatment outcomes, reduce the treatment duration, and improve Hb levels. In this particular investigation, conducted among a cohort of 532 patients with gastrointestinal bleeding, a total of 68 patients underwent endoscopic hemostatic procedures, representing a utilization rate of 12.8% for endoscopic treatment. The indications for endoscopic treatment predominantly included pulsatile bleeding, oozing, exposure of blood vessels, and identification of the primary bleeding site following the removal of blood clots due to various etiologies. Among the 68 patients who underwent endoscopic hemostasis *via* gastroscopy, four cases encountered challenges in achieving hemostasis through endoscopy due to various factors. Within this subgroup, three patients underwent embolization therapy to achieve hemostasis, while one patient required surgical intervention for hemostasis. Among the remaining 64 patients experiencing bleeding, immediate hemostasis was successfully achieved through endoscopic treatment, resulting in an impressive immediate endoscopic hemostasis rate of 94.1%. These results

underscore the effectiveness of endoscopic hemostatic treatment for upper gastrointestinal bleeding. However, it is crucial to remain vigilant against the possibility of rebleeding.

CONCLUSION

In summary, this retrospective study examined the data of patients diagnosed with ANVUGIB by endoscopic examination at our hospital. The results highlighted the distinct characteristics among ANVUGIB patients of different age groups. Although this study was conducted at a single center, it is noteworthy that the age and gender distribution of the patients in this study closely mirrored those reported in previous multicenter studies conducted in China. Furthermore, the therapeutic impact of endoscopic hemostatic treatment was studied, and was found to be effective in managing ANVUGIB, enhancing treatment outcomes, and warrants wider application.

ARTICLE HIGHLIGHTS

Research background

Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) constitutes a prevalent emergency within Gastroenterology, encompassing 80%-90% of all gastrointestinal hemorrhage incidents. This condition is distinguished by its abrupt onset, swift progression, and notably elevated mortality rate.

Research motivation

This research was designed to collect clinical data from patients experiencing ANVUGIB at our hospital. The objective was to identify clinical features unique to our institution and to evaluate the efficacy of endoscopic hemostasis treatment.

Research objectives

The aim is to clarify the distinct clinical characteristics associated with our institution and to assess the therapeutic efficacy of endoscopic hemostasis.

Research methods

We conducted a retrospective analysis of 532 patients diagnosed with ANVUGIB *via* endoscopy at our hospital from March 2021 to March 2023, utilizing our electronic medical records system. Data encompassing general patient demographics, etiological factors, clinical outcomes, and other pertinent variables were scrupulously gathered and examined.

Research results

In the cohort of 532 patients diagnosed with ANVUGIB, the male-to-female ratio was 2.91:1, indicating a higher incidence in males. Notably, 43.6% of these patients reported black stool as their primary symptom, while 27.4% initially presented with hematemesis. On admission, 17% of patients showed symptoms of both hematemesis and black stool. The majority of ANVUGIB patients primarily complained of overt gastrointestinal bleeding. Urgent hematological assessments upon admission revealed that 75.8% of the patients were anemic, with 63.4% suffering from moderate to severe anemia, and 1.5% exhibiting extremely severe anemia (Hemoglobin < 30 g/L). Etiologically, 53.2% experienced bleeding without an identifiable trigger, 24.2% had a history of ingesting gastric mucosa-irritating medications, 24.2% developed bleeding post alcohol consumption, 2.8% linked their bleeding to improper diet, 1.7% to emotional excitement, and 2.3% to fatigue prior to the bleeding episode. Drug-induced ANVUGIB was more common in the elderly compared to middle-aged and younger individuals, while alcohol-related bleeding was more frequent in younger patients. Moreover, diet-related bleeding incidents were predominantly observed in the younger demographic compared to middle-aged individuals. Gastrointestinal endoscopy revealed peptic ulcers as the leading cause of ANVUGIB, accounting for 73.3% of cases, followed by gastrointestinal malignancies (10.9%), acute gastric mucosal lesions (9.8%), and androgenic upper gastrointestinal bleeding (1.5%). Of the 532 patients with gastrointestinal bleeding, 68 underwent endoscopic hemostasis, representing a treatment rate of 12.8%, with a notably high immediate hemostasis success rate of 94.1%.

Research conclusions

Patients across various age groups present with distinct characteristics, and endoscopic hemostatic treatments showed significant efficacy.

Research perspectives

This retrospective analysis focused on patients diagnosed with ANVUGIB *via* endoscopic examination at our hospital. The study underscored the unique characteristics of ANVUGIB patients across various age demographics. Additionally, it determined the therapeutic effectiveness of endoscopic hemostatic treatment, affirming its efficiency in managing ANVUGIB, improving treatment outcomes, and advocating for its wider implementation.

FOOTNOTES

Author contributions: Wang XJ and Shi YP reviewed the literature and participated in drafting the manuscript; Wang XJ drafted the manuscript; Wang L, Li YN, Xu LJ and Zhang Y revised the manuscript for important intellectual content; Wang XJ and Han S reviewed and revised the manuscript; Han S contributed to conception and design of the study, manuscript supervision, financial support; All authors read and approved the final version of this manuscript.

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Country/Territory of origin: China

ORCID number: Xiao-Juan Wang 0000-0003-1127-0252; Shuang Han 0000-0002-2719-260X.

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ORIGINAL ARTICLE

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Construction of the underlying circRNA-miRNA-mRNA regulatory network and a new diagnostic model in ulcerative colitis by bioinformatics analysis

Yu-Yi Yuan, Hui Wu, Qian-Yun Chen, Heng Fan, Bo Shuai

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Yu-Yi Yuan, Hui Wu, Qian-Yun Chen, Heng Fan, Bo Shuai, Department of Integrated Traditional Chinese and Western Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, Hubei Province, China

Corresponding author: Heng Fan, PhD, MD, Chief Physician, Department of Integrated Traditional Chinese and Western Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1277 Jie Fang Avenue, Wuhan 430022, Hubei Province, China. fanheng009@aliyun.com

Abstract

BACKGROUND

Circular RNAs (circRNAs) are involved in the pathogenesis of many diseases through competing endogenous RNA (ceRNA) regulatory mechanisms.

AIM

To investigate a circRNA-related ceRNA regulatory network and a new predictive model by circRNA to understand the diagnostic mechanism of circRNAs in ulcerative colitis (UC).

METHODS

We obtained gene expression profiles of circRNAs, miRNAs, and mRNAs in UC from the Gene Expression Omnibus dataset. The circRNA-miRNA-mRNA network was constructed based on circRNA-miRNA and miRNA-mRNA interactions. Functional enrichment analysis was performed to identify the biological mechanisms involved in circRNAs. We identified the most relevant differential circRNAs for diagnosing UC and constructed a new predictive nomogram, whose efficacy was tested with the C-index, receiver operating characteristic curve (ROC), and decision curve analysis (DCA).

RESULTS

A circRNA-miRNA-mRNA regulatory network was obtained, containing 12 circRNAs, three miRNAs, and 38 mRNAs. Two optimal prognostic-related differentially expressed circRNAs, hsa_circ_0085323 and hsa_circ_0036906, were included to construct a predictive nomogram. The model showed good discrimination, with a C-index of 1(> 0.9, high accuracy). ROC and DCA suggested that the nomogram had a beneficial diagnostic ability.

CONCLUSION
This novel predictive nomogram incorporating hsa_circ_0085323 and hsa_circ_0036906 can be conveniently used to predict the risk of UC. The circRNa-miRNA-mRNA network in UC could be more clinically significant.

Key Words: Circular RNAs; RNA regulatory network; Ulcerative colitis; New predictive model; Bioinformatics; Diagnose

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Core Tip: In this study, we constructed a circRNA-miRNA-mRNA regulatory network to investigate the probable mechanism of circRNAs in ulcerative colitis. Initially, differentially expressed circRNAs (DEcircRNAs), differentially expressed miRNAs (DEmiRNAs), and differentially expressed mRNAs (DEmRNAs) were retrieved using the RNA expression spectrum of circRNA, miRNA, and mRNA in the Gene Expression Omnibus dataset. The competing endogenous RNA (ceRNA) network was then established after determining the DEcircRNA-DEmiRNA and DEmiRNA-DEmRNA interactions using bioinformatics analysis methods. Functional enrichment analysis was performed to evaluate the biological functions of DEmRNAs in the ceRNA network. Ultimately, DEcircRNAs in the circRNA-miRNA-mRNA network were used to construct a new diagnostic model.

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INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) that affects the mucosa and submucosa of the colon and rectum and sometimes a small segment of the terminal ileum. Severe UC is characterised by fever, abnormal C-reactive protein and haemoglobin levels, and other signs of intestinal inflammation[1]. In addition to these clinical symptoms, the diagnosis of UC involves fibreoptic colonoscopy, double-contrast angiography with barium enema, and characteristic biomarkers. Following the expansion of treatment facilities for ulcerative colitis, the number of drugs with new targets is expected to increase rapidly in future[2,3]. However, despite the progress in biology, the information regarding the pathogenesis of UC continues to be limited. Therefore, exploring the molecular mechanism of UC to formulate appropriate therapeutic strategies and diagnose the disease is important.

Circular RNAs (circRNAs), a type of ncRNA, are formed from a covalently closed loop by 50-30 back-splicing or specific splicing[4]. CircRNAs regulate mRNA translation by sponging miRNAs as competing endogenous RNA (ceRNA) or acting as mRNA traps[5,6]. The biological mechanisms of circRNAs fall into six categories: (1) Acting as circRNA sponge miRNA; (2) acting as circRNA sponge RNA-binding protein RBP; (3) acting as a protein-RNA complex member; (4) acting as a protein scaffold; (5) recruiting trans-regulatory factors to regulate transcription; and (6) translation of peptides[7,8]. Previous studies have shown that circRNAs are closely related to many human diseases such as tumours, ischaemic heart disease, rheumatoid arthritis, and degenerative diseases[9]. However, studies on the relationship between UC and circRNAs, especially the expression matrix of circRNAs in UC species, are few[10]. Therefore, whether circRNAs can serve as clinical biomarkers of UC needs to be addressed. We believe that the contributions of circRNAs to UC will become a hotspot in future studies[11]. Commonly, miRNAs recognise the miRNA response elements (MREs) on RNAs that mediate their interaction and binding. These RNAs containing circRNA, lncRNAs, and mRNAs act as competing endogenous RNAs (ceRNAs). They combine with miRNAs through MREs to regulate a series of subsequent life activities [12,13]. Through clinical samples and cell experiments, Li *et al*[14] showed that hsa_circ_0001021 is expressed in epithelial cells and is associated with ZO-1, occludin, and CLDN-2. Furthermore, hsa_circ_0001021 sponges miR-224-5p to upregulate smad4 and increase ZO-1 and occludin to regulate UC epithelial barrier function[14]. However, the potential role of circRNAs in UC remains to be investigated.

In this study, we constructed a circRNA-miRNA-mRNA regulatory network to investigate the probable mechanism of circRNAs in UC. Initially, differentially expressed circRNAs (DEcircRNAs), differentially expressed miRNAs (DEmiRNAs), and differentially expressed mRNAs (DEmRNAs) were retrieved using the RNA expression spectrum of circRNA, miRNA, and mRNA in the Gene Expression Omnibus (GEO) dataset. The ceRNA network was then established after determining the DEcircRNA-DEmiRNA and DEmiRNA-DEmRNA interactions using bioinformatics analysis methods. Functional enrichment analysis was performed to evaluate the biological functions of DEmRNAs in the ceRNA network. Ultimately, DEcircRNAs in the circRNA-miRNA-mRNA network were used to construct a new diagnostic model. The circRNA-miRNA-mRNA network regulatory network and new diagnostic model play an important role in the comprehensive analysis of gene interactions and identification of potential biomarkers that can be used for disease diagnosis, therapy, and prognosis of UC[15,16].

MATERIALS AND METHODS

Data collection

The NCBI GEO (http://www.ncbi.nlm.nih.gov/gds/) public database was used to obtain microarray data. The ctiteria for the selected dataset were as follows: (1) The grouping had biological replication significance; and (2) Colon tissue belonging to UC human or mouse. The circRNA expression profile of UC was derived from GSE131911, which constituted four patients with ulcerative colitis and four healthy controls. The miRNA expression data of UC were retrieved from GSE43009 (including five UC patients and five controls), and the mRNA expression data of UC were acquired from GSE48958 (including nine UC patients and 10 controls). The basics of the three microarray datasets are presented in Table 1.

Recognition of DEcircRNAs, DEmiRNAs, and DEmRNAs

After downloading the raw microarray data, the data were normalised and logarithmically expressed. The associated probe ID was converted to an international uniform name. When multiple probes corresponded to the same gene symbol, they were averaged, and probes that did not match the gene symbol were eliminated. DEcircRNAs, DEmiRNAs, and DEmRNAs between UC and control samples were screened using Bioconductor limma R. The thresholds were the absolute value of $|\log2(\text{fold-change})| > 1.0$, and the adjusted P-value < 0.05.

Prediction of circRNA-miRNA and miRNA-mRNA interactions

The circRNA interactome[20] (https://circinteractome.nia.nih.gov/), a comprehensive database of circRNAs, was used to predict the target circRNAs of the DEmiRNAs. We then deployed the online database Venny 2.1.0 (http://bioinfogp.cnb.csic.es/tools/venny/index.html) to evaluate the intersection of target circRNAs of DEmiRNAs and DEcircRNAs. The target mRNAs of DEmiRNAs were derived from three different miRNA target gene databases, miRTarBase, TargetScan, and miRDB, which intersect with DEmRNAs[21]. In addition, target genes appearing in at least two databases were selected[22].

Structure of the circRNA-miRNA-mRNA regulatory network

Because circRNA can competitively bind miRNA to regulate miRNA expression, only those who conform to circRNA-miRNA and miRNA-mRNA targeting rules can be selected for the construction of ceRNA network. By combining the circRNA-miRNA and miRNA-mRNA pairs, we constructed a circRNA-miRNA-mRNA regulatory network, which was visualised using Cytoscape (version 3.9.1).

Functional and pathway enrichment analysis

To assess functional enrichment, Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed on DEmRNAs using the R package (corrected P-value < 0.05, show category = 5)[23].

Screening circRNA predictors in UC models

The least absolute shrinkage and selection operator (LASSO) algorithm was used to screen statistically significant model features for the subsequent establishment of a risk model for diagnosing UC. LASSO was used the glmnet/R package to screen circRNAs with the optimal predictive features being observed in the circRNA-miRNA-mRNA. Such circRNAs, as the initial part of the ceRNA network, had features with nonzero coefficients in the LASSO regression model[24].

Model establishment and validation

The nomogram was used to establish a model for the expression level of circRNAs and the risk of ulcerative colitis, and the corresponding value on each variable axis was determined according to the expression level of the feature. A vertical line can be formed to intersect the upper ruler at each point on the feature, where the intersection represents the score. The total score was calculated by adding the feature scores. The total score is found on the lower scale and by making a vertical line down that intersects with the risk of ulcerative colitis. Finally, the degree of correlation between circRNAs and the prevalence of ulcerative colitis were determined[25]. To evaluate the performance of the model, this study used the C-index, area under the receiver operating characteristic (ROC) curve, and decision curve analysis (DCA) to verify the diagnostic efficacy of the model. DCA is a decision curve analysis performed by quantifying the net benefit at different threshold probabilities to determine the clinical usefulness of a nomogram. The analytical model can predict the correlation between circRNA and UC and obtain the net benefit at each threshold probability, with P < 0.05 considered statistically significant[26].

RESULTS

Identification of DEcircRNAs, DEmiRNAs, and DEmRNAs

A flowchart illustrating the selection process is shown in Figure 1. The GSE131911 dataset identified 120 DEcircRNAs (38 upregulated and 82 downregulated). Similarly, 19 DEmiRNAs (8 upregulated and 11 downregulated) and 910 DEmRNAs (575 upregulated and 336 downregulated) were identified in GSE43009 and GSE87466, respectively. Subsequently, a heatmap and volcano plot of DEcircRNAs (Figure 2A), DEmiRNAs, and DEmRNAs (Figure 2B and C) were constructed.

Table 1 Gene Expression Omnibus basic information on three groups of microarray data

Data number	Platform	Ref.	Year	Region	Sample content (UC/control)	Type of RNA studied
GSE131911	GPL21825	Hu *et al*[17]	2021	China	4/4	circRNA
GSE43009	GPL16384	Li *et al*[18]	2018	United States	5/5	miRNA
GSE87466	GPL13158	Yang *et al*[19]	2019	China	87/21	mRNA

UC: Ulcerative colitis.

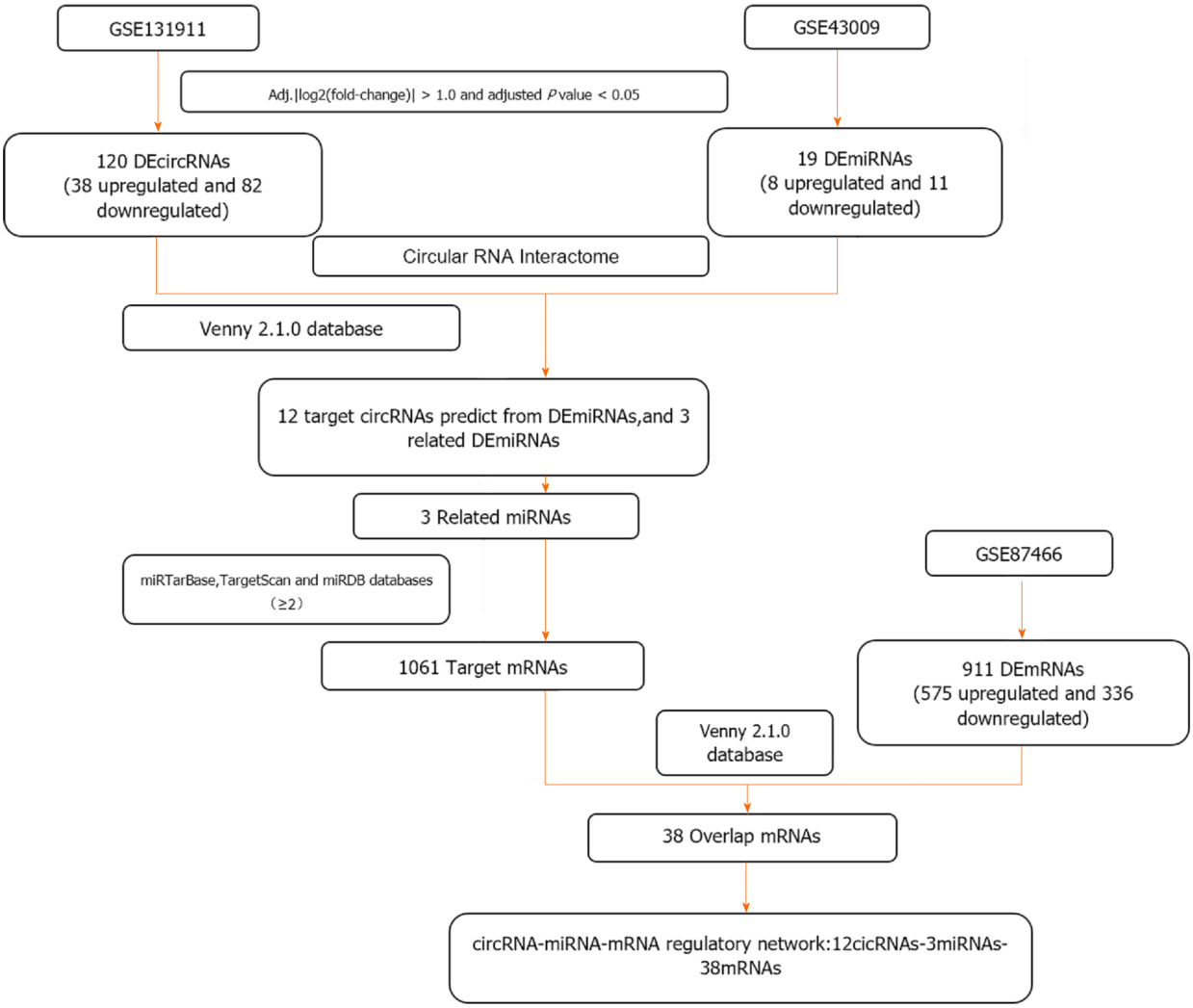


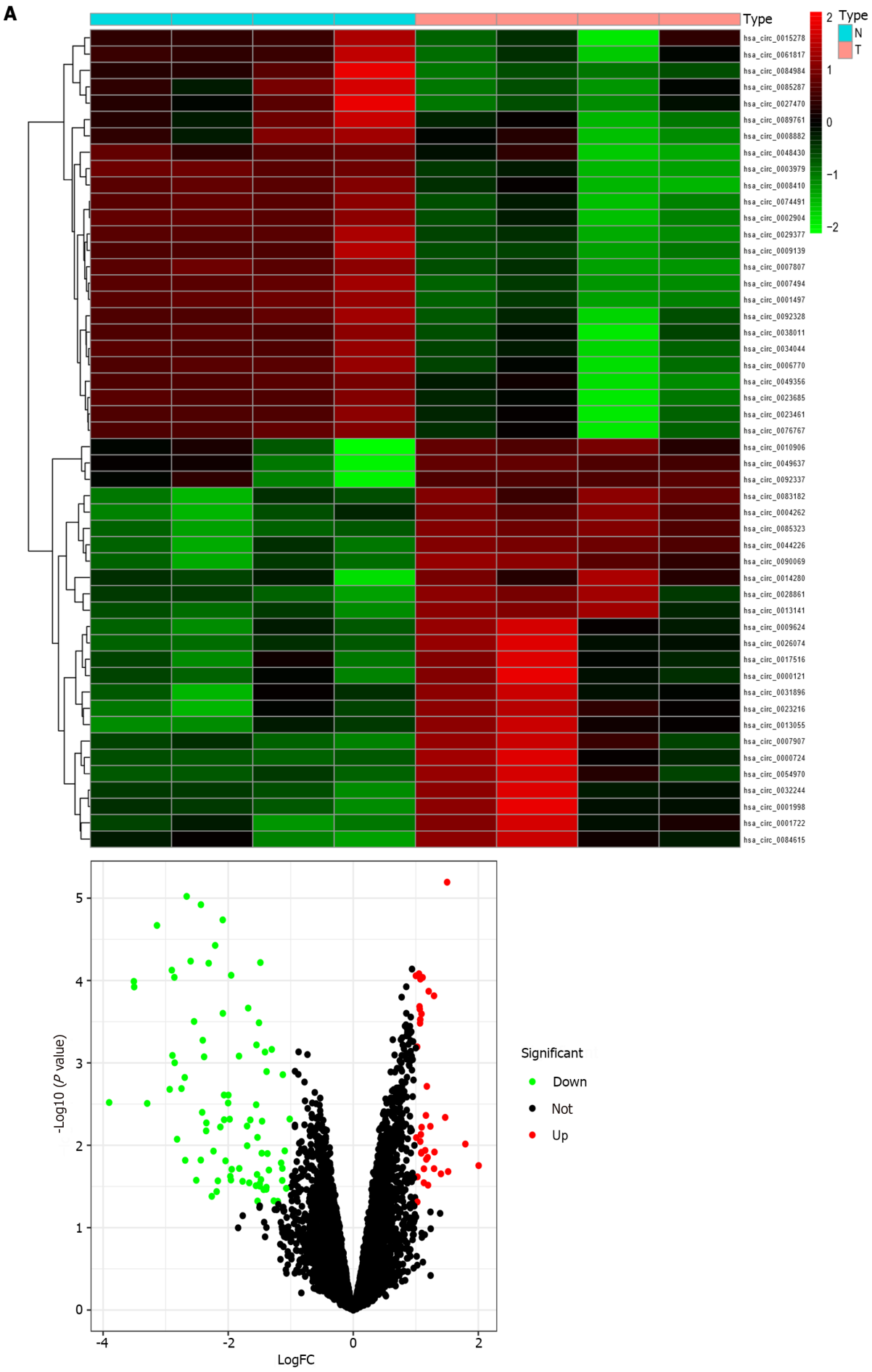
Figure 1 Flow chart screening process of the circRNA-miRNA-mRNA regulatory network.

Constitution of the circRNA-miRNA-mRNA network

First, the target miRNAs predicted by DEcircRNAs and DEmiRNAs were intersected, after which 12 circRNAs and 3 miRNAs were identified. Second, we predicted target mRNAs from three miRNA databases (≥ 2) and considered their intersection with DEmRNAs. Finally, by integrating potential target mRNAs, related miRNAs, and related circRNAs, 12 overlapping circRNAs (hsa_circ_0023461, hsa_circ_0005044, hsa_circ_0007333, hsa_circ_0033572, hsa_circ_0089761, hsa_circ_0036906, hsa_circ_0089762, hsa_circ_0089763, hsa_circ_0012673, hsa_circ_0006770, hsa_circ_0085323, and hsa_circ_0072665), 3 miRNAs, and 38 target mRNAs were allowed to enter the circRNA-miRNA-mRNA network for further study (Figure 3).

GO and KEGG functional enrichment analyses

GO (Figure 4A) and KEGG (Figure 4B) enrichment analyses were performed on the 38 DEmRNAs derived from the previous process. Biological process (BP) analysis revealed that DEmRNAs were predominantly enriched in cellular divalent inorganic cation homeostasis (GO:0072503) and divalent inorganic cation homeostasis (GO:0072507). To the best of our knowledge, the present study is the first to suggest that the occurrence of colitis may be related to homeostasis of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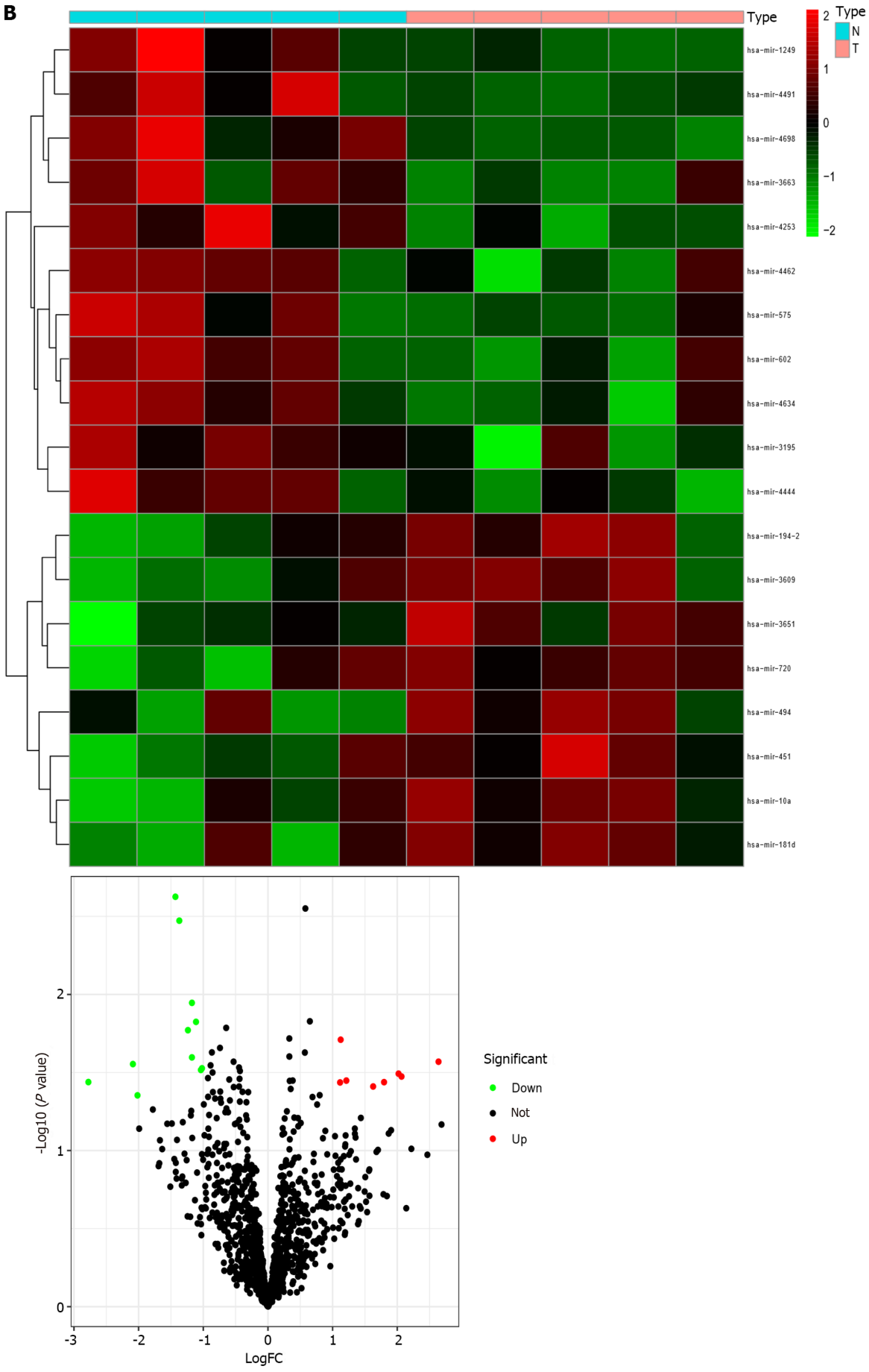
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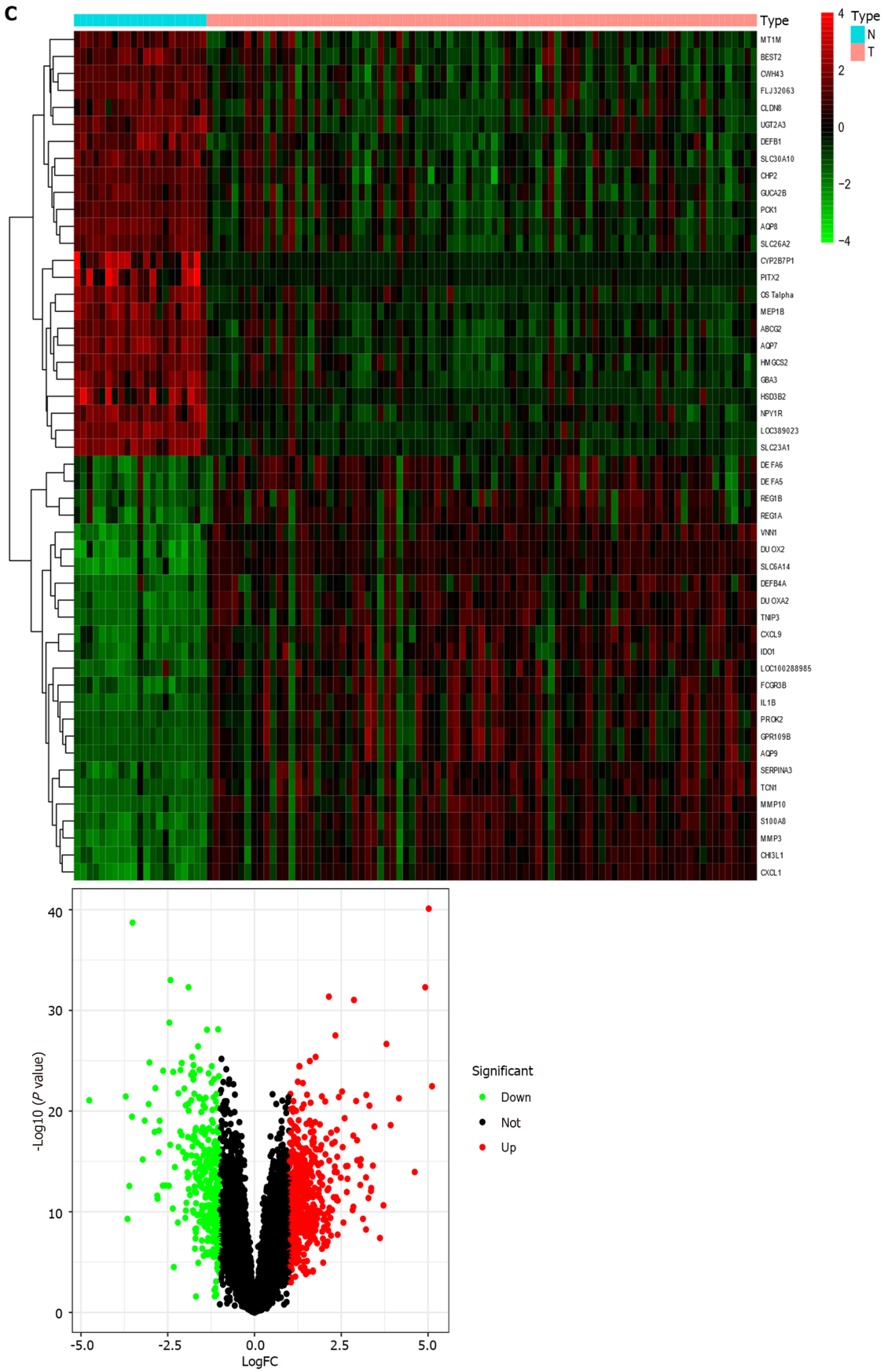


Figure 2 Heatmap and volcano plots. A: Differentially expressed circRNAs; B: Differentially expressed miRNAs; C: Differentially expressed mRNAs.

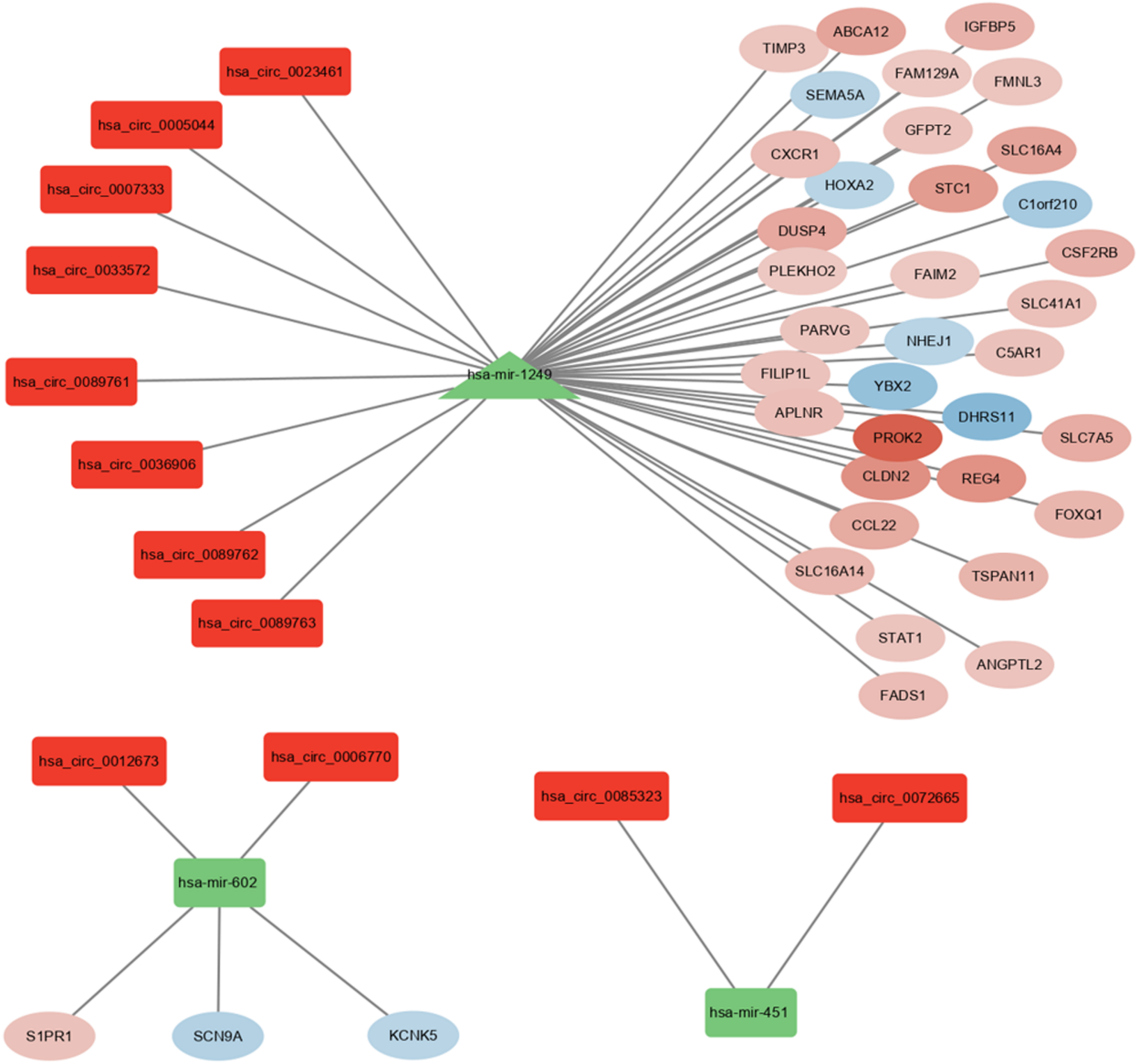


Figure 3 circRNA-miRNA-mRNA network in ulcerative colitis. The red rectangle represents circRNAs, the green triangle represents miRNAs, and the ellipses whose colours change continuously according to the LogFC value represent mRNAs. Red and green mean upregulated and downregulated expression, respectively.

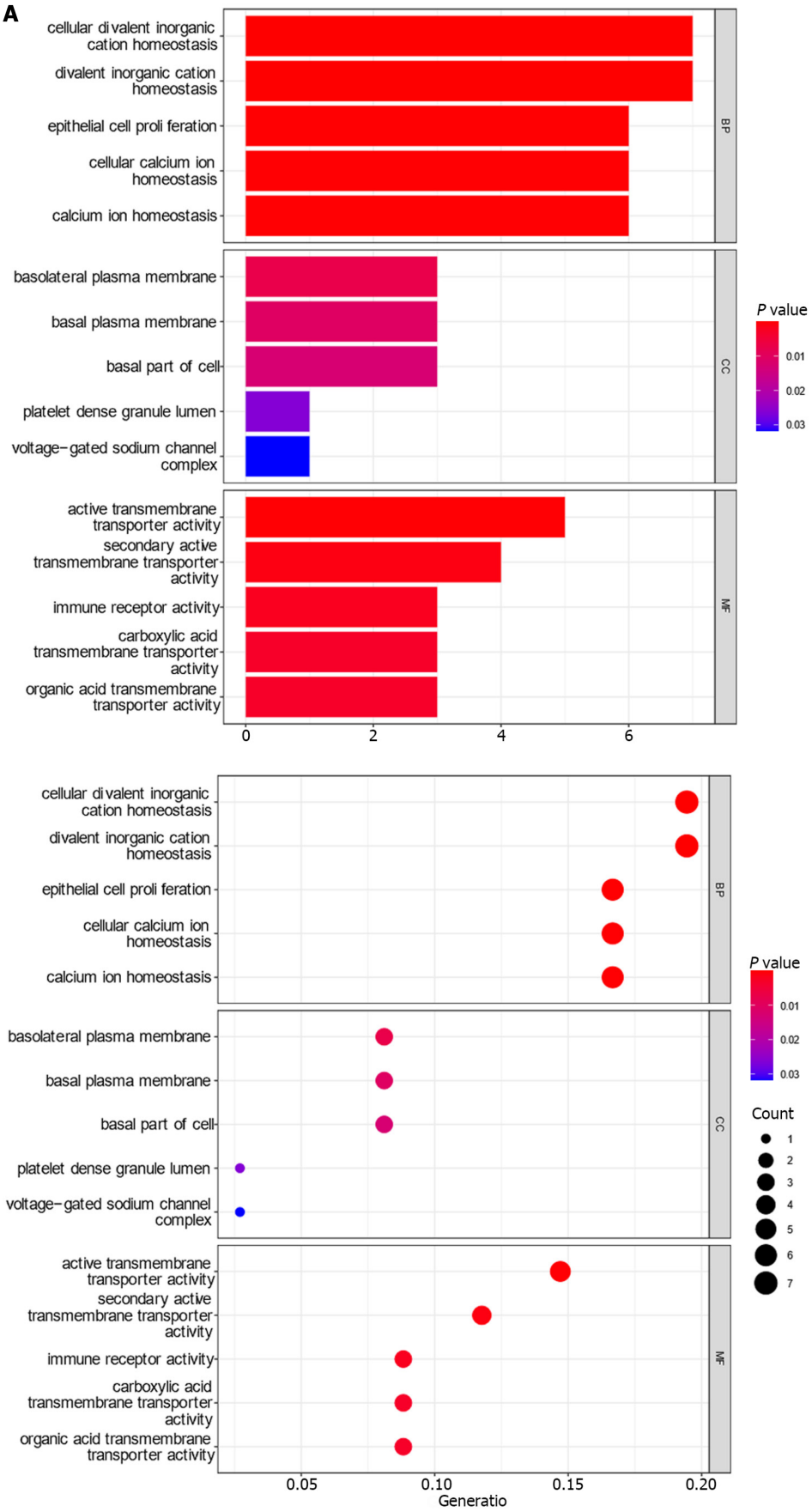
divalent inorganic cations. When considering cellular component (CC), basolateral plasma membrane (GO:0016323), basal plasma membrane (GO:0009925), and basal part of the cell (GO:0045178) were the top three enriched terms. Imbalances in epithelium-matrix interactions have been discussed as a pathomechanism in UC, resulting in dysfunction of the mucous barrier of the colon[27]. Active transmembrane transporter activity (GO:0022804) and secondary active transmembrane transporter activity (GO:0015291) are related to molecular function. Transporters can influence the disposition of chemicals within the intestine by participating in their absorption, distribution, and elimination[28]. KEGG pathway analysis showed that the mRNAs were also considerably concentrated in the T-cell receptor signalling pathway, which confirmed that UC is an autoimmune disease (hsa:04660).

LASSO dissection of circRNAs in circRNA-miRNA-mRNA networks

From the 12 differentially expressed circRNAs and 8 samples, LASSO was used to screen the circRNAs with optimal predictive features. Features with nonzero coefficients were selected in the LASSO regression model. LASSO regression selection revealed that hsa_circ_0085323 and hsa_circ_0036906 were important diagnostic circRNAs (Figures 5A and B).

Establishment and validation of a circRNA prediction model for UC

The optimal model predictors (hsa_circ_0085323 and hsa_circ_0036906) screened from the differential circRNA data in the ceRNA network were used to establish a nomogram to predict the risk of UC (Figure 6A). The Harrell C-index of the model was analysed to quantify the discriminative performance of the nomogram, and the model discrimination performance was 1. The ROC curve, which represents the measurement of the diagnostic accuracy of the predictive model, was 1 (Figure 6B). The decision curve integrates the above models, and the maximum area under the curve is the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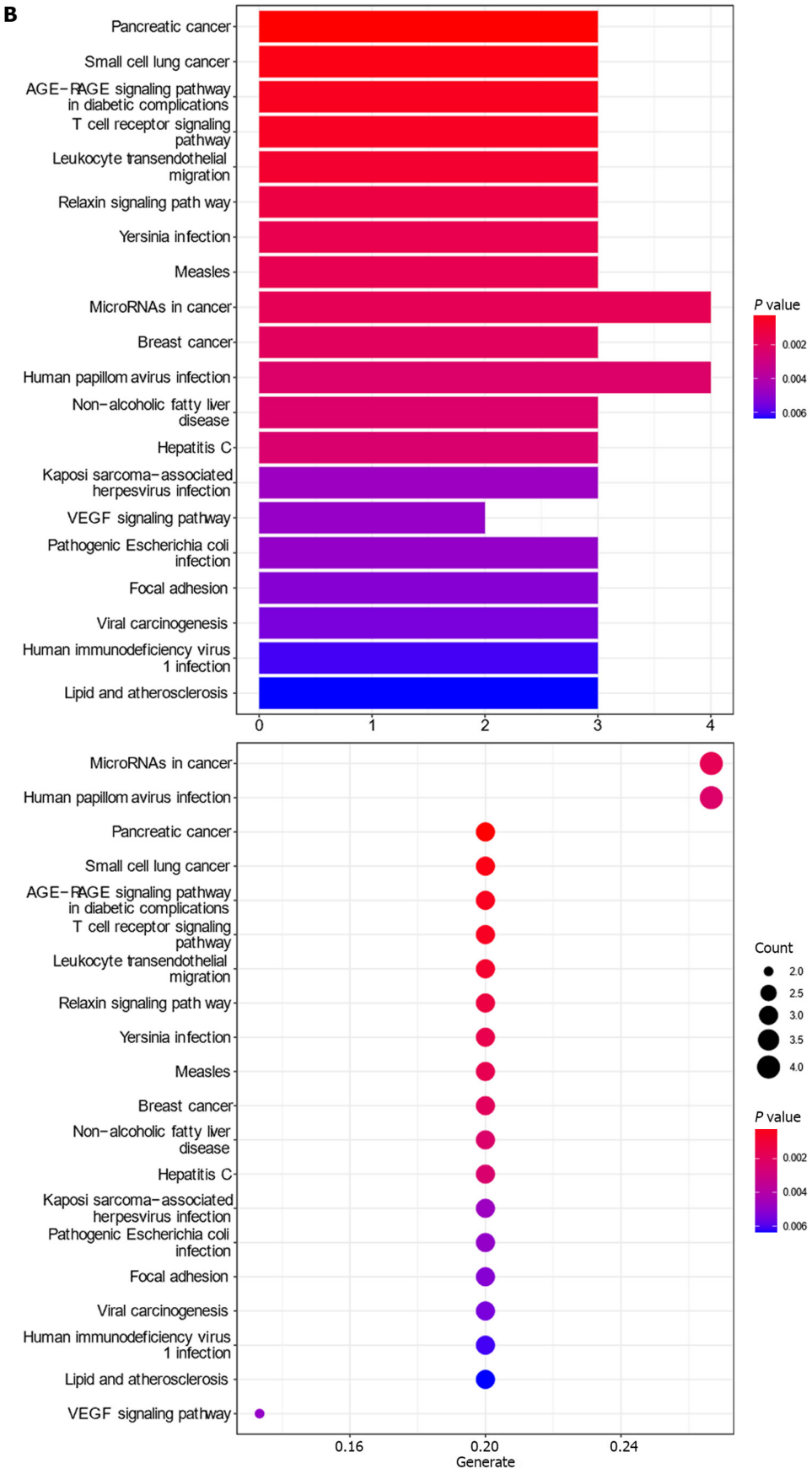

Figure 4 Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway analyses of 38 mRNAs in the network. A: The barplot and bubble plot of Gene Ontology analysis; B: The barplot and bubble plot of the Kyoto Encyclopedia of Genes and Genomes pathway.

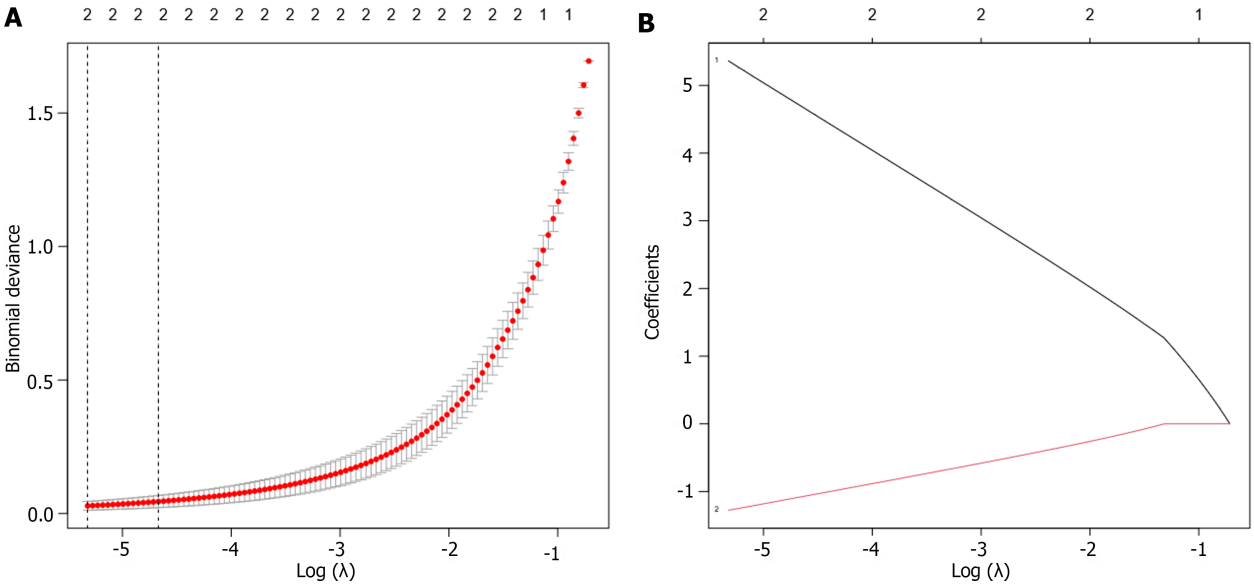

Figure 5 Model diagnostic factors screened by least absolute shrinkage and selection operator. A: The optimal parameter (λ) selection in the least absolute shrinkage and selection operator model used five-fold cross-validation *via* minimum criteria. The partial likelihood deviation (binomial deviation) curve was plotted against log(λ). A dashed vertical line was drawn at the optimal value using the smallest criterion and 1 SE of the smallest criterion (1-SE criterion); B: A coefficient distribution map was generated for log(λ), where the optimal λ was the two features with nonzero coefficients.

maximum benefit (Figure 6C). Because few models can achieve perfect prediction performance, the overfitting results presented by this verification method may be due to the small amount of relevant data. The data amount will be further expanded and related research will be conducted in the future.

DISCUSSION

UC is one of the most serious intestinal diseases and has a poor prognosis. The elevated recurrence rate and therapy resistance of ulcerative colitis after treatment have inspired researchers to explore further the molecular mechanisms and new therapeutic targets and diagnostic markers. Recent progress in circRNA research has revealed the core aspects of circRNA biogenesis and biology. In particular, circRNA is closely related to the pathogenesis of UC. CircRNAs have a relatively stable structure owing to their circular structure. Knockout or overexpression of circRNAs can regulate downstream miRNA-mRNAs. Research on the circRNA-miRNA-mRNA regulatory network has been deeply involved in various tumours, making it vital for the diagnosis, prognosis, and treatment of UC[29].

Following the development of high-throughput genome sequencing technologies and the availability of diverse open databases, computer analysis enables us to build a circRNA-miRNA-mRNA network to help us better understand the cross-talk between RNAs and elucidate the occurrence and development of UC from complex genetic interactions[30]. Numerous studies have demonstrated that circRNAs can modulate intestinal immune imbalances, such as through the autophagy pathway, and can even be used as biomarkers for the diagnosis of IBD[11].

Our study compared UC and normal intestinal mucosa with datasets retrieved from the GEO database to identify DEcircRNAs, DEmiRNAs, and DEmRNAs. CircRNA-miRNA and miRNA-mRNA interactions were subsequently predicted, and 12 circRNAs, 3 miRNAs, and 38 mRNAs were selected to construct the ceRNA network. GO and KEGG enrichment analyses of mRNA in this ceRNA network were also performed. Furthermore, this circRNA-miRNA-mRNA network enhances the precision of potential candidate biomarkers for disease diagnosis and treatment, as it narrows the scope of research.

CircRNAs are naturally occurring RNAs highly expressed in the eukaryotic transcriptome[31]. CircRNAs can target miRNAs with high intensity, reducing their ability to target mRNAs, and are thus optimal biomarkers for UC. We identified two circRNAs (hsa_circ_0085323 and hsa_circ_0036906) using LASSO regression analysis. In addition, we constructed and internally validated a new model to calculate UC risk based on hsa_circ_0085323 and hsa_circ_0036906. Our model used the nomogram because it has been used extensively as a prognostic tool in oncology and medicine[32]. To our knowledge, our study is the first to apply a nomogram to UC. In addition, molecular and subsequent molecular mechanisms were identified in this study, which is an innovative combination.

We performed correlation analyses between the two predicted circRNAs and downstream miRNAs in the ceRNA network. Interestingly, studies have found that hsa-miR-451 is downregulated in colorectal cancer (CRC), which can play a tumour suppressor role by targeting the macrophage migration inhibitory factor and can also inhibit the growth of CRC cells by downregulating the PI3K/AKT pathway[33,34]. Differential analysis showed that hsa_circ_0085323 was upregulated in UC, upstream of hsa-miR-451, confirming that hsa_circ_0085323 increased the risk of UC if it scored higher in the nomogram. Although there are few studies on hsa_circ_0085323, additional studies on hsa-miR-451 can

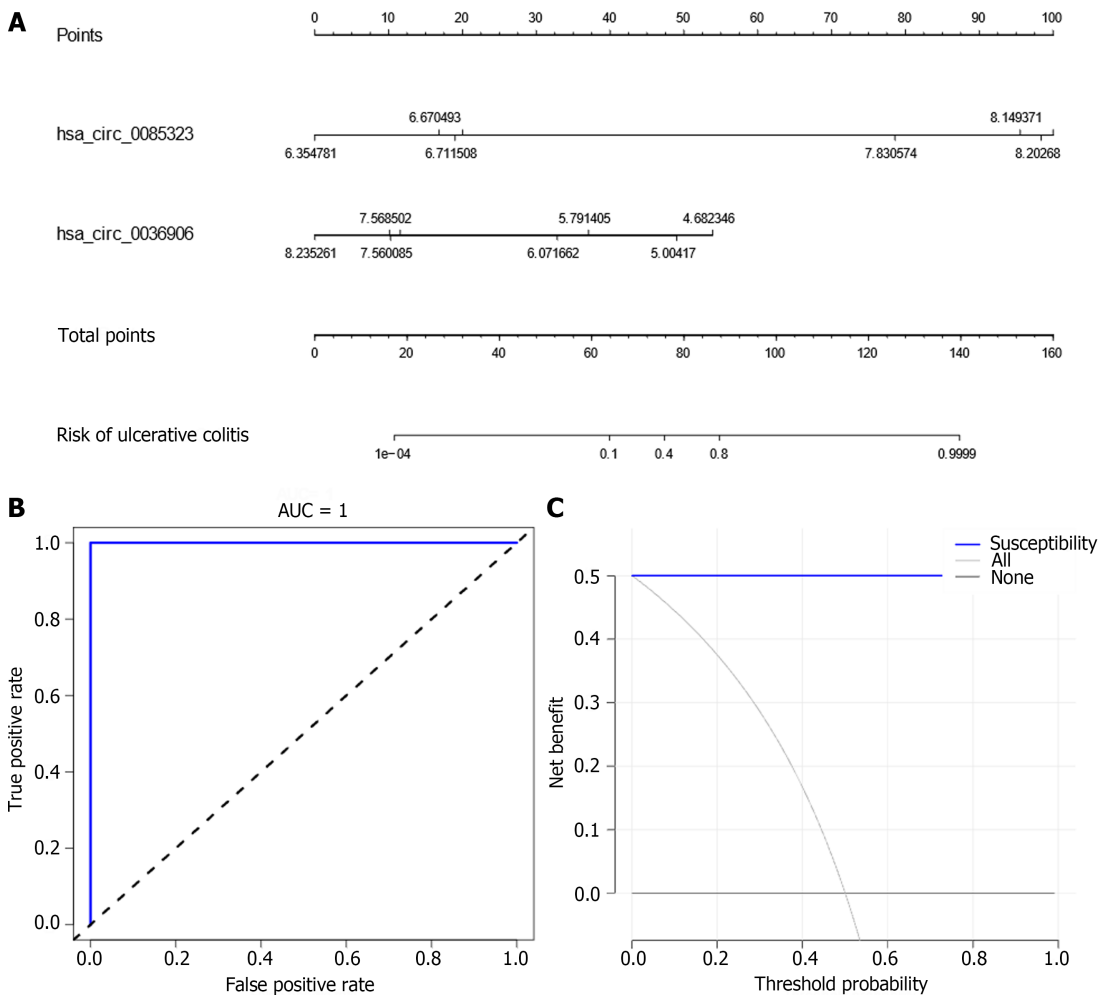

Figure 6 Model establishment and efficacy verification. A: Nomogram model constructed using hsa_circ_0085323 and hsa_circ_0036906; B: Model validation receiver operating characteristic curve; C: decision curve analysis curve for model efficacy test.

provide important evidence. Similarly, miR-1249 can directly target heterogeneous nuclear ribonucleoprotein K to accelerate the malignant phenotype of hepatocellular carcinoma[35]. Prokineticin 2 (PROK2) is an inflammatory cytokine-like molecule mainly expressed by macrophages and neutrophils infiltrating tissue injury sites and is upregulated in biopsy samples from patients with UC[36]. PROK2 is a target gene in the ceRNA network of UC, upstream of which is miR-1249. P53-induced miR-1249 may suppress CRC growth, metastasis, and angiogenesis by targeting vascular endothelial growth factor and high mobility group A2 HMGA2[37]. Hsa_circ_0036906 can act as a sponge for hsa-miR-1249, but the mechanism underlying its regulation of hsa-miR-1249 has not yet been investigated. In the prediction model, the lower the expression of hsa_circ_0036906, the higher the score on the nomogram, which is inconsistent with the circRNA-miRNA-mRNA regulatory network. The specific mechanisms of action of hsa_circ_0036906 and hsa-miR-1249 require further experimental verification. Furthermore, recent studies have explored ceRNA networks in UC, revealing certain distinctions from our own research. For instance, Xu *et al*[38] performed a comprehensive analysis that revealed four central genes regulated by NF-κB, ultimately constructing an lncRNA-miRNA-transcription factor (NF-κB) interaction network. Another study aimed to demonstrate the high diagnostic accuracy of two mRNAs (CTLA4 and STAT1) within the ceRNA network in UC[39]. In contrast, we focused on circRNA as a potential clinical diagnostic marker, deviating from conventional approaches, with circRNA possibly offering improved specificity. Over the past two years, only one article has analysed three mRNAs (FGG, KRT10, and TLR4), six miRNAs (hsa-miR-6875-5p, hsa-miR-1908-5p, hsa-miR-186-5p, hsa-miR-4436a, hsa-miR-520a-5p, and hsa-miR-6763-5p), two lncRNAs (XIST and NEAT1), and two chromosomal regions (NM_001039703 and NM_006267) that produce the most effective circRNAs, participating in the non-coding RNA-associated ceRNA network related to IBD. These elements may serve as potential therapeutic targets. Further research into ceRNA networks in IBD is essential for future investigations[40].

In summary, we successfully constructed a gut mucosa-derived ceRNA regulatory network associated with circRNAs and provided insights into the interactions between various RNA transcripts in UC. We established a promising nomogram model for UC disease risk diagnosis based on circRNA characteristic parameters, indicating biomarkers and subsequent molecular mechanisms. This model and ceRNA network can help predict disease occurrence and treatment.

Our study had certain limitations: (1) The sample size for the dataset obtained from the available public database was too small because the human sample sequencing data related to UC are few, thereby limiting the construction of the ceRNA network only from these three datasets; (2) The clinical sample data were too small, and predicting the risk of all

Chinese UC patients was impossible. The prevalence of UC tends to be individualised. We searched the GEO data set again, looking for a similar data set for sample merging and de-batching. However, we only managed to find the same GSE142106. However, this data set is a mouse sample and did not match the type of sample we had studied before; therefore, we ended up having to use that unique data set. We hope to test our hypothesis by expanding human samples in clinical trials in the future; (3) Risk factor analysis did not include all potential factors affecting changes in circRNA expression; (4) Although the robustness of our nomograms was extensively checked by internal validation using bootstrapping tests, no external validation was performed. Experimental techniques, such as qPCR, should be used to detect circRNA expression to validate the accuracy of our model. At a deeper level, we also look forward to the results of experimental validation in clinical samples. We wish to validate the results of this paper; however, adverse effects may be inevitable. Under the premise that there is no logical problem, both negative and positive results are worth thinking about; and (5) We found that hsa_circ_0085323 and hsa_circ_0036906 have no corresponding homologous genes in mice and rats[41]. Therefore, the next step of qPCR validation must be achieved in humans. As a result of temporal limitations and various additional considerations, the incorporation of ethical authorization, along with adherence to the Helsinki Declaration and acquisition of patient consent, has yet to be actualized and will be duly acknowledged in a forthcoming publication. After passing ethics, we made every effort to collect blood samples from patients with UC for experimental validation.

CONCLUSION

This study for the first time presents the potential role of the circRNA-miRNA-mRNA regulatory network in UC in a relatively intuitive way and provides a novel idea for constructing predictive nomograms from DEcircRNAs in the ceRNA network. Diagnostic nomograms based on DEcircRNA signatures may provide a more intuitive method for UC disease risk prediction and facilitate more optimized treatment strategies.

ARTICLE HIGHLIGHTS

Research background

Ulcerative colitis (UC) is an inflammatory bowel disease that affects the mucosal and submucosal layers of the colon and rectum. With advancements in the diagnosis and treatment of UC, the prospect of rapidly increasing the number of drugs with new targets is anticipated. However, despite progress in the biological understanding, information regarding the pathogenesis of UC remains limited. Therefore, exploring the molecular mechanisms of UC is of paramount importance for formulating appropriate therapeutic strategies and diagnosing the disease.

Research motivation

The primary focus of the research is to construct a competing endogenous RNA (ceRNA) network in UC and elucidate the mechanistic role of this network in the pathogenesis of UC. Additionally, using circular RNA (circRNA) as characteristic parameters, a diagnostic model for UC has been developed. Future endeavors involve expanding clinical UC sample data, applying the research methodology and approach outlined in this study, and conducting experimental validation. The goal is to further identify a more comprehensive ceRNA network and circRNAs with enhanced clinical diagnostic value.

Research objectives

The primary objective of this study is to construct a ceRNA network in UC and identify circRNAs serving as diagnostic biomarkers for UC. Ultimately, we successfully built a circRNA-miRNA-mRNA network in UC, identifying two circRNAs with clinical diagnostic value. Further exploration in this direction is anticipated to contribute to the innovation of diagnostic biomarkers for UC and provide additional insights into the crucial significance of non-coding RNA networks in UC.

Research methods

Three GSE datasets related to UC were obtained from the Gene Expression Omnibus database. Difference analysis was performed on the three GSE data sets, and differences in circRNA, miRNA and mRNA were identified. Difference analysis was performed on the three GSE data sets, and differences in circRNA, miRNA and mRNA were identified. A circRNA-miRNA-mRNA regulatory network was constructed, and Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analyses were performed on the differential mRNAs. A circRNA-miRNA-mRNA regulatory network was constructed, and GO and KEGG analyses were performed on the differential mRNAs. circRNA predictors in UC models were screened and a model was established and validated.

Research results

We have successfully constructed a ceRNA regulatory network originating from intestinal mucosa associated with circRNAs, providing insights into the interactions among various RNA transcripts in UC. Utilizing circRNA characteristic parameters, we developed a promising nomogram model for UC disease risk diagnosis, highlighting the involvement of

biomarkers and subsequent molecular mechanisms. This model and the ceRNA network can aid in predicting the onset and treatment of the disease. Further experimental verification in clinical UC samples is needed in the future.

Research conclusions

This study introduces the theoretical framework of circRNA as a diagnostic biomarker for clinical identification of UC. The novel approach proposed involves the circRNA-miRNA-mRNA network as a mechanistic pathway for subsequent therapeutic interventions in UC.

Research perspectives

The future research direction will focus on observing the significance of circRNAs as diagnostic biomarkers for UC within a clinical context.

FOOTNOTES

Co-first authors: Yu-Yi Yuan, Hui Wu and Qian-Yun Chen.

Co-corresponding authors: Heng Fan and Bo Shuai.

Author contributions: Yuan YY, Fan H and Shuai B designed the research study; Yuan YY, Wu H and Chen QY performed the research; Fan H and Shuai B contributed new reagents and analytic tools; Yuan YY, Wu H and Chen QY analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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Country/Territory of origin: China

ORCID number: Heng Fan 0000-0002-1100-0757; Bo Shuai 0000-0002-9298-8129.

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ORIGINAL ARTICLE

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Exploring the autophagy-related pathogenesis of active ulcerative colitis

Zhuo-Zhi Gong, Teng Li, He Yan, Min-Hao Xu, Yue Lian, Yi-Xuan Yang, Wei Wei, Tao Liu

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Zhuo-Zhi Gong, Teng Li, He Yan, Yue Lian, Wei Wei, Tao Liu, Wangjing Hospital, China Academy of Chinese Medical Sciences, Beijing 100102, China

Min-Hao Xu, College of Traditional Chinese Medicine, School of Traditional Chinese Medicine, Beijing 100102, China

Yi-Xuan Yang, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China

Corresponding author: Tao Liu, PhD, Associate Professor, Chief Doctor, Wangjing Hospital, China Academy of Chinese Medical Sciences, Huajiadi Street, Chaoyang District, Beijing 100102, China. ltlyf2@163.com

Abstract

BACKGROUND

The pathogenesis of ulcerative colitis (UC) is complex, and recent therapeutic advances remain unable to fully alleviate the condition.

AIM

To inform the development of novel UC treatments, bioinformatics was used to explore the autophagy-related pathogenesis associated with the active phase of UC.

METHODS

The GEO database was searched for UC-related datasets that included healthy controls who met the screening criteria. Differential analysis was conducted to obtain differentially expressed genes (DEGs). Au-tophagy-related targets were collected and intersected with the DEGs to identiy differentially expressed au-tophagy-related genes (DEARGs) associated with active UC. DEARGs were then subjected to KEGG, GO, and DisGeNET disease enrichment analyses using R software. Differential analysis of immune infiltrating cells was performed using the CiberSort algorithm. The least absolute shrinkage and selection operator algorithm and protein-protein interaction network were used to narrow down the DEARGs, and the top five targets in the Dgree ranking were designated as core targets.

RESULTS

A total of 4822 DEGs were obtained, of which 58 were classified as DEARGs.

SERPINA1, BAG3, HSPA5, CASP1, and CX3CL1 were identified as core targets. GO enrichment analysis revealed that DEARGs were primarily enriched in processes related to autophagy regulation and macroautophagy. KEGG enrichment analysis showed that DEARGs were predominantly associated with NOD-like receptor signaling and other signaling pathways. Disease enrichment analysis indicated that DEARGs were significantly linked to diseases such as malignant glioma and middle cerebral artery occlusion. Immune infiltration analysis demonstrated a higher presence of immune cells like activated memory CD4 T cells and follicular helper T cells in active UC patients than in healthy controls.

CONCLUSION

Autophagy is closely related to the active phase of UC and the potential targets obtained from the analysis in this study may provide new insight into the treatment of active UC patients.

Key Words: Ulcerative colitis; Autophagy; Bioinformatic; Targets; Pathogenesis

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Core Tip: This study used bioinformatics to explore the autophagy-related pathogenesis of ulcerative colitis (UC) during its active phase. A total of 58 differentially expressed autophagy-related genes (DEARGs) were found in gene expression datasets from UC patients and healthy controls. Of these, SERPINA1, BAG3, HSPA5, CASP1, and CX3CL1 were identified as core targets. Enrichment analysis highlighted the involvement of DEARGs in autophagy regulation, and macroautophagy, in addition to NOD-like receptor signaling and other pathways. These DEARGs were also shown to be associated with diseases like malignant glioma and middle cerebral artery occlusion. Immune infiltration analysis revealed an increased presence of immune cells, including activated memory CD4 T cells and follicular helper T cells in active UC pa-tients than in healthy controls. This study suggests that autophagy plays a significant role in the active phase of UC and identifies potential targets for novel UC treatments.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic, recurrent inflammatory disease in humans that profoundly affects normal functioning [1]. It has both active and remission phases that are classified according to disease severity. UC is characterized by symptoms such as weight loss, diarrhea, rectal bleeding, abdominal pain, and inflammation of the mucous membranes that extend from the rectum to the distal part of the colon[2]. Approximately 5 million people are affected by UC worldwide and recent studies indicate that the incidence is increasing[3]. UC is thought to result from a combination of genetic and environmental factors and is closely linked to compromised intestinal epithelial barriers, a dysregulated microbiome, and impaired immune responses[3].

Autophagy is a finely coordinated process that segregates misfolded proteins, damaged or aged organelles, and mutated proteins into double-membrane vesicles called autophagosomes. The autophagosomes later merge with lysosomes and degrade these components[4]. Three main forms of autophagy have been described to date: microautophagy, chaperone-mediated autophagy, and macroautophagy[5]. Autophagy is shown to be a key mediator in the pathophysiological processes of UC. From a physiological perspective, autophagy plays a critical role in maintaining intestinal balance, regulating interactions between gut microbiota and both the innate and adaptive immune systems, and protecting the host against intestinal pathogens[5]. Autophagy also reduces endoplasmic reticulum stress associated with diverse inflammatory and immune disorders[6], helping to restore gut homeostasis. For example, estrogen-related receptor alpha (ESRRa) contributes to maintaining intestinal balance by activating autophagy and regulating the gut microbiome, thereby protecting the host from inflammation and mitochondrial dysfunction[7]. Meanwhile, autotaxin (ATX) inhibits autophagy through the mTOR pathway, causing significant damage to the intestinal epithelial barrier of colitis patients[8]. During intestinal inflammation, specific bacterial species in the microbiome, including adherent invasive *Escherichia coli*, can adhere to intestinal epithelial cells and evade autophagic elimination by phagocytic macrophages[9]. The situational or excessive induction of autophagy can adversely impact cells by initiating autophagic cell death. The lack of erbin, a protein essential for epithelial cell polarity, markedly worsens the initiation of autophagic processes and autophagic cell death in mice with DSS-induced colitis[10]. Damage to intestinal epithelial cells initiates inflammation and intensifies the severity of UC symptoms[11].

Given the importance of autophagy in preserving intestinal balance and the role of autophagy dysfunction in UC development, identifying autophagy-related disease predictors is essential for the design of new UC treatments. The current study uses bioinformatics to define gene expression patterns associated with the autophagy-related pathogenesis

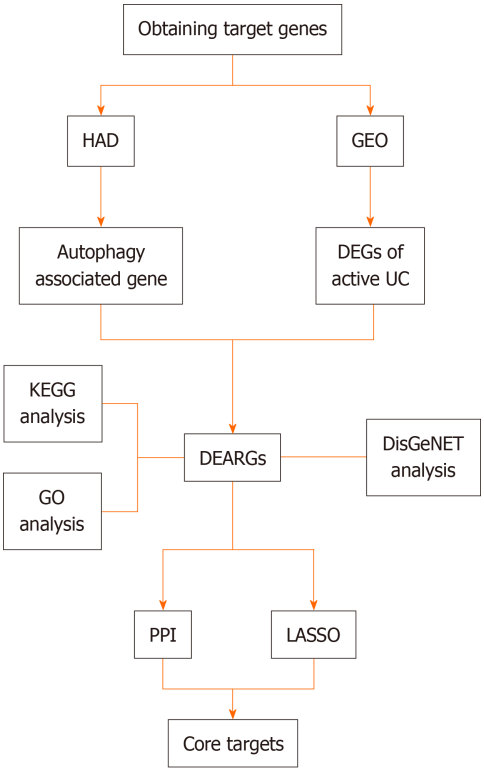

Figure 1 Study flow chart. HAD: Human Autophagy Database; GEO: Gene Expression Omnibus database; UC: Ulcerative colitis; DEGs: Differentially expressed genes; DEARGs: Differentially expressed autophagy-related genes; KEGG: Kyoto Encyclopedia of Genes and Genomes; GO: Gene Ontology; PPI: Protein-Protein Interaction; LASSO: Least absolute shrinkage and selection operator.

of active UC (Figure 1).

MATERIALS AND METHODS

Identification of active UC targets and difference analysis

Datasets related to active UC which included normal control and active UC samples and had a sample size > 30 were obtained from the GEO database (https://www.ncbi.nlm.nih.gov/gds/). The selected data set was normalized and the "limma" package was downloaded using "Bioconductor." R 4.3.1 software was then used to perform differential gene analysis on targets identified in the dataset. A $|\log FC| \geq 0.585$ and an adj. $P < 0.05$ were used to obtain differentially expressed genes (DEGs).

Acquisition of differentially expressed autophagy-related genes in patients with active UC

To obtain differentially expressed autophagy-related genes (DEARGs), autophagy-related genes were downloaded from the Human Autophagy Database (http://www.autophagy.lu/). Using the "Venn Diagram" package in R, autophagy-related targets were intersected with the DEGs, identifying DEARGs as the central targets for further analysis. DEARG heat maps were generated using the "limma" and "pheatmap" packages.

Analysis of immune cell infiltration

The immune microenvironment is typically composed of immune cells, inflammatory cells, fibroblasts, and mesenchymal stem cells, along with various cytokines and chemokines. Assessing immune cell infiltration is vital for predicting disease progression and treatment response. Several methods exist to analyze immune cell infiltration, including CiberSort, an inverse convolution algorithm developed by BinderG. This method calculates the cellular composition of complex tissues based on normalized gene expression data, allowing specific cell types to be quantified. The CiberSort deconvolution algorithm was used with 100 simulations and subsequent analyses were conducted with a significance threshold of $P < 0.05$ to determine the proportion of immune cells in different samples. The results were visualized using the "ggpubr" package in R.

Assessment of biological variables associated with the DEARGs

Gene ontology (GO) analysis categorizes genes into biological processes (BP), molecular functions (MF), and cellular components (CC), which help to inform their biological functions. The Kyoto Encyclopedia of Genes and Genomes (KEGG) is a database that integrates genomic, chemical, and systemic information. It is often used for the functional

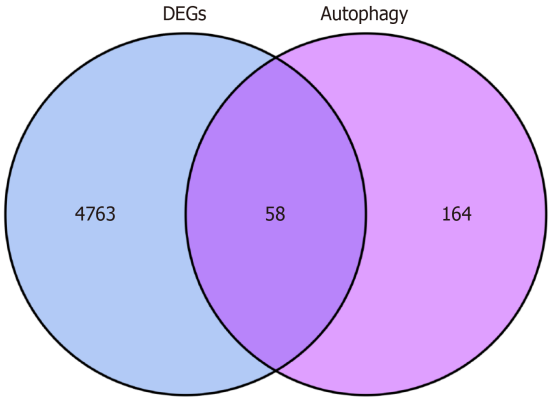

Figure 2 Intersection of autophagy-related targets and differentially expressed genes. There are 4821 differentially expressed genes and 232 autophagy-related targets. A total of 58 differentially expressed autophagy-related genes intersected. DEGs: Differentially expressed genes.

annotation of genes to understand their associated activities and pathways of action. To further understand the target functions of autophagy in patients with active UC and the associated signaling pathways, the "clusterProfiler" package was downloaded from Bioconductor, and GO and KEGG enrichment analysis of the DEARGs was conducted using R. The "clusterProfiler" package was downloaded from "Bioconductor" and the DEARGs were analyzed by GO and KEGG enrichment analysis using R with a threshold value of $P < 0.05$.

Analysis of disease enrichment in DisGeNET

To explore the role of autophagy in UC-related diseases, DEARGs were input into the Metascape platform (https://metascape.org/) using "*H. sapiens*" as the species setting for both "Input" and "Analysis." The "Summary of enrichment analysis in DisGeNET" was then exported.

Construction of the least absolute shrinkage and selection operator al-gorithm and protein-protein interaction network

For more precise identification of the core targets, the least absolute shrinkage and selection operator (LASSO) algorithm was used along with the construction of a protein-protein interaction (PPI) network to refine DEARG selection and predict key biomarkers. The LASSO algorithm is more effective than ordinary least squares estimation at extracting essential variables and simplifying the model, particularly when using multiple variables. PPI analysis helps identify inter-actions among DEARGs and refine the selection.

The LASSO algorithm was used for DEARG validation and feature gene selection using the "glmnet" package in R. The identified genes were then uploaded to the String database (https://cn.string-db.org/) with a "minimum required interaction score" of 0.15 and the results were imported into Cytoscape 3.9.1. To further refine the selection, the "Cyto-NCA" plugin was used to rank the targets based on degree values, selecting the top five as core targets.

RESULTS

Acquisition of DEGs

GEO database screening identified two UC-related datasets: GSE87466 and GSE53306. GSE53306 includes data on differential gene expression between the active and quiescent stages of UC, providing insight into the disease characteristics. The dataset, which has information on 40 individuals, including 16 active UC cases and 12 normal controls, was published on December 13, 2014, and last updated on December 22, 2017. GSE87466 includes data on gene expression in mucosal biopsies from adult patients with moderate to severe active UC. The dataset has information on 87 UC active samples and 21 normal control samples and was first published on September 29, 2016, and last updated on March 2, 2019. The datasets were downloaded and exported, the data were de-duplicated and normalized, and differential analysis was conducted with R software using GSE87466 and GSE53306 as the base and supplemental datasets, respectively. GPL13158 and GPL14951 were used as the platform files. This analysis yielded 4,822 DEGs from the GSE87466 and GSE53306 datasets.

DEARG acquisition

A total of 232 autophagy-related genes were obtained from the Human Autophagy Database (http://www.autophagy.lu/). These autophagy-related genes were intersected with the DEGs, resulting in 58 DEARGs (Figure 2). R was then used to analyze the DEARGs and generate heat map and volcano map (Figure 3).

Analysis of immune cell infiltration

The Cibersort algorithm was used to evaluate immune cell infiltration in two distinct immune states. The following immune cell types were more abundant in active UC cases than in healthy controls: activated memory CD4 T cells, fo-

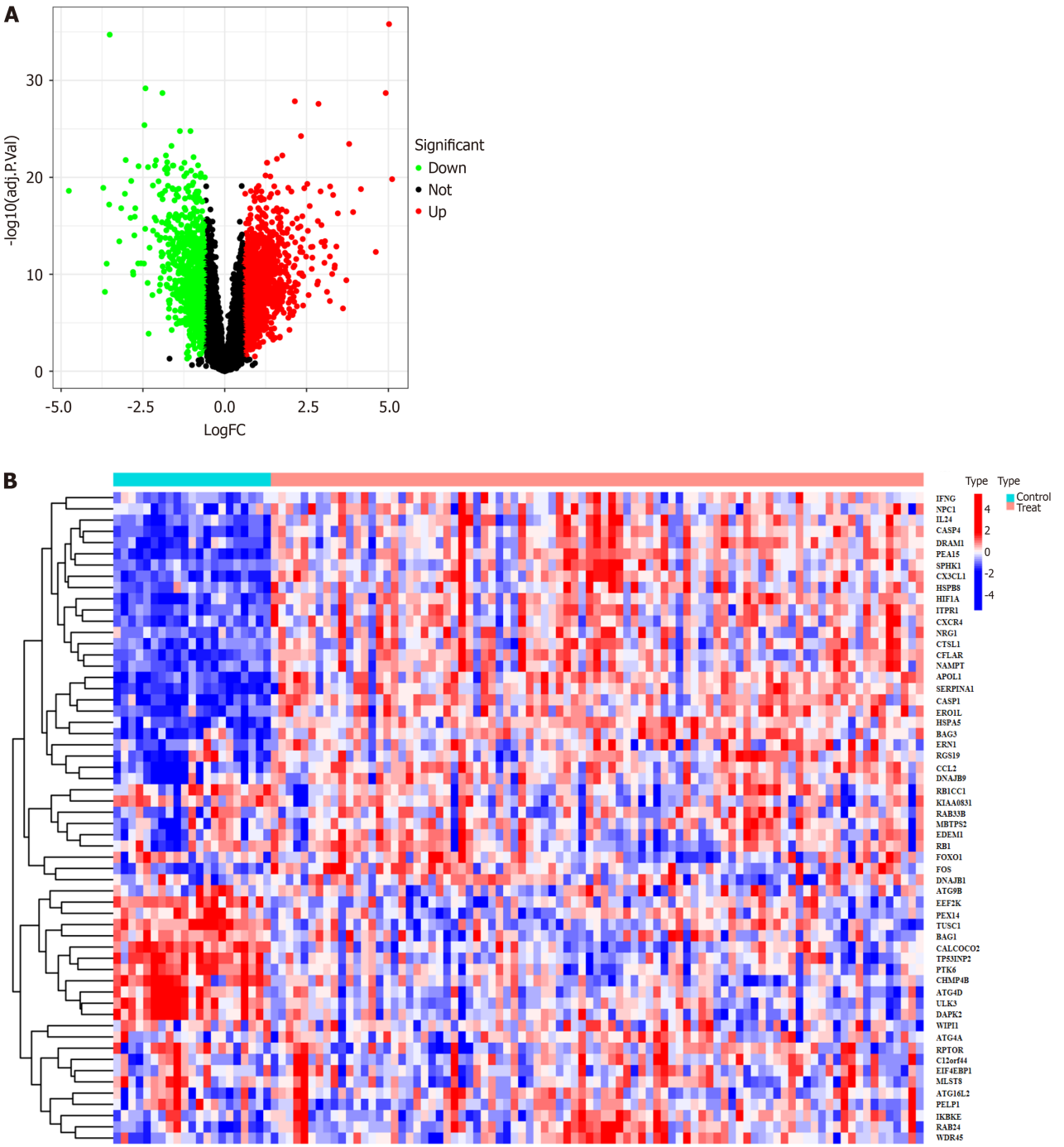

Figure 3 Volcano map and heat map showing expression of the differentially expressed autophagy-related genes. A: The downregulated targets are represented by green dots, the upregulated targets are represented by red dots, and the black dots indicate no significant difference in expression between active ulcerative colitis patients and healthy controls. Heat map showing expression of the differentially expressed autophagy-related genes; B: The blue color indicates low expression, while the red color indicates high expression.

llicular helper T cells, γδ T cells, M0 macrophages, M1 macrophages, activated dendritic cells, activated mast cells, and neutrophils. The "ggpubr" package in R was used to visualize the differential analysis results of immune cell infiltration in each sample. A $P < 0.05$ was considered statistically significant.

The following immune cell types were significantly higher in the UC group than in the healthy control group: activated memory CD4 T cells ($P < 0.001$), follicular helper T cells ($P < 0.05$), gamma delta T cells ($P < 0.05$), M0 macrophages ($P < 0.001$), M1 macrophages ($P < 0.001$), activated dendritic cells ($P < 0.001$), activated mast cells ($P < 0.001$), and neutrophils ($P < 0.001$). Meanwhile, CD8 T cells ($P < 0.05$), resting memory CD4 T cells ($P < 0.05$), regulatory T cells (Tregs) ($P < 0.001$), activated NK cells ($P < 0.01$), monocytes ($P < 0.01$), M2 macrophages ($P < 0.001$), resting dendritic cells ($P < 0.05$), and resting mast cells ($P < 0.001$) were significantly higher in the healthy control group than in the active UC group. No significant differences were observed in naive B cells, memory B cells, plasma cells, naive CD4 T cells, resting NK cells, and eosinophils between active UC cases and healthy controls (Figure 4).

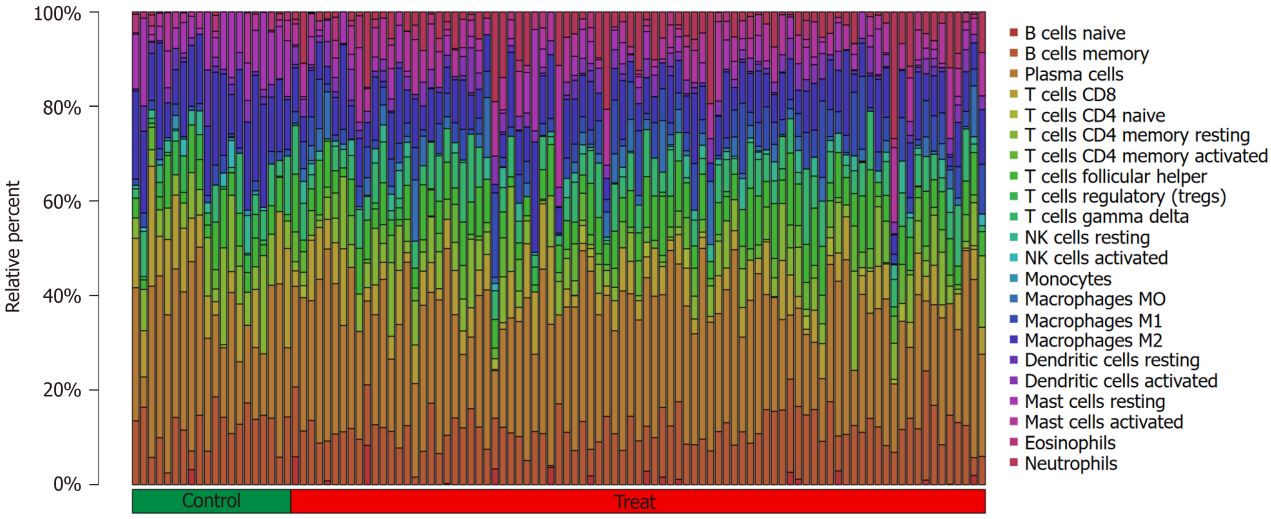

Figure 4 Proportion of immune cells in samples from the active ulcerative colitis group and healthy controls.

Biological variables related to the DEARGs

BP analysis revealed that the DEARGs were primarily associated with the regulation of autophagy, macroautophagy, autophagosome assembly, autophagosome organization, and vacuole organization. CC analysis showed that the DEARGs were primarily enriched in autophagosomes, phagophore assembly sites, and phagophore assembly site membranes. MF analysis found that DEARGs were mainly involved in chaperone binding, ubiquitin protein ligase binding, and heat shock protein binding (Figure 5A). KEGG enrichment analysis indicated that the DEARGs were predominantly enriched in autophagy-animal, autophagy-other, lipid and atherosclerosis, protein processing in the endoplasmic reticulum, and influenza A-related pathways (Figure 5B).

DisGeNET disease enrichment analysis

The Metascape "Summary of enrichment analysis in DisGeNET" revealed that the DEARGs were mainly enriched in malignant glioma, middle cerebral artery occlusion, infection, glomerulonephritis, and other diseases (Figure 6).

Construction of the LASSO algorithm and PPI

The LASSO algorithm narrowed the range of DEARGs and identified 13 targets: proliferation and apoptosis adaptor protein 15 (PEA15), heat shock 70-kDa protein 5 (HSPA5), caspase 1 (CASP1), serine protease inhibitor A1 (SERPINA1), C-X3-C chemokine ligand 1 (CX3CL1), Bcl2-associated athanogene 3 (BAG3), tumor protein p53 inducible nuclear protein 2 (TP53INP2), and peroxisomal biogenesis factor 14 (PEX14) (Figure 7). Their relationships were further established using the String database. The Cytoscape 3.9.1 software "CytoNCA" plug-in was used to sort the 13 targets according to their degree values, and the top five were selected as the core targets. The Fold Change (logFC) of these targets was obtained from the difference analysis results. All five were up-regulated and had the following parameters: SERPINA1 (logFC = 1.051), BAG3 (logFC = 0.661), HSPA5 (logFC = 0.790), CASP1 (logFC = 1.231), and CX3CL1 (logFC = 0.837) (Figure 8).

DISCUSSION

The current study identified HSPA5, CASP1, SERPINA1, CX3CL1, and BAG3 as core autophagy-related targets in active UC, all of which were upregulated during the disease. Key signaling pathways linked to these targets included autophagy in animals, other autophagy pathways, and lipid and atherosclerosis pathways. DisGeNET enrichment analysis found that middle cerebral artery occlusion, glomerulonephritis, and active UC were interrelated risk factors associated with autophagy. Active UC patients were found to have significantly higher counts of activated memory CD4 T cells, follicular helper T cells, gamma delta T cells, M0 macrophages, M1 macrophages, activated dendritic cells, mast cells, and neutrophils than healthy controls.

The results, including those predicted using core targeting and immune infiltration analysis, are supported by existing literature. R-HSPA5 is a specific form of HSPA5 that is localized in the endoplasmic reticulum (ER) and shown to play a critical role in autophagy-mediated lysosomal protein hydrolysis. Significant overexpression of HSPA5 mRNA and protein is found in UC patient tissues[12-14]. CASP1 expression in macrophages impairs autophagy, triggering inflammatory vesicle activation, a key factor associated with diseases such as active UC[15]. Activated CASP1 is critical for DSS-induced colitis[16-18]. Soendergaard *et al*[19] identified SERPINA1 as a potential biomarker of mild to moderate UC activity. Elevated CX3CL1 levels interact with CX3CR1, inhibiting autophagy in Kupffer cells[20]. CX3CL1 induces the infiltration and activation of CX3CR1-expressing cells, stimulating iNOS expression, a key mediator in DSS-induced colitis. These findings suggest that CX3CL1 may have potential for use in UC treatments[21,22]. Effector memory CD4 T cells induce IL-7 expression, leading to inflammation in the lamina propria of the intestinal mucosa[23]. During UC pathogenesis, Tfh

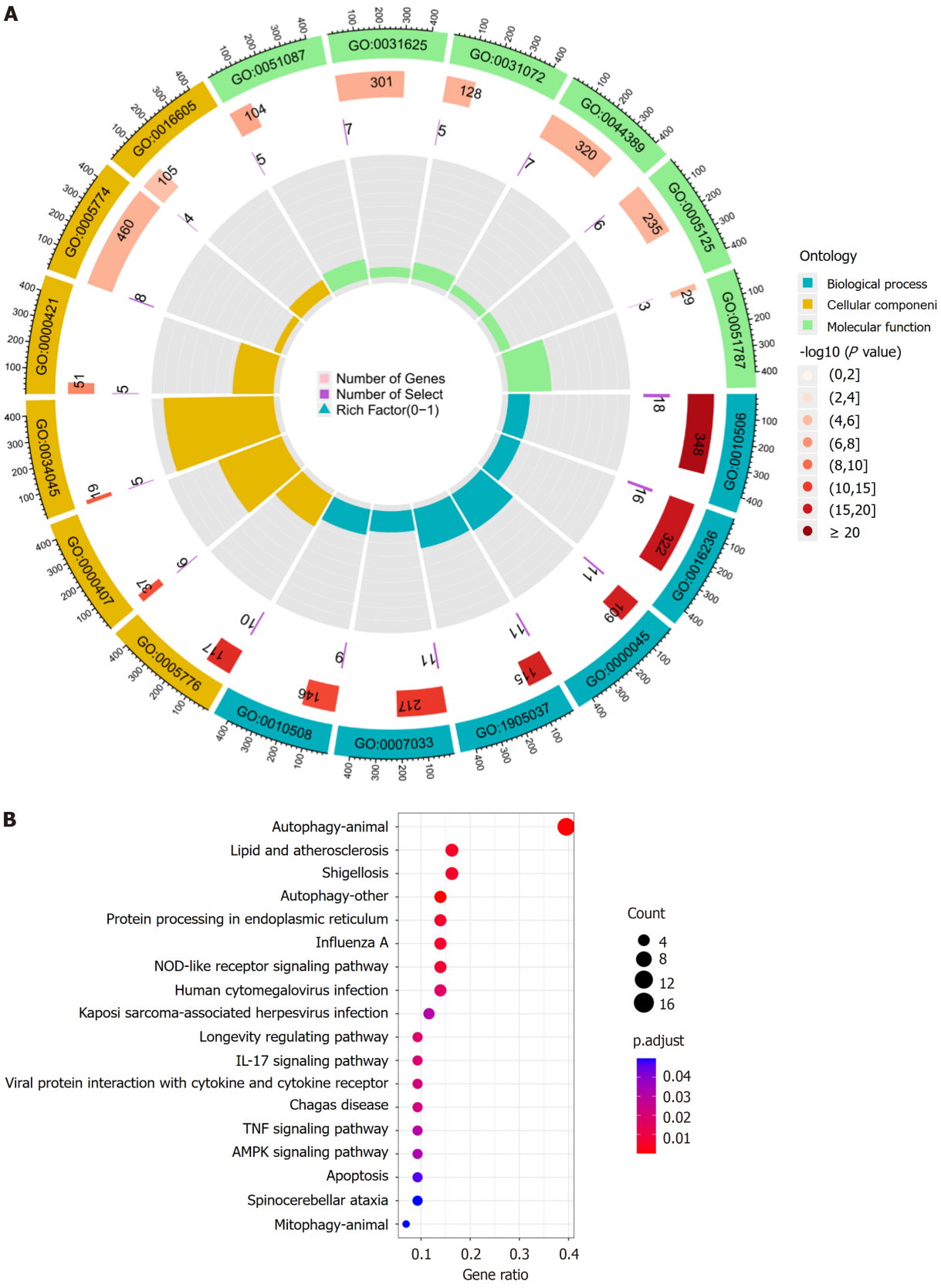

Figure 5 Results of gene ontology enrichment analysis. A: The blue part represents biological processes, the yellow part represents cellular components and the green part represents molecular functions. the height of the bar in the inner circle is proportional to the degree of enrichment. Results of Kyoto Encyclopedia of Genes and Genomes enrichment analysis; B: The horizontal coordinate is the number of enriched differentially expressed autophagy-related genes and the color of the node changes from red to purple according to the adjustment.

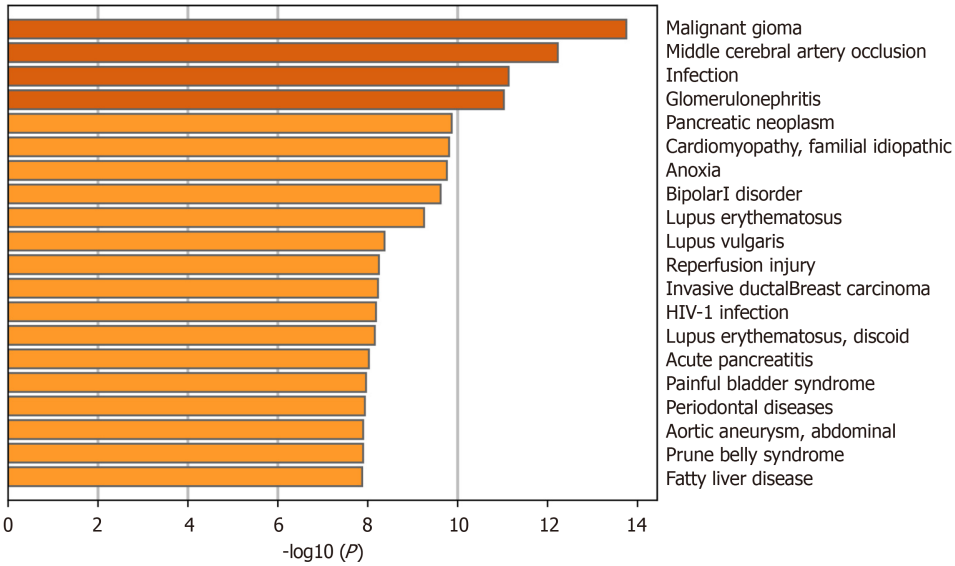

Figure 6 Validation of core targets in DisGeNET. The more yellow the color of the bar, the higher the correlation.

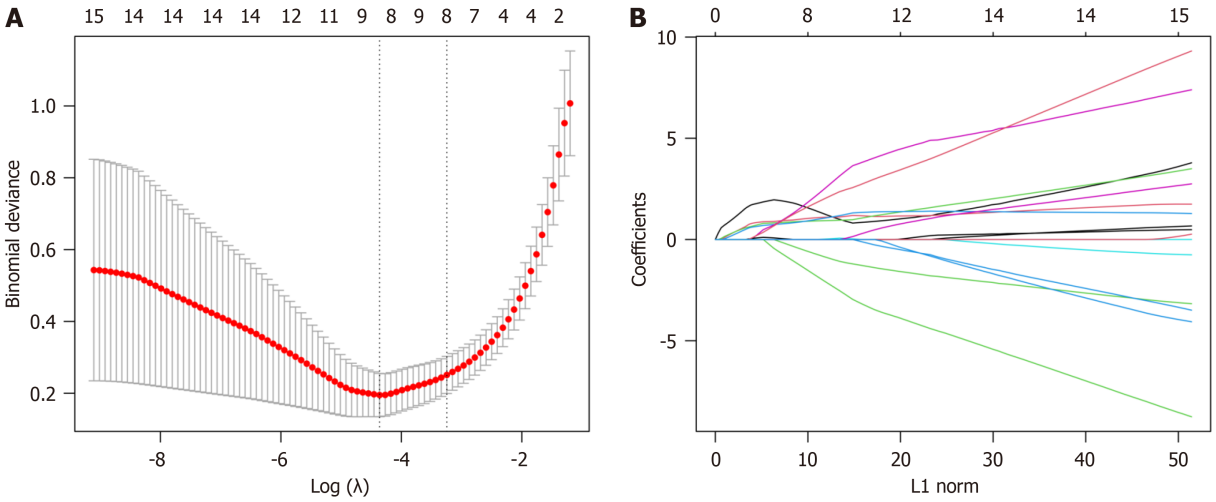

Figure 7 Results of least absolute shrinkage and selection operator regression model. A: Cross-validation error curve; B: Least absolute shrinkage and selection operator regression coefficient path plot.

cell functional abnormalities and imbalances disrupt the immune barrier of the intestinal mucosa, triggering immune disorders and the development of UC[24]. Inagaki-Ohara *et al*[25] found that UC naturally occurs in γδ T-cell-deficient mice. Mast cells (MC), commonly found in capillaries of the intestinal mucosa, are increased in inflammatory bowel disease (IBD) patients. They contain basophilic granules that release inflammatory factors during stress[26,27]. The IL-33/ST2 pathway, together with IgE signaling, mediates MC degranulation, inducing the release of inflammatory factors and initiating a cascade response[28]. Reduced NK cell levels affect mucosal flora responses, resulting in immune abnormalities and inflammatory changes in the colon[29]. Cherfane *et al*[30] identified an association between the number of peripheral blood mononuclear cells in UC patients and disease activity, suggesting that monocyte count could serve as a potential UC biomarker. The Th1/Th2 cell imbalance, along with the overexpression and activation of co-stimulatory molecules on dendritic cells, can trigger monocyte migration to the intestine, causing inflammation and potential damage to the intestinal mucosa[31,32].

The disease enrichment analysis results discussed here are confirmed by prior studies. Different stages of IBD are linked to the development of thrombosis, with IBD episodes or activity serving as a primary risk factor[33]. The predicted core genes are critical to the pathogenesis+ADs- hSPA5, for example, offering neuroprotection in ischemic strokes[34]. BAG3 overexpression is shown to improve neurological outcomes associated with middle cerebral artery embolism in mice, reducing infarct volume and enhancing cell survival by activating autophagy and inhibiting apoptosis[35]. Ischemia-induced neuronal autophagy is shown to exacerbate microglial inflammation post-stroke, possibly due to the reduced CX3CL1 expression in autophagic neurons[36]. Growing evidence suggests that autophagy plays a role in renal disease pathogenesis[37,38]. Glomerulonephritis emergence or exacerbation often coincides with IBD and subsides following effective IBD treatment[39]. CX3CL1 and CXCL10, induced by the core targets in this study, initiate activated

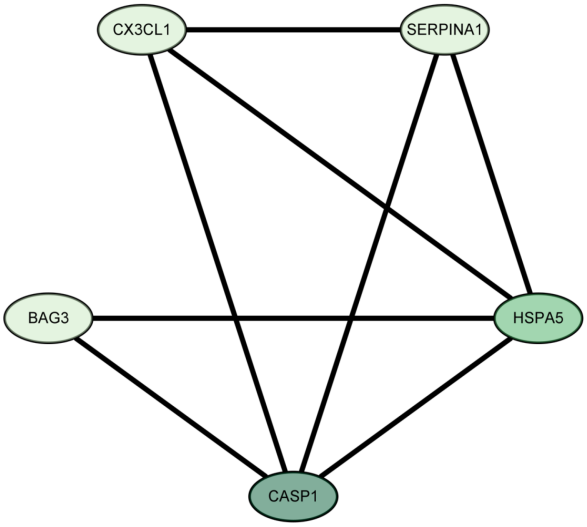

Figure 8 The five core targets and their relationship. The greener the color of the node, the higher the value of the degree, and the more important the relationship.

leukocyte infiltration into glomerular cells[40-42]. The NLRP3-ASC-caspase-1 inflammasome mitigates glomerular dysfunction by producing IL-1[43,44].

CONCLUSION

In summary, HSPA5, CASP1, SERPINA1, CX3CL1, and BAG3 were identified as core autophagy-related targets that are upregulated in active UC patients. These targets are associated with key signaling pathways, including autophagy in animals, other autophagy pathways, and lipid and atherosclerosis pathways. DisGeNET enrichment analysis also revealed a significant connection between middle cerebral artery occlusion, glomerulonephritis, and the autophagy-related pathogenesis of active UC. In addition, active UC patients exhibited significantly higher counts of various immune cells than healthy controls, indicating the occurrence of immune dysregulation. These findings provide valuable insight into the role of autophagy in UC pathogenesis and have potential implications for the development of novel targeted the-rapies.

ARTICLE HIGHLIGHTS

Research background

The etiology of ulcerative colitis (UC), a chronic inflammatory bowel disease (IBD), remains poorly understood. The pathogenesis of UC is complex and is influenced by genetic, environmental, and immune-related factors. While some recent progress has been made in the development of effective UC treatments, few patients experience complete relief of their symptoms. Thus, finding new therapeutic avenues to improve UC patient quality of life remains an urgent need. Autophagy is a cellular self-degradation and repair process that can help remove harmful proteins and organelles from cells and maintain intracellular homeostasis. Recent studies suggest that autophagy may play a key role in the pathogenesis and progression of IBD.

Research motivation

The motivation of this study was to provide an in-depth investigation of the autophagy-related pathogenesis of active phase UC. Bioinformatics analysis was used to better understand whether autophagy plays a key role in active UC and which autophagy-related genes may contribute to the disease process.

Research objectives

This study sought to provide new ideas and potential therapeutic targets for the treatment of active UC to better understand the pathogenesis of the disease and improve clinical symptoms.

Research methods

A bioinformatics approach was used to compare gene expression data between patients with active UC and healthy controls to identify core genes associated with autophagy and to obtain more information about the role of autophagy in this disease.

Research results

HSPA5, CASP1, SERPINA1, CX3CL1, and BAG3 were identified as core targets associated with autophagy-related pathogenesis in active UC, all of which were upregulated. Key signaling pathways linked to these targets include autophagy in animals, other autophagy pathways, and lipids and atherosclerosis pathways. DisGeNET enrichment analysis showed that middle cerebral artery occlusion, glomerulonephritis, and active UC were interrelated risk factors associated with autophagy. Active UC patients had significantly higher counts of activated memory CD4 T cells, follicular helper T cells, gamma delta T cells, M0 macrophages, M1 macrophages, activated dendritic cells, mast cells, and neutrophils than healthy controls.

Research conclusions

HSPA5, CASP1, SERPINA1, CX3CL1, and BAG3 were identified as core autophagy-related targets in active UC patients, all of which were upregulated. These targets are associated with key signaling pathways, including autophagy in animals, other autophagy pathways, and lipid and atherosclerosis pathways. DisGeNET enrichment analysis revealed a significant connection between middle cerebral artery occlusion, glomerulonephritis, and the autophagy-related pathogenesis of active UC. In addition, active UC patients had significantly elevated counts of various immune cells, indicating that immune function is dysregulated. These findings provide valuable insight into the role of autophagy in UC pathogenesis and could be used to inform the development of targeted therapeutic interventions.

Research perspectives

Future research in this field should focus on better understanding the molecular mechanisms by which HSPA5, CASP1, SERPINA1, CX3CL1, and BAG3 contribute to autophagy in patients with active UC. Investigating the specific roles of these core targets in UC pathogenesis and their interactions with the identified key signaling molecules should be a priority. Interventions that target the core autophagy-related genes and pathways could offer promising treatment options for active UC patients. It is also important to further explore the immune dysregulation observed in UC patients, particularly the elevated immune cell counts, to understand better the inflammatory processes involved and inform the development of immunomodulatory strategies to manage UC.

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FOOTNOTES

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ORCID number: Tao Liu 0009-0007-0428-4986.

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CASE REPORT

Low-molecular-weight heparin and preeclampsia — does the sword cut both ways? Three case reports and review of literature

Dan Shan, Tao Li, Xi Tan, Ya-Yi Hu

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Dan Shan, Tao Li, Xi Tan, Ya-Yi Hu, Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu 610000, Sichuan Province, China

Dan Shan, Tao Li, Xi Tan, Key Laboratory of Birth Defects and Related Diseases of Women and Children, Sichuan University, Ministry of Education, Chengdu 610000, Sichuan, China

Corresponding author: Ya-Yi Hu, MD, Chairman, Chief Doctor, Director, Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, No. 20 Renmin South Road, Section 3, Chengdu 610000, Sichuan Province, China.
sometreasure@sina.cn

Abstract

BACKGROUND

Low-molecular-weight heparins (LMWH) are the most commonly used anticoagulants during pregnancy. It is considered to be the drug of choice due to its safety in not crossing placenta. Considering the beneficial effect in the improvement of microcirculation, prophylactic application of LMWH in patients with preeclampsia became a trend. However, the bleeding risk related with LMWH in preeclampsia patients has seldomly been evaluated. This current study aimed to identify the potential risks regarding LMWH application in patients with preeclampsia.

CASE SUMMARY

Herein we present a case series of three pregnant women diagnosed with preeclampsia on LMWH therapy during pregnancy. All the cases experienced catastrophic hemorrhagic events. After reviewing the twenty-one meta-analyses, the bleeding risk related with LMWH seems ignorable. Only one study analyzed the bleeding risk of LMWH and found a significantly higher risk of developing PPH in women receiving LMWH. Other studies reported minor bleeding risks, none of these were serious enough to stop LMWH treatment. Possibilities of bleeding either from uterus or from intrabdominal organs in preeclampsia patients on LMWH therapy should not be ignored. Intensive management of blood pressure even after delivery and homeostasis suture in surgery are crucial.

CONCLUSION

Consideration should be given to the balance between benefits and risks of LMWH in patients with preeclampsia.

Key Words: Pregnancy; Preeclampsia; Low-molecular-weight heparin; Hemorrhage; Case report

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Core Tip: Benefits and risks of low molecular weight heparins in pregnant patients diagnosed with preeclampsia should be carefully assessed. Strict control of blood pressure is needed to prevent further bleeding events.

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INTRODUCTION

Due to its safety in not crossing the placental-fetal barrier, low-molecular-weight heparin (LMWH) is widely used in several placenta-mediated complications[1-4]. Many randomized controlled trials (RCTs) and meta-analyses regarding the improving function in placental micro-cocirculation of LMWH were conducted. However, heterogeneities in participant recruitment and difference in underlying physiopathological mechanisms of these placenta-mediated pregnancy complications contributed to controversial results. Most studies reported that LMWH is the anticoagulant of choice in pregnancy because of its favorable maternal safety profiles[5]. The safety parameters in long-term application of LMWH during pregnancy still needs to be considered. The safety parameters of LMWH including bleeding risk, allergy, heparin-induced thrombocytopenia, or heparin-induced osteoporosis were seldomly summarized. Especially the bleeding risk associated with LMWH, which might be seriously underestimated. The bleeding risk in pregnant women using LMWH is still a subject of debate.

Most studies on LMWH application in pregnant women reported ignorable bleeding risks[6-9]. However, in patients with preeclampsia, a population with high risk of postpartum hemorrhage, the information on bleeding risk related with LMWH was insufficiently evaluated. In spite, previous studies implied LMWH was an ideal treatment by indicating the efficacy of LMWH in preventing the development of preeclampsia and improving pregnancy outcomes. To illustrate the bleeding risk related with LMWH therapy in patients with preeclampsia, herein, we report three cases and review the literature.

CASE PRESENTATION

Chief complaints

Case 1: Case 1 was a 34-year-old pregnant woman with a singleton fetus. She had high blood pressure for more than one month.

Case 2: Case 2 was a 36-year-old woman with a singleton fetus. She had high blood pressure and proteinuria for 3 wk.

Case 3: Case 3 was a 38-year-old woman diagnosed with preeclampsia. She was delivered by CS 5 d before and huge hematoma formation was found 2 d before.

History of present illness

Case 1: She was diagnosed with preeclampsia at 28th gestational week at local hospital and was admitted to our hospital due to poorly controlled blood pressure on 29th gestational week.

Case 2: She had regular antenatal care and was admitted to our hospital at 28 gestational weeks. Her blood pressure was controlled but she was still presented with severe proteinuria and elevated liver enzymes.

Case 3: She was transferred to our hospital five days after CS because of uncontrolled blood pressure and huge hematoma formation in the abdominal wall. She had irregular antenatal care at a local hospital and emergency CS was performed by the local hospital at 36th gestational week due to the presentation of severe headache and uncontrolled blood pressure. Antihypertensive drugs and LWMH was prescribed after CS in the local hospital. She was discharged three days after CS, but she presented with aggressive abdominal pain one day before she was transferred to our hospital. The blood pressure was as high as 180/100 mmHg at admission.

History of past illness

Case 1: She was diagnosed with hypertension in her previous pregnancy 3 years ago.

Case 2: There was no significant past history.

Case 3: There was no significant past history.

Personal and family history

Case 1: There was no significant personal or family history.

Case 2: There was no significant personal or family history.

Case 3: Her sister was diagnosed with preeclampsia 2 years before during pregnancy.

Physical examination

Case 1: On physical examination, both of the patient's lower extremities showed severe pitting edema.

Case 2: On physical examination, the left leg showed mild edema and the rest of the examination was unremarkable.

Case 3: On physical examination, the patient had an anemic appearance, but the rest of the examination was unremarkable.

Laboratory examinations

Case 1: The patient had hypoproteinemia. The plasma albumin was 28 g/L.

Case 2: The antinuclear antibodies, anti-nucleosome antibodies, anti-SSA antibodies, anti-Ro52 antibodies and anti-β2-glycoprotein antibodies were positive. Suspicion of obstetric antiphospholipid syndrome (OAPS) and Sjogren's syndrome were made after consultation by rheumatologic doctors.

Case 3: Laboratory findings revealed hypochromic anemia with hemoglobin level of 7.1 g/dL.

Imaging examinations

Case 1: The ultrasonography revealed intrauterine growth restriction (IUGR) and elevated umbilical artery flow velocity S/D value.

Case 2: The ultrasonography revealed the growth of the fetus was appropriate.

Case 3: Huge hematoma formation was found in the anterior abdominal wall (14.1 cm × 3.4 cm × 10.4 cm).

FINAL DIAGNOSIS

Case 1

Severe preeclampsia, intrauterine growth restriction.

Case 2

Severe preeclampsia, pregnancy complicated with immune disorders: OAPS and Sjogren's syndrome.

Case 3

Severe preeclampsia, hematoma in abdominal wall.

TREATMENT

Case 1

Magnesium sulfate, antihypertensive therapy and LMWH were prescribed. At 31 gestational weeks, emergent CS was performed due to repeated non-response non-stress tests on fetal monitoring. The CS was successful with a baby of Apgar score 8-9-9 was born. However, hours after CS, her blood pressure declined progressively and the vital signs were not stable. Blood tests implied significantly decreased hemoglobin and abdominal paracentesis revealed hemoperitoneum. An emergent relaparotomy was performed. Large amount of fresh blood with clots were found in the abdomen (uncoagulable blood 1660 mL, blood clots 670 g). Bleeding was found in a small mesenteric artery. After evacuation of blood clots and hemostasis suture, the patient was transferred to the intensive care unit and then the general ward.

Case 2

Antihypertensive therapy, hepatoprotective treatments, immune regulation and LMWH were given as the rheumatologic doctor suggested. At 32 gestational weeks, she had upper abdominal pain and vomiting after an unhygienic diet. Acute gastroenteritis was first suspected. Symptomatic and supportive treatment was given but the symptoms were not relieved. She had uncontrolled vomiting and the upper abdominal pain was aggressive. Abdominal ultrasound revealed

large amount of ascites which emerged in short time. Emergent CS was performed. A female fetus with an Apgar score 3-6-8-9 was born. Large amounts of blood clots accumulated in the pelvic cavity, spleen and liver area. A small rupture with bleeding with a diameter of approximately 1cm was found in the Glisson's capsule behind the gall bladder, which was repaired meticulously by a hepatobiliary surgeon during surgery.

Case 3

Intensive antihypertensive therapy was immediately administered. Intravenous antihypertensive medications were converted to oral antihypertensive medications progressively for three days after admission. Conservative treatments for hematoma with activating blood circulation herbs were applied after communication with the patients. The hematoma shrank to 10.1 cm × 3.0 cm × 8.9 cm at the 8 d after admission (Figure 1).

OUTCOME AND FOLLOW-UP

Case 1

The patient recovered well and was discharged on day seven after CS.

Case 2

The patient recovered well and was discharged on day eight after delivery.

Case 3

The hematoma shrank to 6.0 cm x 2.0 cm x 3.0 cm two months later (Figure 2).

DISCUSSION

Low-molecular-weight heparin thromboprophylaxis recommendations differ across clinical practice guidelines for patients with preeclampsia[2-4,10,11]. Application of LMWH was not a common treatment option for patients at high risk for preeclampsia in the past decades in China. However, as the maternal mortality rate caused by pulmonary embolism increased, more attention was given to the LMWH prophylaxis and treatment in pregnant women in recent years. Lack of experience in LMWH usage sometimes put the obstetricians in a dilemma in balancing the benefits and risks. Here we reported three severe bleeding events in patients with preeclampsia receiving LMWH.

The hemorrhagic event caused by mesenteric artery was a rare event in case one. During pregnancy, the physiological changes of abdominal vessels during pregnancy included increased blood supply and hypostasis resulting from an enlarged uterus. Suspicion of spontaneous rupture in mesenteric artery is a possible and reasonable cause considering the uncontrolled blood pressure in this patient. Common tocolytic applications is an effective method for uterine bleeding, but functioned less in controlling bleeding from the mesenteric arteries. High blood pressure and LMWH significantly increased the possibility for aggressive intrabdominal bleeding. Case two of our report was diagnosed as acute gastroenteritis, with an initial history of unhygienic diet at first. Possibility of intrabdominal bleeding was considered due to the continuous presentation of vomiting with abdominal pain and large amount of ascites which emerged in a short time detected by ultrasound. Preeclampsia and sudden increased abdominal pressure during vomiting might lead to small rupture in Glisson's capsule. With the application of LMWH, subsequent severe hemorrhage from liver, of which the blood supplementation significantly increased compared with that in non-pregnancies, put the patient in hypovolemic shock immediately. Although being a rare event in pregnant women, spontaneous bleeding from abdominal organ and large vessels was reported in pregnant women in the literature, especially in patients with preeclampsia[12-14]. It was reported that sub-capsular liver hematoma occurred in 1%–2% of patients with HELLP syndrome[13,14]. The presentation of hematoma might be nonspecific. Possible complaints of patients might be nausea and right upper quadrant discomfort. But in pregnant women, none of these symptoms are typical, this certainly would lead to the possibility of misdiagnosis. Huge hematoma formation in case 3 indicated the urgent needs for strict control of blood pressure even after delivery. Management of blood pressure is still crucial in postpartum patients. The uncontrolled blood pressure after the CS together with LMWH led to hematoma formation in the pregnant woman's uncompacted abdominal wall in case three.

Due to its pharmacological properties in improving microcirculation, the efficacy of LMWH has been evaluated in several pregnancy related complications in recent decades. The review on LMWH application in patients with preeclampsia patients were not identified by searching Pubmed and Embase databases. However, we found several meta-analyses regarding the preventive and treatment effect of LMWH on antiphospholipid syndrome (APS), recurrent pregnancy loss (RPL), venous thromboembolism (VTE), preeclampsia, IUGR and small for gestational age (SGA). A total of 21 studies were summarized (Table 1)[6-9,15-31]. However, by analyzing these researches, we found limited information on bleeding risk either antenatally or postnatally. Only one study by Sirico *et al*[28] analysed thromboprophylaxis with LMWH in women during the third trimester of pregnancy. Some studies reported increased risk in minor bleeding[18,24,25,31]. Majority of the meta-analyses found no significant difference in bleeding events rate in LMWH group compared with LDA or placebo. No studies reported hepatic hematoma or major bleeding events from intrabdominal vessel.

Table 1 Summary of the literature review findings for low-molecular-weight heparin application in pregnancy

Ref.	Year	Included population	Number of studies included	Comparison	Efficacy	Safety: Bleeding risk
Areia *et al* [15]	2016	Women with hereditary thrombophilia	4 studies; 222 participants	LMWH + LDA *vs* LDA	No difference was found with regard to live births rate in LMWH + LDA group versus LDA group	Not reported
Bettiol *et al* [16]	2021	Pregnant women at high risk of FGR, defined as those with at least one of the follow: history of FGR in the previous pregnancies, history of late pregnancy loss or recurrent early pregnancy loss, hypertensive disorders, inherited or acquired thrombophilia	30 studies; 4326 participants	LMWH/UFH/LDA/other antiplatelet agents *vs* control	Low molecular weight heparin (LMWH), alone or associated with low-dose aspirin (LDA), appeared more efficacious than controls in preventing FGR	No treatment was associated with an increased risk of bleeding
Cruz-Lemini *et al*[6]	2022	Patients who had any known risk factors for developing PE, and medical history including thrombophilia, autoimmune diseases, and chronic hypertension	15 studies; 2795 participants	LMWH ± LDA *vs* control; LMWH *vs* LDA	In high-risk women, LMWH was associated with a reduction in the development of PE, SGA and perinatal death	No statistically significant difference in bleeding was found between LMWH and control, regardless of whether or not LMWH was combined with aspirin
Dias *et al* [17]	2021	Women with a history of recurrent abortion without an identified cause	7 studies 1855 participants	LMWH *vs* control	The LMWH group had a higher incidence of continuous pregnancy after the 20th week of gestation	There was no statistically significant difference between the groups on hemorrhagic events
Guerby *et al*[18]	2021	Pregnant women with APS	13 studies; 1916 participants	LMWH/UFH ± LDA *vs* LDA/IVIG	Heparin and LMWH, associated or not to aspirin, significantly increased the rate of live birth and decreased the rate of preeclampsia	Treatment with heparin and LMWH was associated with a significant increase in minor bleeding (bruises, epistaxis) (RR 2.58, 95%CI 1.03-6.43)
Hamulyák *et al*[19]	2020	Women with persistent (on two separate occasions) aPL, either lupus anticoagulant (LAC), anticardiolipin (aCL) or aβ(2)-glycoprotein-I antibodies [aβ(2)GPI] or a combination, and recurrent pregnancy loss	11 studies; 1672 participants	LMWH/UFH ± LDA *vs* LDA; LMWH/UFH ± LDA *vs* control	Heparin plus aspirin may increase the number of live births. Heparin plus aspirin may reduce the risk of pregnancy loss. We are uncertain if heparin plus aspirin has any effect on the risk of pre-eclampsia, preterm delivery or intrauterine growth restriction, compared with aspirin alone	We are very uncertain if heparin plus aspirin has any effect on bleeding in the mother compared with aspirin alone
Intzes *et al* [20]	2021	Women with or without hereditary thrombophilia and recurrent pregnancy loss	12 studies; 2298 participants	LMWH *vs* control	LMWH on live birth rates is not significant in women with or without thrombophilia	Not reported
Jacobson *et al*[21]	2020	Pregnant women receiving enoxaparin	24 studies	Enoxaparin *vs* control	In patients with a history of recurrent pregnancy loss, the rates of pregnancy loss were significantly lower for enoxaparin compared to untreated controls	Bleeding events were non-significantly compared between enoxaparin with untreated controls or aspirin
Jiang *et al* [9]	2021	Pregnant women with recurrent pregnancy loss	8 studies; 1854 participants	LMWH *vs* control	LMWH had significantly improved live births rates and reduced miscarriage rates	Receiving LMWHs had no substantial impact on bleeding episodes
Liu *et al*[8]	2021	Patients with recurrent pregnant loss	6 studies; 1034 participants	Enoxaparin *vs* control	Enoxaparin has no obvious impact on live births, abortion rate, birth weight, preterm delivery and preeclampsia	Enoxaparin has no obvious impact on postpartum hemorrhage

Liu *et al* [22]	2020	Naturally pregnant women aged 18 or older with a diagnosis of recurrent pregnancy loss and APS	12 studies; 1910 participants	LMWH/UFH + LDA *vs* control	LMWH plus aspirin had a higher live birth rate than aspirin alone, UFH plus aspirin showed a higher live birth rate than aspirin alone	Not reported
Lu *et al*[23]	2019	Women with APS and recurrent spontaneous abortion	19 studies; 1251 participants	LMWH/UFH ± LDA *vs* LDA; LMWH/UFH ± LDA *vs* control	With respect to live birth, it was remarkably improved in aspirin plus heparin or heparin alone group compared with aspirin alone group. Low-dose aspirin plus heparin therapy was significant reduce the risk of preeclampsia	Aspirin plus heparin therapy did not significantly increase minor bleeding risk
Mastrolia *et al*[24]	2016	Pregnant women at risk for developing preeclampsia, IUGR, placental abruption, spontaneous preterm delivery and fetal death	5 studies; 403 participants	LMWH *vs* control	The overall use of LMWH was associated with a risk reduction for preeclampsia and IUGR	Minor bleeding complication in two patients in LMWH group
Middleton *et al*[25]	2021	Women who were pregnant or had given birth in the previous six weeks, at increased risk of VTE, were included. Women at increased risk were those having/following a caesarean section, with an acquired or inherited thrombophilia, and/or other risk factors for VTE	29 studies; 3839 participants	LMWH/UFH *vs* control; LMWH *vs* UFH	Evidence was very uncertain for antenatal (± postnatal) prophylaxis for prevent thromboembolic event (PE and DVT)	Evidence was very uncertain on adverse effects sufficient to stop treatment caused by bleeding. Only one study reported adverse effects sufficient to stop treatment caused by bleeding during LMWH treatment (3 patients with placenta previa)
Roberge *et al*[26]	2016	Women with previous history of PE	8 studies; 885 participants	LMWH/UFH ± LDA *vs* LDA	In women with previous history of PE, treatment with LMWH and aspirin, compared to aspirin alone, was associated with a significant reduction in PE and birth of SGA neonates	Not reported
Rodger *et al*[27]	2016	Women pregnant at the time of the study with a history of previous pregnancy that had been complicated by one or more of the following: pre-eclampsia, placental abruption, birth of an SGA neonate, pregnancy loss after 16 wk' gestation, or two losses after 12 wk' gestation	8 studies; 963 participants	LMWH *vs* control	LMWH did not significantly reduce the risk of recurrent placenta-mediated pregnancy complications. In subgroup analyses, LMWH in multicenter trials reduced the placenta-mediated pregnancy complications in women with previous abruption	In the antepartum period, there is no significant difference in risk for major bleeding. In the peripartum and postpartum periods, the incidence of major bleeding did not differ between the treatment and control groups
Sirico *et al* [28]	2019	Women who underwent thromboprophylaxis with LMWH during the third trimester of pregnancy	8 studies; 22162 participants	LMWH *vs* control	Not reported	Women treated with LMWH had an higher risk of PPH (RR 1.45, 95%CI 1.02 to 2.05) compared to controls. There was no difference in mean of blood loss at delivery and in risk of blood transfusion at delivery
Urban *et al* [7]	2021	Patients affected by obstetric APS, with or without thrombotic APS	8 studies; 395 participants	UFH/LMWH + LDA *vs* LDA; LMWH + LDA *vs* UFH + LDA; LDA + UFH + IVIg *vs* LDA + UFH	No difference among treatments emerged in terms of FGR prevention, but estimates were largely imprecise	No treatment was associated with an increased risk of bleeding
Wang *et al* [29]	2020	Women with subsequent pregnancies who previously had early onset or severe PE	7 studies; 1035 participants	LMWH *vs* LDA; LMWH *vs* control	There were risk reductions on PE rate, small-for-gestational-age neonate rate. LMWH led to an increase in gestational length and neonatal weight	Not reported
Yan *et al* [30]	2022	Patients with unexplained recurrent miscarriage with negative antiphospholipid	7 studies; 1849 participants	LMWH ± LDA *vs* control	No substantial influence on miscarriage rate and the occurrence rate of pre-	Not reported

		antibodies			eclampsia	
Yang *et al* [31]	2018	Women undergoing IVF/ICSI	5 studies; 935 participants	LMWH *vs* control	No significant differences for live birth rate, clinical pregnancy rate and miscarriage rate were found between the low-molecular-weight heparin and control groups	One study reported five cases of minor vaginal bleeding in women receiving LMWH treatment, but not serious enough to stop the use of LMWH

For the above studies, patients in the control group received no treatments or placebo. APS: Anti-phospholipid syndrome; aPL: Antiphospholipid antibodies; DVT: Deep vein thrombosis; IUGR: Intrauterine growth restriction; IVIG: Intravenous immune globulin; LDA: Low dose aspirin; LMWH: Low molecular weight heparin; PE: Preeclampsia; SGA: Small for gestational age; UFH: Unfractionated heparin.

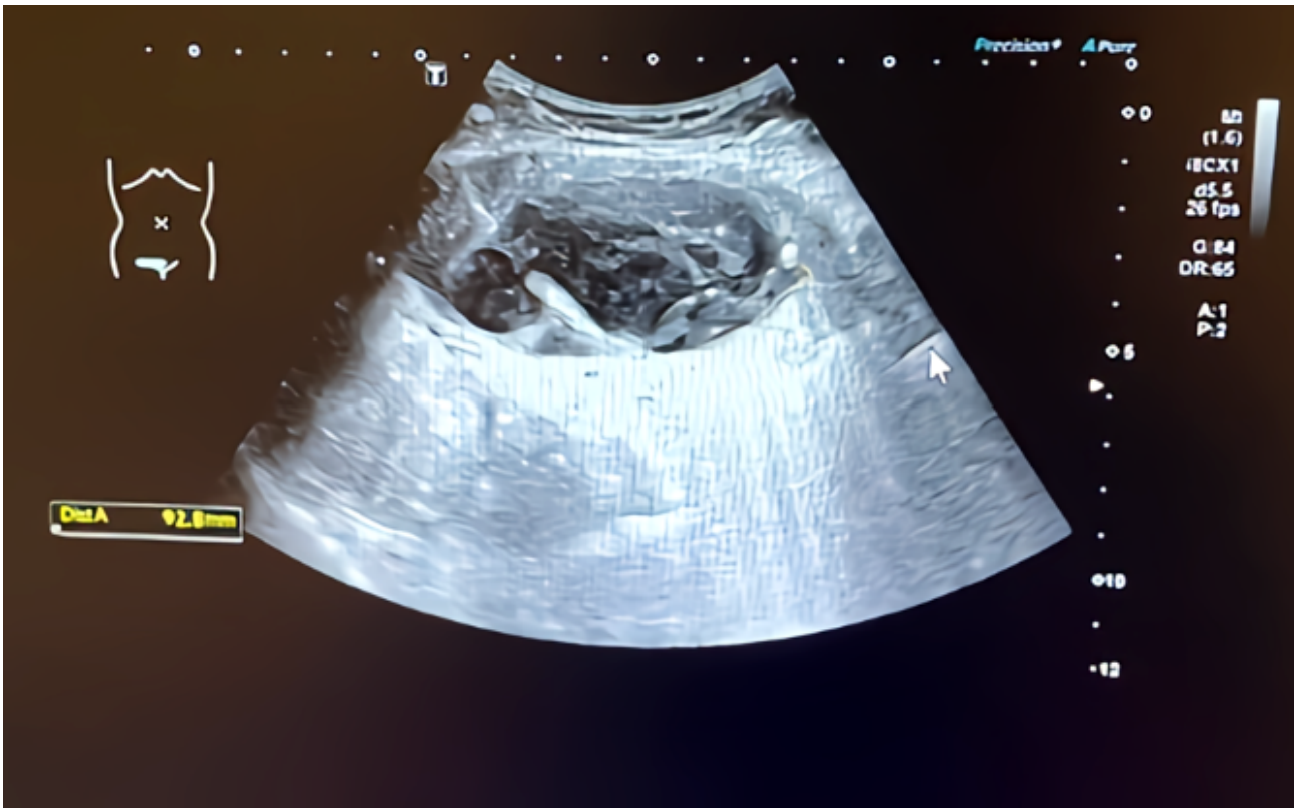

Figure 1 Huge hematoma formation in the anterior abdominal wall in case 3.

Three meta-analyses focused on patients with preeclampsia[6,26,29]. These studies reported consistencies of the beneficial effect on reduction of PE rate from LMWH treatment. The reduction on SGA development were testified and neonatal birthweight were also improved. However, only one study reported non-significant difference in bleeding risk of LMWH in patients with preeclampsia[6]. The bleeding risk of LMWH was not reported in other two studies.

Similar with our reported cases, Sirico et. al reported augmented risk of bleeding[28]. They included eight randomized controlled trails and indicated that women who received LMWH during pregnancy had a significantly higher risk of developing post-partum hemorrhage (PPH). No difference was found in the mean blood loss during delivery or risk for blood transfusion. Except for PPH, serious antenatal bleeding in patients with placenta previa was also reported as an important reason to quite LMWH treatment[25]. Despite recognizing this as a small probability event, the safety of LMWH in patients with high risk of antenatal hemorrhage should be evaluated. For minor bleeding events, one study reported increased risk in LMWH group from nine trials. The risk for bruises and epistaxis was 2 times higher in patients in heparin group[18]. Bloody vaginal discharge, minor vaginal bleeding and subcutaneous hemorrhage from injection point were also reported. However, none of these symptoms were serious. None of these minor bleeding events stopped patients from LMWH treatment.

Notably, the indication of LMWH application in these three patients worth our serious consideration. Due to its advantages in the safety to the fetus and less possibility of causing osteopenia, LMWH is the recommended treatment in pregnant women over unfractionated heparin (UFH)[32]. In our three cases, both of these patients were treated with a prophylaxis dose of LMWH. However, since LMWH did not have direct antihypertensive function, application of LMWH in PE patients renders more consideration. Despite its benefiting effects in improving microcirculation, LMWH is not included in the treatment strategy of PE patients[33-35] and patients with IUGR risk factors[36-39] as suggested by many

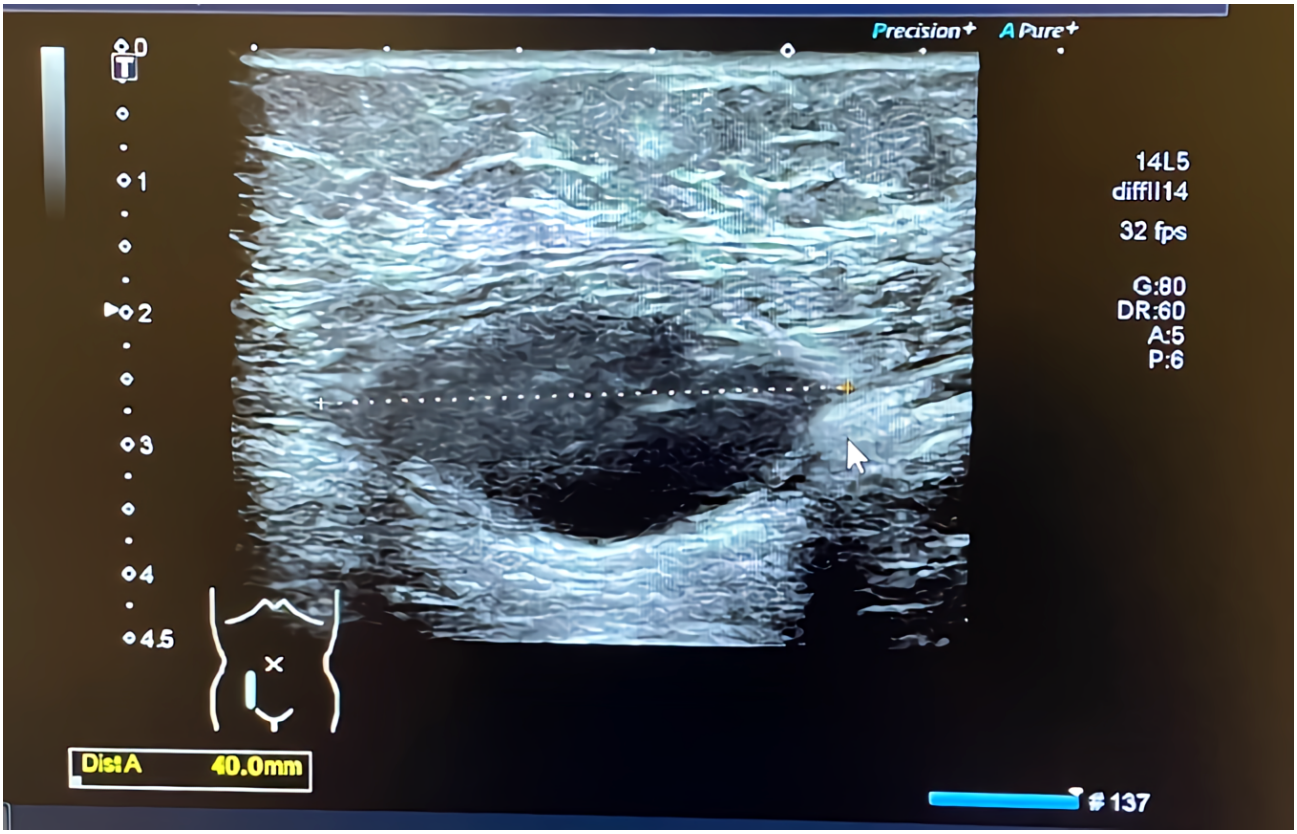

Figure 2 The huge hematoma shrank after two months in case 3.

guidelines. In case 1 and case 3, the LMWH was prescribed in view of improving the microcirculation in preeclampsia patients. In case 2, LMWH was given due to the suspicion of immune disorders. OAPS was suspected in this case although the patient lack other diagnostic criteria. Whether or not LMWH could improve the pregnancy outcomes in patients with PE and IUGR is still in debate. From the meta-analyses we included, it seemed that the beneficial effect of LMWH in improving some key obstetric outcomes in pregnancies including birth live rates, pregnancy loss rates, SGA and IUGR still seemed controversial. The absence of effect of LMWH in these placenta-mediated pregnancy complications might reflect the multifactorial pathophysiology. The safety parameter of LMWH for the fetus has already been assessed, since it does not pass the placental barrier. The safety parameter of LMWH for the mothers was not adequately estimated. The association of anticoagulation with bleeding should still be postulated.

Bearing in mind the benefits and risks of LMWH in the treatment and prevention of preeclampsia, the application of LMWH should be reconsidered. In patients with preeclampsia and IUGR, LMWH was not included in the treatment strategy, but prophylaxis application of LMWH might have beneficial effect for improving microcirculations. However, the overall effect of improving pregnancy outcomes in these patients is still in debate. If prescribed, a planned labour was recommended with enough time interval from last dose of LMWH. In emergency situations, careful check and hemostasis procedures are crucial during CS. Careful management of blood pressure after delivery have key significance in preventing complications after delivery. Obstetricians should be remind of the elevated bleeding risk in patients with preeclampsia taking LMWH.

CONCLUSION

Pending further data to establish a balance between benefits and risks of LMWH in patients with preeclampsia, the cases in our report represented the nonnegligible bleeding risks during LMWH therapy. When patients presented signs suggestive of hemorrhage without vaginal bleeding, the possibility of intraabdominal hemorrhage should be taken into consideration. If conservative management is inadequate, exploratory laparotomy should be implemented.

FOOTNOTES

Author contributions: Shan D, Hu YY, and Li T made substantial contributions to conception and design; Shan D, Tan X and Li T helped in drafting the manuscript; Hu YY supervised of this study and gave final approval of the version to be published; all authors read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: Dan Shan 0000-0002-9108-1453; Ya-Yi Hu 0000-0001-6865-2388.

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CASE REPORT

Pulmonary alveolar proteinosis induced by X-linked agammaglobulinemia: A case report

Ting Zhang, Ming Li, Li Tan, Xin Li

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Ting Zhang, Ming Li, Li Tan, Department of Respiratory Medicine, Kunming Children´s Hospital, Kunming 650228, Yunnan Province, China

Xin Li, Department of Emergency, Kunming Children's Hospital, Kunming 650228, Yunnan Province, China

Corresponding author: Xin Li, MM, Doctor, Kunming Children's Hospital, No. 288 Qianxing Road, Kunming 650228, Yunnan Province, China. 546918754@qq.com

Abstract

BACKGROUND

Pulmonary alveolar proteinosis (PAP) and X-linked agammaglobulinemia (XLA) are rare diseases in children. Many theories infer that immunodeficiency can induce PAP, but these reports are almost all review articles, and there is little clinical evidence. We report the case of a child with both PAP and XLA.

CASE SUMMARY

A 4-month-old boy sought medical treatment due to coughing and difficulty in breathing for > 2 wk. He had been hospitalized multiple times due to respiratory infections and diarrhea. Chest computed tomography and alveolar lavage fluid showed typical PAP-related manifestations. Genetic testing confirmed that the boy also had XLA. Following total lung alveolar lavage and intravenous immunoglobulin replacement therapy, the boy recovered and was discharged. During the follow-up period, the number of respiratory infections was significantly reduced, and PAP did not recur.

CONCLUSION

XLA can induce PAP and improving immune function contributes to the prognosis of children with this type of PAP.

Key Words: Pulmonary alveolar proteinosis; X-linked agammaglobulinemia; Children; Immunodeficiency; Alveolar lavage; Case report

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Core Tip: Pulmonary alveolar proteinosis (PAP) and X-linked agammaglobulinemia (XLA) are both rare diseases in children. This article shares the diagnosis and treatment process of a special case to confirm that XLA was a secondary cause of PAP which improved with intravenous immunoglobulin treatment.

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INTRODUCTION

Pulmonary alveolar proteinosis (PAP) and X-linked agammaglobulinemia (XLA) are rare diseases in children. Many studies have suggested that immunodeficiency can induce PAP. However, only two cases of PAP induced by immune deficiency have been reported[1-3], and the remaining studies are almost all review articles. Therefore, more clinical data are needed to prove the correlation between PAP and immunodeficiency.

XLA is an X-linked recessive genetic disease. This is due to a defect in Bruton's tyrosine kinase (BTK). The differentiation of primitive B lymphocytes to mature B lymphocytes is impaired. There is a lack of B lymphocytes and plasma cells in the peripheral blood, and this leads to insufficient immunoglobulin synthesis. Therefore, children with XLA are prone to repeated bacterial infections and autoimmune diseases[4,5].

According to the etiology, PAP can be divided into congenital, acquired and idiopathic PAP[6]. Congenital PAP is an autosomal recessive disorder. It is caused by a defect in the surface-active substance protein or the gene encoding granulocyte–macrophage colony-stimulating factor (GM-CSF)[7,8]. Idiopathic PAP is caused by a large amount of GM-CSF self-neutralizing antibodies in the body, which block the function of GM-CSF. Therefore, the function of alveolar macrophages is severely affected, resulting in decreased alveolar surfactant clearance[9]. The pathogenesis of acquired PAP is unclear. It is currently believed to be related to various autoimmune, infectious, malignant and environmental etiologies[10].

CASE PRESENTATION

Chief complaints

The 4-month-old male patient had an acute cough, expectoration and difficulty breathing for > 10 d.

History of present illness

The child developed paroxysmal cough and phlegm 2 wk previously, along with difficulty breathing, runny nose, diarrhea, and cyanosis around the mouth. The symptoms did not improve after receiving penicillin infusion at the local hospital.

History of past illness

The child is gravida 2 para 2 and was a full-term birth. The birth process was smooth, with no asphyxia or respiratory distress. His birth weight was ~3 kg. He has suffered pneumonia and diarrhea many times since birth. However, no abnormalities were found on chest imaging except for pulmonary infection.

Personal and family history

There was no other relevant personal or family history.

Physical examination

The patient's body temperature was 36.5C, heart rate 136 bpm, respiratory rate 62 breaths/min, fingertip oxygen saturation (SpO_2) 86%, and body weight 7.2 kg. Upon examination, his lips were cyanotic, no swollen superficial lymph nodes were noted throughout the body, respiratory sounds in both lungs were rough, and fine moist rales were heard in both lungs. Physical examination of the heart, abdomen and nervous system did not reveal any abnormalities.

Laboratory examinations

Blood tests revealed that his erythrocyte sedimentation rate, liver and kidney function, and C-reactive protein level were normal. The myocardial enzyme spectrum was normal except for lactate dehydrogenase (704 U/L). Humoral immunity showed the following: Ig 14.0 g/L, IgG 0.93 g/L, IgM 0.29 g/L, IgA 0.0 g/L, complement C3 0.40 g/L, complement C4 0.11 g/L, and total IgE 1 U/mL. Lymphocyte subpopulation determination was as follows: $CD3^+$ 95.49%, $CD3^+CD4^+$ 65.58%, $CD16^+CD56^+$ 3.58% and $CD19^+$ 0.03%. No pathogens were found in blood and sputum tests.

His bronchoalveolar lavage fluid was milky white and Periodic acid–Schiff staining was positive (Figure 1). Genetic testing [whole exome sequencing revealed that the BTK gene (located at chrX:100608340) had a hemizygous mutation (c.1751-1g>A)]. Thus, he was diagnosed with PAP and XLA. Genetic testing did not find gene mutations related to PAP [2] [such as surfactant protein B, surfactant protein C, ATP-binding cassette subfamily A member 3 (ABCA3), Nkx homeobox-1 gene (NKX2-1), and granulocyte-monocyte colony stimulating factor receptor genes]. No respiratory pathogens were detected in blood, sputum and alveolar lavage fluid.

Imaging examinations

Chest spiral computed tomography plain scan showed a significant decrease in the transparency of both lungs, with ground glass or butterfly-shaped changes in both lungs, and a large bubble in the upper lobe of the right lung (Figure 1). Tracheoscopy revealed that his alveolar lavage fluid was pale milky white.

FINAL DIAGNOSIS

PAP and XLA.

TREATMENT

The patient received ceftriaxone, total lung lavage, and infusion of intravenous immunoglobulin (IVIG).

OUTCOME AND FOLLOW-UP

After discharge, the patient received regular IVIG replacement therapy. During 1 year of follow-up, his respiratory tract infection frequency significantly decreased, and all were mild infections. He did not exhibit symptoms of PAP such as excessive phlegm or difficulty breathing, and there were no special features on chest imaging. Therefore, the child has not yet undergone a second bronchoscopy examination.

DISCUSSION

Current studies suggest that PAP is related to a decrease in macrophage clearance. The Toll-like receptor (TLR) pathway is an important signal pathway regulating the function of macrophages. BTK is an important regulatory molecule in the TLR pathway, which is involved in the regulation of cytokine production, phagocytosis, differentiation and the function of macrophages after TLR activation[11,12]. Therefore, XLA may directly induce PAP. At the same time, XLA children can be prone to repeated pulmonary infections, leading to PAP. Based on the above theory, we believe that XLA is one of the potential causes of PAP. Therefore, improving immune function may benefit the prognosis of children with PAP caused by immunodeficiency.

The child in this report had a history of multiple respiratory infections and diarrhea. Based on his genetic examination, chest imaging, and alveolar lavage fluid examination, he met the diagnostic criteria for PAP and XLA. In addition, his laboratory test results did not find GM-CSF autoantibodies, and genetic testing did not identify gene mutations related to PAP[2] (such as surfactant protein B, surfactant protein C, ABCA3, NKX2-1, and GM-CSF receptor genes). No respiratory pathogens were detected in blood, sputum and alveolar lavage fluid. His mother, brother, father and neighbors did not have PAP-related symptoms. Moreover, his residence was free from industrial pollution. Based on a previous analysis of the etiology of PAP, this patient's PAP was considered to be secondary to immunodeficiency.

At present, the most effective treatment for PAP is massive whole lung lavage[13]. Large volume whole lung lavage can directly remove the protein-like substances deposited in the alveoli, reduce macrophage inhibitory factors in the alveoli and distal bronchioles, improve the function of alveolar macrophages, and thus improve lung ventilation and function. However, for acquired PAP, we believe that the treatment of primary disease might be equally important. Tanaka-Kubota *et al*[3] studied children with PAP secondary to immunosuppression. In their study, the children only received lung lavage at the beginning, and the children's PAP symptoms improved, but soon relapsed. After cell transplantation, long-term relief of the symptoms of PAP was achieved. All cases (our report and Tanaka–Kubota's studies) suggest that XLA was a secondary cause of PAP which improved with IVIG treatment.

CONCLUSION

We describe a child with XLA and PAP. It is suggested that XLA may cause PAP, and immunotherapy was helpful in improving the prognosis of this child with PAP acquired due to immunodeficiency.

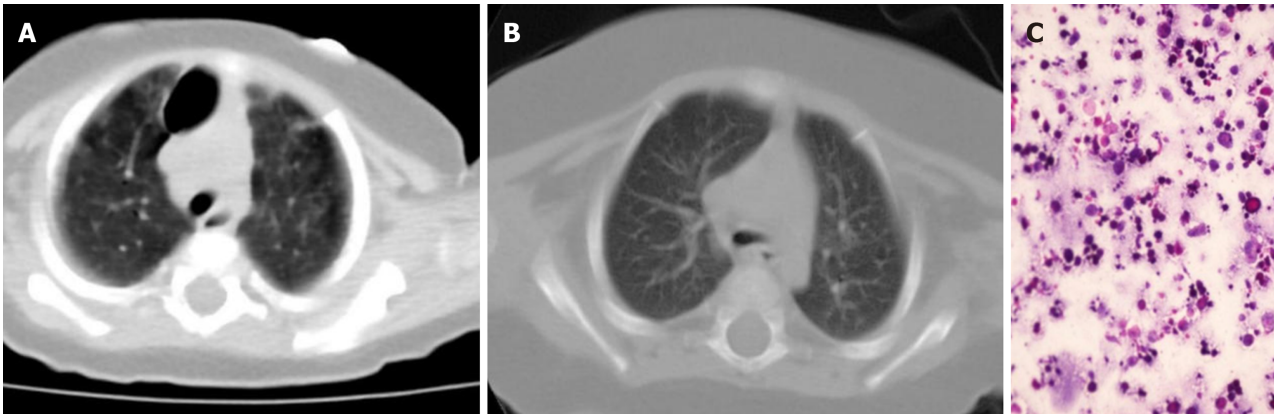

Figure 1 Lung imaging before and after treatment. A: Before treatment, the transparency of both lungs decreased, presenting as ground glass or butterfly-shaped changes, with a large bubble in the right upper lung; B: After alveolar lavage, there was a significant improvement in bilateral lung lesions; C: Periodic acid–Schiff staining of bronchoalveolar lavage fluid was positive.

FOOTNOTES

Co-first authors: Ting Zhang and Ming Li.

Author contributions: Zhang T managed the case, wrote and corrected the manuscript; Li X assisted with writing, correction, and reconstruction of the manuscript; All authors have read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: Xin Li 0000-0003-0337-5740.

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CASE REPORT

Gradient inflammation in the pancreatic stump after pancreaticoduodenectomy: Two case reports and review of literature

Tie-Gong Wang, Liang Tian, Xiao-Ling Zhang, Lei Zhang, Xiu-Lei Zhao, De-Shuai Kong

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Tie-Gong Wang, Lei Zhang, Xiu-Lei Zhao, De-Shuai Kong, Department of Surgery, Cangzhou Central Hospital, Cangzhou 061000, Hebei Province, China

Liang Tian, Xiao-Ling Zhang, Department of Pathology, Cangzhou Central Hospital, Cangzhou 061000, Hebei Province, China

Corresponding author: Tie-Gong Wang, MD, PhD, Attending Doctor, Department of Surgery, Cangzhou Central Hospital, No. 16 Xinhuaxi, Cangzhou 061000, Hebei Province, China. healthbycliff@gmail.com

Abstract

BACKGROUND

Postoperative pancreatic fistula (POPF) contributes significantly to morbidity and mortality after pancreaticoduodenectomy (PD). However, the underlying mechanisms remain unclear. This study explored this pathology in the pancreatic stumps and elucidated the mechanisms of POPF following PD.

CASE SUMMARY

Pathological analysis and 16S rRNA gene sequencing were performed on specimens obtained from two patients who underwent complete pancreatectomy for grade C POPF after PD. Gradient inflammation is present in the pancreatic stump. The apoptosis was lower than that in the normal pancreas. Moreover, neu-trophil-dominated inflammatory cells are concentrated in the ductal system. No-tably, neutrophils migrated through the ductal wall in acinar duct metaplasia-formed ducts. Additionally, evidence indicates that gut microbes migrate from the digestive tract. Gradient inflammation occurs in pancreatic stumps after PD.

CONCLUSION

The mechanisms underlying POPF include high biochemical activity in the pancreas, mechanical injury, and digestive reflux. To prevent POPF and address pancreatic inflammation and reflux, breaking the link with anastomotic dehi-scence is practical.

Key Words: Pancreaticoduodenectomy; Postoperative pancreatic fistula; Inflammation; Digestive reflux; Case report

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Core Tip: Postoperative pancreatic fistula (POPF) is a major complication of pancreaticoduodenectomy. However, the underlying mechanisms remain unclear. Compared to the relatively simple histological structure of the gastrointestinal wall, pancreatic stump is undoubtedly the crucial factor in the occurrence of POPF. This study systemically investigated the pathology in pancreatic stumps and provided insights into the underlying mechanisms of POPF. Gradient inflammation and digestive reflux are present in the pancreatic stumps. As the understanding of the role of inflammation in POPF increases, effectively managing the side effects of inflammation will bring about a significant possibility of terminating POPF.

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INTRODUCTION

Postoperative pancreatic fistula (POPF) is a mechanical issue caused by the leakage of fluid from the pancreatic remnant into the abdominal cavity when pancreatic anastomosis fails[1]. It is a significant contributor to postoperative morbidity and mortality after pancreaticoduodenectomy (PD) and results in high social and financial costs. Currently, no effective strategies have been developed to prevent POPF[2,3].

Long-term clinical observations have suggested that postoperative pancreatitis (POP) correlates with the occurrence of POPF after PD[4,5]. Analysis of drained fluids and animal studies provide indirect evidence linking trypsinogen activation and inflammation around the site of pancreatoenteric anastomosis to the onset of POPF on the first postoperative day[6]. However, the exact mechanisms behind POPF and the pathology in the pancreatic stump remain unclear[7,8]. At present, the limited sample size of pancreatic stumps at each center has stunted the comprehensive analysis of POPF. This study aimed to investigate the pathology and microbiology of pancreatic stumps and elucidate the underlying mechanisms of POPF.

The diagnosis and classification of pancreatic fistula in this study followed the guidelines of the International Study Group on Pancreatic Fistula[9]. A grade A POPF is characterized as a leak with no significant clinical effects, while grades B and C POPFs are considered clinically relevant due to their impact on the patients' health.

CASE PRESENTATION

Chief complaints

Case 1: A 60-year-old female who reported yellow urine for 20 d.

Case 2: A 66-year-old male who found jaundice for three months.

History of present illness

Case 1: 20 d ago, the patient noticed yellow urine and sought treatment at a local hospital for gastric disease, but there was no improvement. The patient began experiencing poor appetite, accompanied by an aversion to greasy food, upper abdominal bloating, occasional clay-colored stools, and itching skin. There were no symptoms of fever, acid reflux, nausea, vomiting, or chest tightness.

Case 2: The patient first presented with generalized jaundice without any obvious cause three months ago, accompanied by yellowing of the eyes and urine. There was no nausea, vomiting, abdominal pain, or bloating. The patient did not experience fever, chills, diarrhea, urgency after defecation, or loss of appetite.

History of past illness

Case 1: The patient underwent an appendectomy 43 years ago; has a three-year history of diabetes and hyperlipidemia.

Case 2: Two months ago, the patient experienced a lacunar stroke.

Personal and family history

Neither patient had a personal or family history of similar diseases.

Physical examination

Those two patients had similar performance. The patients are lucid and in good spirits. The skin and sclera of the entire body are jaundiced. The abdomen is flat, with no visible peristalsis or wave-like movements. There is no tenderness, rebound tenderness, or muscular tension throughout the abdomen. The liver and spleen are not palpable, and Murphy's sign is negative. Abdominal percussion produces a tympanic sound, and shifting dullness is negative. There is no per-

cussion pain in the liver area or bilateral renal area. Bowel sounds are present and normal.

Laboratory examinations

The laboratory test results for these two patients both indicate obstructive jaundice, accompanied by elevated levels of carbohydrate antigen 199.

Pathology and apoptosis: Two experienced pathologists independently evaluated the pathology without prior knowledge of clinical information. The specimens were cut into 4-μm-thick sections and stained with hematoxylin and eosin for pathological examination. The presence of pancreatic ducts and centroacinar cells was detected using a mouse anti-cytokeratin 19 (CK19) antibody (ZM-0074; OriGene Technologies), followed by a secondary antibody using the ultraView Universal Diaminobenzidine (DAB) Detection Kit (Roche).

The inflammatory index was calculated using a histological scoring system for acute pancreatitis, including edema, inflammatory cell infiltration, and necrosis[10]. Furthermore, the occurrence of apoptosis was assessed using a terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay with a Cell Death Detection Kit from Roche. The cell nuclei were stained with TUNEL to visualize apoptosis. Pancreatic head tissue was used as a control to define the normal level of inflammation and apoptosis.

Microbiome and 16S rRNA bacterial gene sequencing: DNA was extracted from each sample, preserved in formalin, and embedded in paraffin (Norgen BioTek, Thorold, ON, Canada). Thirty nanograms of DNA were obtained from each sample and subjected to polymerase chain reaction (PCR) amplification. The hypervariable V3-V4 regions were targeted using primers 338F (5′-ACTCCTACGGGAGGCAGCA-3′) and 806R (5′-GGACTACHVGGGTWTCTAAT-3′) for amplification, which consisted of the following steps: 30 s at 94 °C, 30 s at 50 °C, and 60 s at 72 °C, which were repeated for 30 cycles. The PCR products were evaluated by agarose gel electrophoresis at 170 voltages for 30 min on a 1% (w/v) gel with 600 ng of amplified DNA in each well.

Purified PCR products were sequenced using a MiSeq platform (Illumina, United States), and image analysis, base calling, and error estimation were performed using the Illumina Analysis Pipeline (Version 2.6). Sequences shorter than 230 bp with low-quality scores, containing ambiguous bases, or those that did not match the primer sequences and barcode tags were screened. The qualified reads were grouped into operational taxonomic units (OTUs) with a similarity level of 97%. Alpha diversity indices were calculated and presented as Chao's, Shannon-Wiener's, and Simpson's indices and the number of OTUs[11]. The distances between samples were determined using principal component analysis (PCA)[12]. PCA is a multivariate analysis that reduces data dimensionality while preserving covariance. The most attractive property of PCA is that the distances between clusters reflect their genetic and geographical distances[13]. The evolutionary distances between the microbial communities in each sample were calculated using Bray-Curtis algorithms and observed using an unweighted pair group method with an arithmetic mean (UPGMA) clustering tree to show dissimilarity (1-similarity) at the phylum, class, order, family, and genus levels[14].

Statistical analysis: Statistical analysis was conducted to determine the significance of the results. One sample *t*-test was employed in the microbial analysis. A *P*-value of less than 0.05 was considered statistically significant, and all calculations were carried out using IBM SPSS statistics version 26.0.

Pathology in the pancreatic stumps: The pancreatic stumps exhibit widespread inflammation and other pathological alterations. Subcapsular hematoma is common and extends deep into the parenchyma surrounding the suture, whereas it is relatively sparse in the tail. Neutrophils were the dominant inflammatory cells that infiltrated the glandular and interlobular structures (Figure 1A, B, and D). Necrotic foci were scattered throughout the stump, with the center exhibiting homogeneous staining and surrounded by plasma cells, neutrophils, lymphocytes, and eosinophils (Figure 1C).

Apoptotic activity in the pancreatic head decreased or disappeared after POPF, resulting in cell proliferation throughout the stump (Figure 1H and I). The glandular lobes were swollen with disrupted and dispersed acini, acinar cell nuclei increased in size, and chromatin density was reduced (Figure 1A-C). Gradient inflammation is observed in the stump.

Inflammatory and red blood cells (RBC) were also concentrated in the ductal system, including the main pancreatic duct, interlobular duct, and abnormal ducts formed by acinar duct metaplasia (ADM) (Figure 1D and E). Notably, the concentration of neutrophils in the ductal system was significantly higher than that in the local vasculature. The ducts formed by the ADM are the weakest parts of the entire ductal network, where the blood-duct barrier is destroyed. The increased permeability of the ductal system allows the migration of blood cells, particularly neutrophils, from the blood vessels into the space between the acinar cells and basal membrane and then into the lumen of the ductal system (Figure 1G). ADM could be detected throughout the entire pancreatic stump, exhibiting no discernible pattern in its distribution. Moreover, the ductal system was unfavorable for the survival of blood cells as they decomposed (Figure 1E and F). RBCs lose their membranes, and neutrophils are decomposed, leaving fragmented nuclei.

The expression of CK19 becomes strongly positive in the pancreatic stump compared with that in the normal parenchyma (Figure 1J and K). During ADM, acinar cells lose their normal shape and function and transform into ductal-like cells. Moreover, the ducts formed by ADM differed significantly in appearance from normal ducts and were characterized by duck-like cells and irregular lumens (Figure 1L). The original acinar cells were either pushed aside by the newly formed duct-like cells or incorporated into the newly formed ducts. Furthermore, it seems that the pressure in the lumen increased, resulting in the dilation of the regional ducts formed by the ADM (Figure 1M).

Microbial distribution and digestive reflux in pancreatic stumps: We conducted microbial analyses, including bacterial and fungal analyses, on both patients. Unfortunately, the vast majority of the fungal sequences could not be identified, so

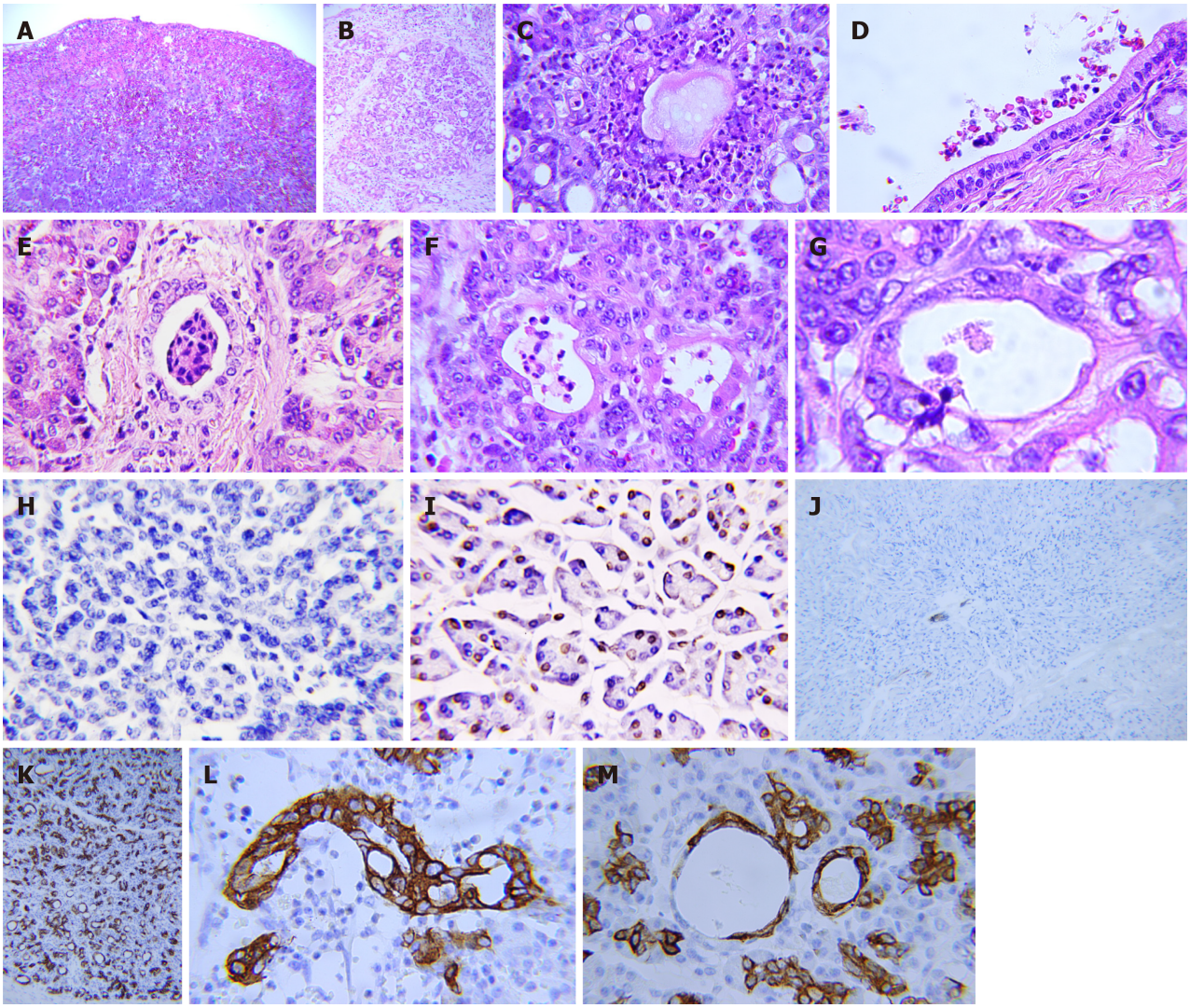


Figure 1 Pathology in the pancreatic stump with postoperative pancreatic fistula after pancreaticoduodenectomy. A: Subserosal hematoma; B: Infiltration of inflammatory cells in glandular lobes and interlobular structures; C: Necrotic foci; D: Concentration of inflammatory cells and red blood cells in the main pancreatic duct; E: Destruction of inflammatory cells in the interlobular duct; F: Decomposition of inflammatory cells in the acinar duct metaplasia (ADM)-formed ducts; G: Transmigration of a neutrophil through the ADM-formed duct; H: Weakening or disappearance of apoptosis in the pancreatic stump after pancreaticoduodenectomy (transferase dUTP nick-end labeling); I: Normal level of apoptosis in control tissue of the pancreatic head before the postoperative pancreatic fistula (transferase dUTP nick-end labeling); J: Normal level of cytokeratin 19 (CK19) expression in the pancreas; K: Strong expression of CK19 in the pancreatic stump after pancreaticoduodenectomy; L: Malformation of the ADM-formed duct; M: Dilatation of the ADM-formed ducts.

we focused solely on the bacteria. The length of the sequence was 400-440 bp. For further analysis, we selected a subset of 26301 tags from each sample in the patient 1 and 31277 tags in the patient 2. The alpha diversity indices are presented in Table 1. Our analysis revealed a statistically significant increase in OTUs in the stump compared to those in the duodenum (P = 0.000 for patient 1, P = 0.042 for patient 2), but no significant difference was observed in the pancreatic head (P = 0.729 in patient 1, P = 0.161 in patient 2).

At the genus level, the most common bacteria found in the patient 1 samples are *Bacillus*, *Bacteroides*, *Escherichia-Shigella*, and *Faecalibacterium*, along with some unidentified species. The most abundant genera are Bacillus, Comamonas, Stenotrophomonas, Bacteroides, and Pelomonas.

Furthermore, the dominant bacterial species exhibited a declining distribution with increasing distance from the transection plane. The dissimilarity and variability of the samples are shown in Figure 2A and B. The distances between the samples demonstrated a much more clustered distribution in the patient 1 than in the patient 2 through PCA. However, the proportion of bacterial DNA and microbiome in the samples varied in the jejunum, pancreatic head, and pancreatic stump. The UPGMA clustering analysis indicated that the microbial community distribution adjacent to the transection plane in these two patients was similar to that in the jejunum (Figure 2C and D). The preoperative distribution of bacterial DNA in the pancreatic head was comparable to that in the pancreatic tail, where the inflammatory response was relatively slow.

Table 1 Bacterial alpha diversity indices in the jejunum, pancreatic head, and stump

Sample ID	Clean_Tags	Final_Tags	Chao's index	Shannon-Wiener's index	Simpson's index	OTUs
PLDB0	158140	26301	52.20	1.01	0.24	34
PLPB0	33717	26301	332.00	5.08	0.85	318
PLPB1	54270	26301	522.35	1.68	0.34	324
PLPB2	59038	26301	422.91	1.81	0.36	249
PLPB3	27489	26301	339.00	1.72	0.36	250
PLPB4	33657	26301	207.33	1.62	0.41	109
PLPB5	29017	26301	405.02	2.05	0.41	310
PLPB6	44928	26301	487.23	4.08	0.69	439
PLPB7	115402	26301	444.89	6.06	0.96	338
PLPB8	168118	26301	537.00	6.48	0.97	418
PZDB0	165233	31277	140.00	1.25	0.32	35
PZPB0	183971	31277	100.50	2.00	0.47	89
PZPB1	47561	31277	68.00	1.48	0.34	44
PZPB2	38512	31277	241.87	1.45	0.31	189
PZPB3	48707	31277	86.10	1.04	0.27	49
PZPB4	32320	31277	241.97	1.27	0.28	184
PZPB5	34351	31277	275.18	2.04	0.47	183
PZPB6	65726	31277	408.28	6.00	0.95	381

OUT: Operational taxonomic units.

Imaging examinations

Case 1: Computed tomography (CT) examination showed that there was a mass in the middle and lower sections of the common bile duct, with dilation of the intrahepatic and extrahepatic bile ducts.

Case 2: Magnetic resonance imaging suggested a duodenal mass, and a biopsy confirmed it as duodenal adenocarcinoma.

FINAL DIAGNOSIS

Case 1

Biliary carcinoma.

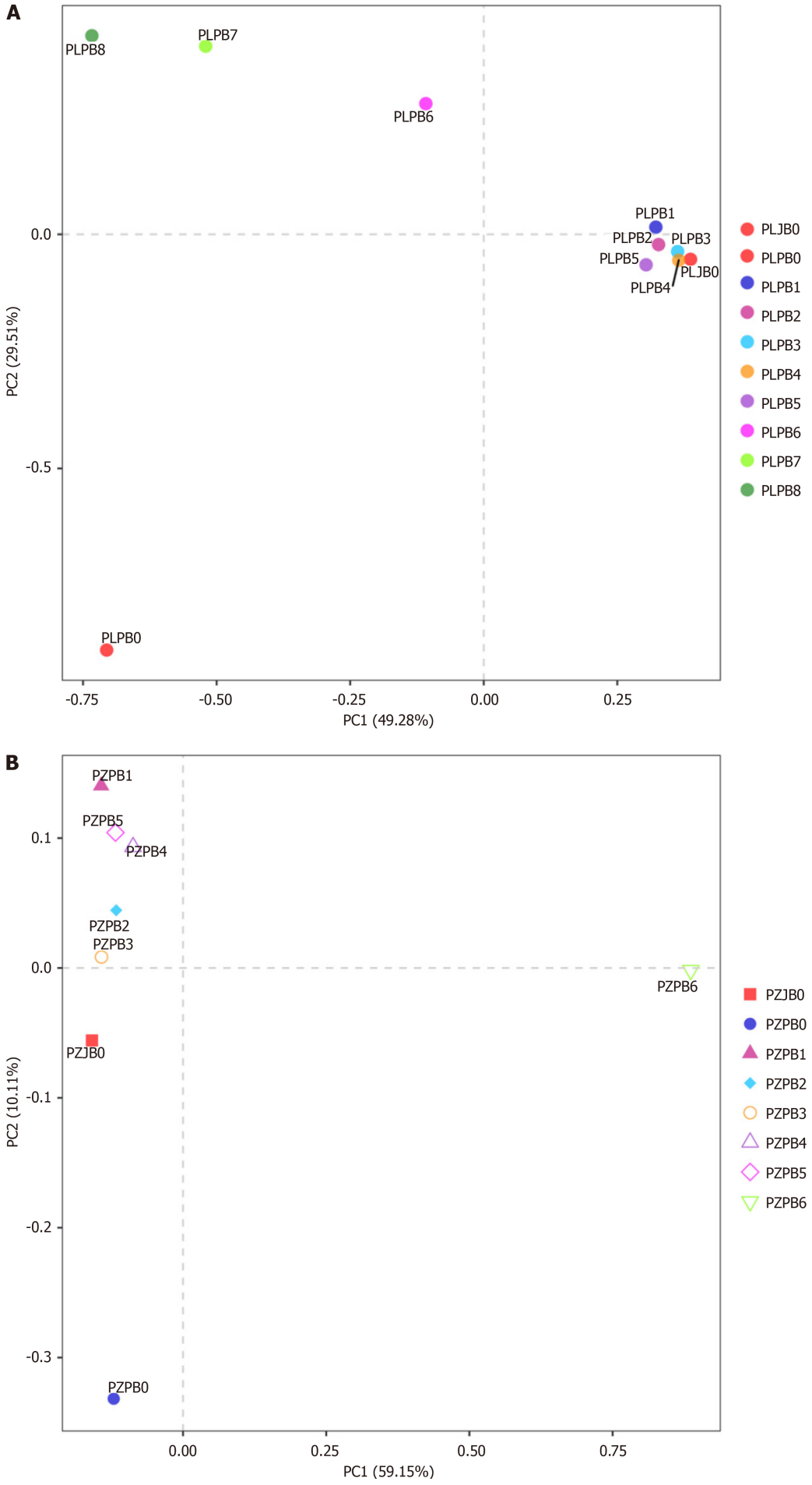
Case 2

Duodenal carcinoma.

TREATMENT

Those two patients accepted conventional PDs. The pancreas was transected at the neck in front of the portal vein, and a modified Blumgart anastomosis was performed in all cases. A U-suture was placed 1 cm from the transection plane. Then, 3-0 polypropylene and 5-0 polydioxanone (both from Ethicon) were used in the outer and inner layers. Catheters with a range of 5-8 Fr were placed in the stump and fixed using anchoring sutures.

POPF happened in both cases within 6 d postoperatively. And those two patients accepted total pancreatectomy after life-threatening and repeat abdominal bleeding. We collected two pancreatic stump samples measuring 12 cm × 6 cm × 3 cm and 12 cm × 4 cm × 2 cm. Eight and six slices of the specimens were sequentially obtained with an interval of 1.5-2.0 cm from the transection plane to the pancreatic tail. In addition, patient-matched specimens from the jejunum and pancreatic head, labeled PLJ0, PLP0, PZJ0, and PZP0, were obtained from prior surgeries and used as controls.


A
PLPB8
PLPB7
PLPB6
PLPB1
PLPB2
PLPB3
PLPB5
PLPB4
PLJB0
PLPB0
0.0
-0.5
PC2 (29.51%)
-0.75
-0.50
-0.25
0.00
0.25
PC1 (49.28%)
PLJB0
PLPB0
PLPB1
PLPB2
PLPB3
PLPB4
PLPB5
PLPB6
PLPB7
PLPB8
B
PZPB1
PZPB5
PZPB4
PZPB2
PZPB3
PZPB6
PZJB0
PZPB0
0.1
0.0
-0.1
-0.2
-0.3
PC2 (10.11%)
0.00
0.25
0.50
0.75
PC1 (59.15%)
PZJB0
PZPB0
PZPB1
PZPB2
PZPB3
PZPB4
PZPB5
PZPB6

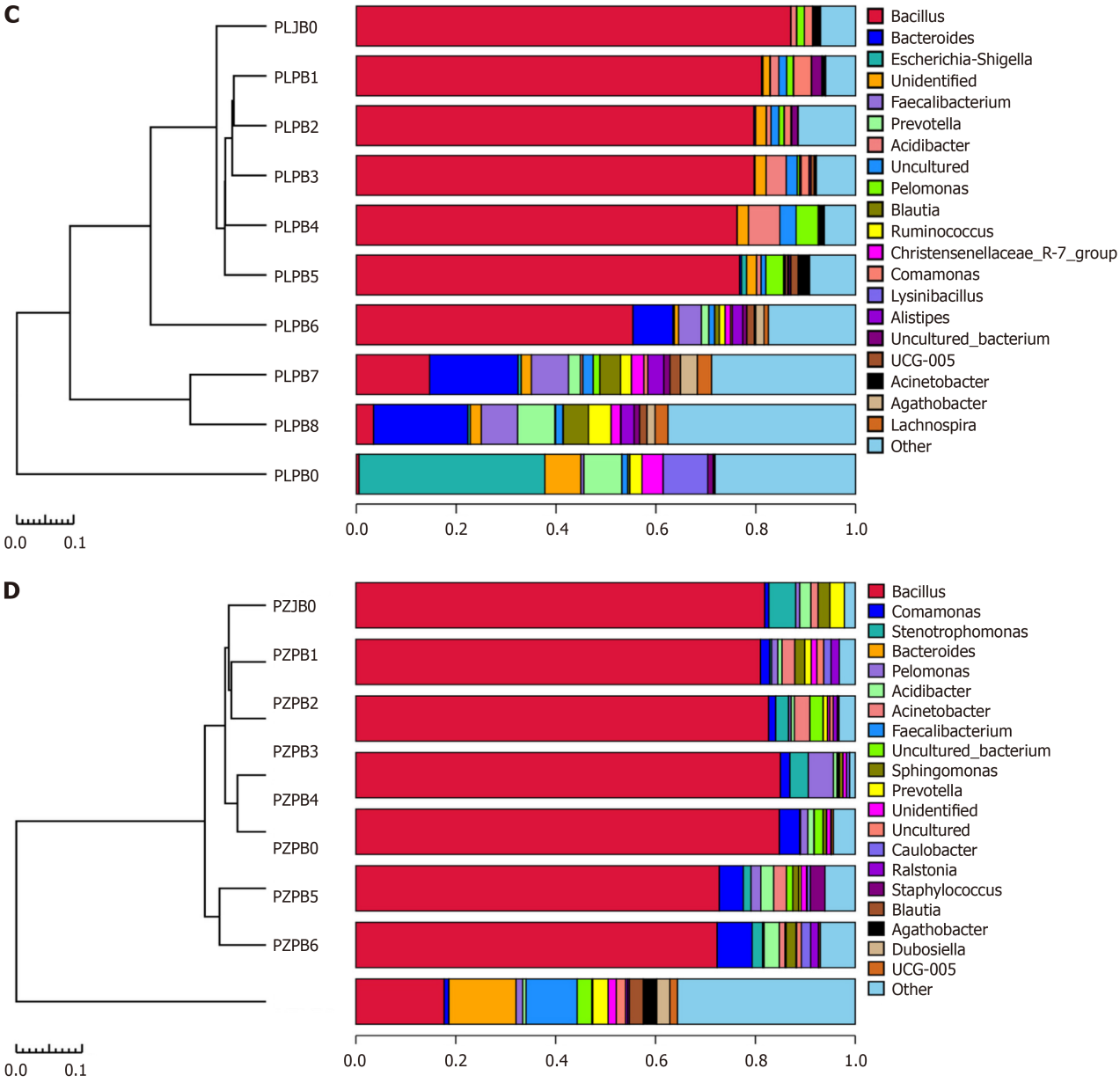


Figure 2 Principal component analysis and unweighted pair group method with arithmetic mean analysis of bacterial distribution in both patients' specimens. A: Principal component analysis (PCA) of bacterial distribution in patient 1; B: PCA of bacterial distribution in patient 2; C: Unweighted pair group method with arithmetic mean (UPGMA) clustering tree of the bacterial community in patient 1; D: UPGMA clustering tree of the bacterial community in patient 2. PLJB: Bacteria in patient 1's jejunum; PLPB: Bacteria in patient 1's pancreas; PZJB: Bacteria in patient 2's jejunum; PZPB: Bacteria in patient 2's pancreas.

OUTCOME AND FOLLOW-UP

Case 1

This patient passed away in the seventh month after surgery due to severe malnutrition and multiple organ disfunction syndrome.

Case 2

This patient passed away on the day 11 after the first surgery due to multiple infections and multiple organ disfunction syndrome.

DISCUSSION

POPF is a major and unresolved complication of PD. Recent studies have indicated that POPF is associated with POP; however, the exact mechanism remains unknown. One reasonable hypothesis suggests that the local activation of pancreatic enzymes triggers POPF, leading to increased damage to acinar cells, ischemia, manipulation of the gland, and

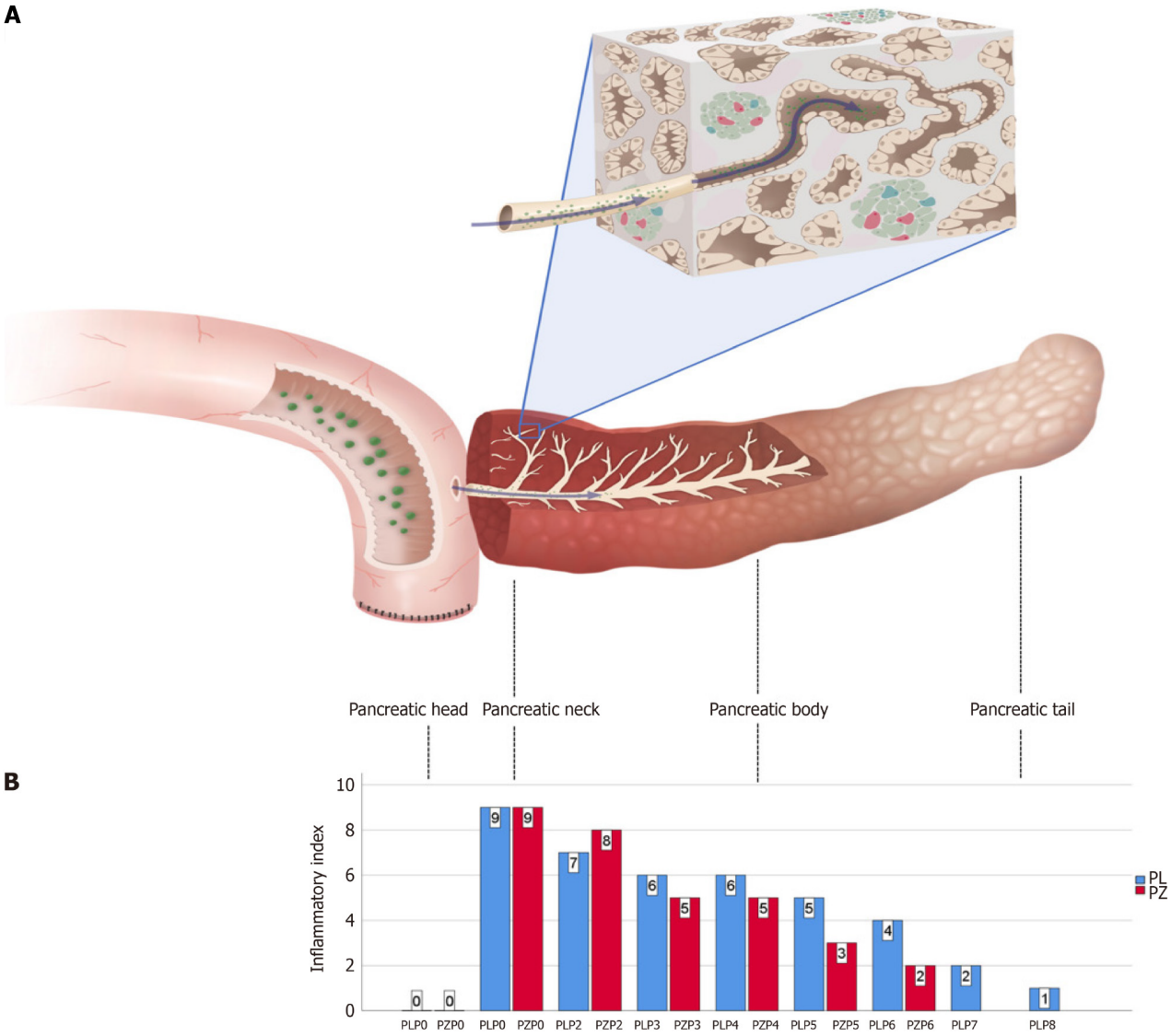


Figure 3 Gradient inflammation and digestive reflux in pancreatic stump after pancreaticoduodenectomy. A: Schematic representation of digestive reflux in pancreaticojejunostomy. The digestive fluid passes through the anastomosis and reaches deep into the pancreatic ductal system, accompanied by the high-level biochemical activity of the pancreas and mechanical injury, resulting in a gradient of inflammation in the stump; B: Inflammatory index in the pancreatic stump ranges from nine to one. The pancreatic heads are used as controls and labeled as PLP0 and PZP0.

blockage of the pancreatic duct[15]. However, no solid evidence for this has been reported to date.

No consensus exists currently regarding the definition of POP. Although serum amylase, lipase, and urinary trypsinogen levels are often used as diagnostic criteria for pancreatitis[16,17], previous studies utilizing CT imaging have found that only 26% of patients (13/50) showed radiological evidence of the condition[18].

Adults' acinar cells are highly plastic and can undergo trans-differentiation into a progenitor-like cell type with ductal characteristics, which has been linked to multiple mechanisms, including ductal ectasia[19], the activation of nuclear factor-kappaB[20], Notch receptors[21], and epidermal growth factor receptor[22]. ADM is a critical feature of the façade that militates pancreatic regeneration after injury and is an essential protective mechanism during pancreatitis[23].

Inflammation may drive ADM in pancreatitis cases[20]. In our study, ADM-induced ducts exhibited distinct morphological features that differentiated them from normal ducts, including increased lumen size and elongated ductal cells. Moreover, no previous studies have reported increased ductal permeability in patients with pancreatitis. However, a case study has documented the presence of neutrophil-predominant inflammatory cell infiltration, ADM, and fibrosis in a patient with pancreatitis induced by pembrolizumab[24]. Our study showed that the blood-duct barrier was destroyed, and the ducts formed by ADM served as sites for the transmigration of neutrophils and RBCs through the duct wall.

The significant accumulation of neutrophil-dominant inflammatory cells within the ductal system and the gradient distribution of bacteria from the intestine suggest that inflammatory agents originate from the intestine, traverse the site of anastomosis, and accumulate in the ductal system. Further evidence of this reflux is the decomposition of blood cells in the ductal system, as the activated enzymes in the system are not conducive to the survival of blood cells. Intra-acinar trypsin activation within the pancreas is enough to cause acute pancreatitis[25]. The reflux of digestive fluid could exacerbate local pancreatitis caused by mechanical injuries, such as sutures or dissection (Figure 3).

Theoretically, intestinal fluid can flow through the anastomosis site or stent into the stump and has the potential to activate trypsin during Blumgart anastomosis. However, the small size of the jejunal loop incision (2-3 mm) minimizes enteric fluid reflux. In contrast, invagination with pancreaticojejunostomy is associated with increased reflux[26]. This difference in reflux may explain why Blumgart anastomosis minimizes severe complications after PD[27]. Additionally, gastric juice performs less biologically than intestinal fluid, making pancreaticogastrostomy a safer alternative to pancreaticojejunostomy[28].

The main distinction between pancreaticojejunostomy and other digestive anastomoses is the high level of biological activity of the pancreas, which is characterized by its enzymatic secretory capacity[29]. Some researchers have suspected that suture placement is induced by the placement of sutures[6]. Our study found that suture placement can lead to parenchymal damage and the formation of suture-induced hematomas that extend deep into the parenchyma.

Based on these findings, the underlying mechanisms of POPF include high-level biochemical activity in the pancreas, mechanical injury, and digestive reflux. These three mechanisms contribute to the increased incidence and prolonged healing of POPF. The inflammatory response in the stump reached its peak on day 4 after PD and did not heal even 30 d after surgery.

Additionally, various risk factors, including soft tissue texture, small pancreatic duct[30], ischemia, ductal obstruction, excessive blood loss, high intraoperative fluid intake[31], elevated bilirubin level, large body mass index[32], low fibrosis [33], high acinar cell density, and acinar marginal content[34], increase the complexity of surgical maneuvers, resulting in anastomotic failure due to the heightened local tension created by inflammation and reflux.

Regardless of the surgical techniques employed, including stents[35], various methods of pancreaticojejunostomy and pancreaticogastrostomy[26], fibrin sealants, autologous tissue patches, bioabsorbable mesh[36], externally draining of pancreatic fluid[37], and the application of somatostatin[38], mechanical damage to the pancreas and digestive reflux cannot be entirely avoided. Therefore, surgeons have limited flexibility when treating each patient.

Due to the unavoidable suture and POPF, a paradox arises. Preventing pancreatitis in the stump or achieving a flawless and strong anastomosis for each patient is not possible. Nonetheless, implementing measures to eliminate reflux and prevent pancreatic fluid from entering the abdominal cavity in the event of anastomotic failure has great potential to mitigate the incidence and severity of POPF.

CONCLUSION

POPF is a complex condition that is caused by increased biochemical activity, mechanical damage, and digestive reflux. Currently, manipulation of the pancreatic stump and reflux into the pancreatic duct cannot be avoided. Based on these findings, stopping reflux and reducing inflammation in the pancreatic stump can decrease the occurrence of pancreatic fistulas. However, a more practical approach is to allow for the presence of inflammation and anastomotic dehiscence while controlling the proper flow of pancreatic juice, thereby breaking the logical relationship between anastomotic dehiscence and POPF.

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FOOTNOTES

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ORCID number: Tie-Gong Wang 0000-0001-6616-5930.

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CASE REPORT

Low interleukin-10 level indicates a good prognosis in *Salmonella enterica* serovar typhimurium-induced pediatric hemophagocytic lymphohistiocytosis: A case report

Yuan-Yuan Chen, Xiang-Zhi Xu, Xiao-Jun Xu

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Yuan-Yuan Chen, Xiao-Jun Xu, Division/Center of Pediatric Hematology Oncology, Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, China

Xiang-Zhi Xu, Pediatric Intensive Care Unit, Children's Hospital of Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang Province, China

Corresponding author: Xiao-Jun Xu, MD, Chief Doctor, Division/Center of Pediatric Hematology Oncology, Children's Hospital of Zhejiang University School of Medicine, No. 57 Zhugan Road, Hangzhou 310003, Zhejiang Province, China. xuxiaojun@zju.edu.cn

Abstract

BACKGROUND

Secondary hemophagocytic lymphohistiocytosis (sHLH) triggered by *Salmonella enterica* serovar Typhimurium is rare in pediatric patients. There is no consensus on how to treat *S. typhimurium*-triggered sHLH.

CASE SUMMARY

A 9-year-old boy with intermittent fever for 3 d presented to our hospital with positive results for *S. typhimurium*, human rhinovirus, and *Mycoplasma pneumoniae* infections. At the time of admission to our institution, the patient's T helper 1/T helper 2 cytokine levels were 326 pg/mL for interleukin 6 (IL-6), 9.1 pg/mL for IL-10, and 246.7 pg/mL for interferon-gamma (IFN-γ), for which the ratio of IL-10 to IFN-γ was 0.04. In this study, the patient received meropenem, linezolid, and cefoperazone/sulbactam in combination with high-dose methylprednisolone therapy (10 mg/kg/d for 3 d) and antishock supportive treatment twice. After careful evaluation, this patient did not receive HLH chemotherapy and recovered well.

CONCLUSION

S. Typhimurium infection-triggered sHLH patient had a ratio of IL-10 to IFN-γ ≤ 1.33, an IL-10 concentration ≤ 10.0 pg/mL, and/or an IFN-γ concentration ≤ 225 pg/mL at admission. Early antimicrobial and supportive treatment was sufficient, and the HLH-94/2004 protocol was not necessary under these conditions.

Key Words: Hemophagocytic lymphohistiocytosis; Cytokine pattern; Interferon gamma;

Interleukin-10; *Salmonella enterica* serovar Typhimurium; Case report

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Core Tip: *Salmonella enterica* serovar Typhimurium is one kind of pathogen that can trigger secondary hemophagocytic lymphohistiocytosis (sHLH). There is no consensus on how to treat *S.* Typhimurium-triggered sHLH. Compared to controls, an *S.* Typhimurium-triggered sHLH patient showed a ratio of interleukin-10 (IL-10) to interferon-gamma (IFN-γ) ≤ 1.33, an IL-10 concentration ≤ 10.0 pg/mL, and/or IFN-γ concentration ≤ 225 pg/mL on admission. The HLH-94/2004 protocol was not necessary, and early antimicrobial and supportive treatment was sufficient.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome composed of clinical findings such as fever, hepatosplenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in the bone marrow or spleen or lymph nodes, low or absent natural killer cell activity, and elevated levels of serum ferritin (SF) and soluble cluster of differentiation 25 (CD25)[1]. HLH comprises two conditions: primary HLH (pHLH) and secondary HLH (sHLH). pHLH occurs in the presence of an underlying predisposing genetic defect in the cytolytic pathway, whereas sHLH is acquired in the setting of an infectious, malignant, or autoimmune cause without genetic defects[2].

sHLH can be triggered by the Epstein-Barr virus (EBV)[3], cytomegalovirus[4], and *Salmonella enterica* serovar *typhimurium*[5,6], *etc. S. typhimurium* is a Gram-negative bacterium that depends on an essential inflammatory response to colonize the intestinal tract, causing self-limiting gastroenteritis in humans[7,8]. *S. typhimurium* alone, in some animal models, could be an independent trigger of sHLH[9]. Some pediatric patients infected with *S. typhimurium* progress to sHLH[10]. Cytokine storm syndrome is a life-threatening systemic inflammatory state characterized by elevated levels of circulating cytokines and immune cell hyperactivation[11]. In our previous study, we reported a specific cytokine pattern for HLH: interleukin 10 (IL-10) > 60 pg/mL, interferon gamma (IFN-γ) > 75 pg/mL, and IL-6 > 51.1 pg/mL[12]. Patients with a ratio of IL-10 to IFN-γ > 1.33 combined with IFN-γ ≤ 225 pg/mL were considered to have pHLH, whereas sHLH patients usually had a ratio of IL-10 to IFN-γ ≤ 1.33[13]. Moreover, an IL-10 concentration ≥ 456 pg/mL was an independent prognostic factor for early death[14].

In this study, a patient who developed HLH due to *S. typhimurium* infection is described. His IL-10 concentration was 9.1 pg/mL, and the ratio of IL-10 to IFN-γ was 0.04 at admission. Seven patients infected with *S. typhimurium* and three EBV-HLH patients were included as controls. The HLH patient did not receive chemotherapy, and after anti-infection therapy and supportive treatments, he recovered very well.

CASE PRESENTATION

Chief complaints

A 9-year-old Chinese boy was admitted to the hospital due to an intermittent fever for 3 d.

History of present illness

Approximately 3 d before admission, the patient presented with a fever of 39.3 °C without any inductive or provocative factors, and his complete blood count (CBC) showed pancytopenia. His white blood cell count was 2.33 × 10^9/L, his hemoglobin level was 96 g/L, and his platelet was 25 × 10^9/L. He did not have any symptoms of cough, vomiting, or diarrhea.

History of past illness

The patient had no relevant medical history.

Personal and family history

There were no special features in the patient's background or family history, and there was no consanguinity.

Physical examination

At the time of admission, the patient had an intermittent fever for 3 d. His abdomen was distended, and there was no

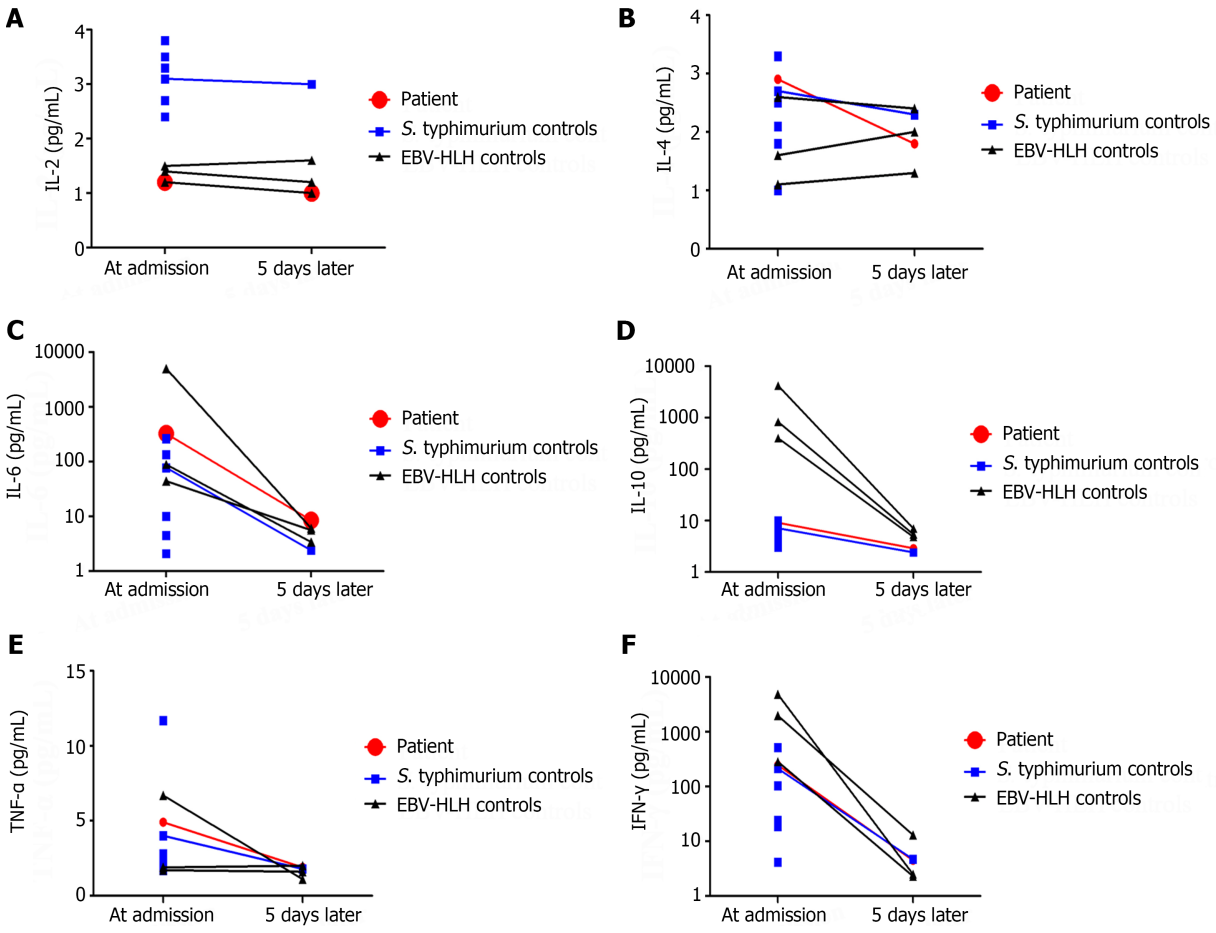

Figure 1 T helper 1/T helper 2 cytokine levels at admission and 5 d later. A: Interleukin 2 (IL-2) is shown for this patient, 7 *Salmonella enterica* serovar *typhimurium* (*S. typhimurium*)-infected controls, and 3 Epstein-Barr virus-hemophagocytic lymphohistiocytosis (EBV-HLH) controls; B: IL-4 is shown for the patient and controls; C: IL-6 is shown for the patient and controls; D: IL-10 is shown for the patient and controls; E: Tumor necrosis factor-alpha (TNF-α) is shown for the patient and controls; F: Interferon-gamma (IFN-γ) is shown for the patient and controls.

enlargement of the spleen or liver below his costal margins. No palpable lymphadenopathy was observed. Physiological reflexes were normal. The Bacillus Calmette-Guerin vaccination scar was normal, and no rashes were observed on his skin. The vital signs of the patient during hospitalization are shown in Table 1.

Laboratory examinations

His soluble CD25 concentration was 2646.9 pg/mL. Bone marrow biopsy revealed some hemophagocytic histiocytes and a decreased number of megakaryocytes. T helper 1/T helper 2 (Th1/Th2) cytokine levels, including those of IL-2, IL-4, IL-6, IL-10, tumor necrosis factor-alpha (TNF-α), and IFN-γ, were quantitatively determined with a human Th1/Th2 Cytokine Kit II (BD Biosciences, San Jose, CA, United States) during the course of the disease (Figures 1 and 2). The results of the CBC comparison (Figure 3), C-reactive protein, procalcitonin, fibrinogen, triglyceride, and SF levels are shown in Table 1. The other laboratory findings are shown in Table 2.

Imaging examinations

B-ultrasound of the abdomen and chest computed tomography showed no abnormalities.

FINAL DIAGNOSIS

The final diagnosis was sHLH due to *S. typhimurium* infection. The diagnosis of HLH was established on the basis of fever, cytopenia, hypofibrinogenemia, and hemophagocytosis in the bone marrow; elevated levels of SF; and increased soluble CD25, which fulfilled more than five criteria. The diagnosis of *S. typhimurium* infection was confirmed by blood culture.

Table 1 Clinical indexes from admission to discharge

Testing date	WBC as × 10^9/L	ALC as × 10^9/L	ANC as × 10^9/L	Hb in g/L	PLT as × 10^9/L	CRP in mg/L	PCT in ng/mL	Fib in g/L	TG in mmol/L	SF in mg/L	T in C	HR, times/min	RR, times/min	BP in mmHg	SpO2, %
September 25, 2022	2.33	0.57	1.63	96	25	10.88	2.32	2.23	1.03	> 1500	39.4	128	20	78/40	> 95%
September 26, 2022	2.74	0.83	1.8	109	36	11.52	2.8	1.93	1.39	> 1500	35.6	16	30	91/70	> 95%
September 27, 2022	2.75	0.76	1.91	98	26	6.2	2.6	NT	NT	NT	35.5	78	20	103/67	> 95%
September 28, 2022	2.14	0.82	1.2	87	76	2.69	NT	NT	NT	1835.0	35.8	74	18	105/73	> 95%
September 29, 2022	2.51	1.08	1.23	89	70	1.01	NT	1.26	NT	NT	36.0	77	19	100/75	> 95%
September 30, 2022	2.81	0.97	1.71	92	58	0.48	NT	1.12	1.7	NT	36.0	102	18	83/54	> 95%
October 2, 2022	4.82	3.03	1.58	87	37	0.64	NT	1.59	NT	725.2	37.3	86	20	86/60	> 95%
October 3, 2022	3.93	2.23	1.63	81	38	0.38	0.291	NT	NT	NT	37.1	72	22	72/44	> 95%
October 4, 2022	6.31	4.73	1.35	84	29	0.5	NT	NT	NT	NT	38.4	123	23	90/58	> 95%
October 5, 2022	4.11	2.72	1.19	77	31	0.87	NT	NT	NT	NT	37.9	112	22	82/57	> 95%
October 6, 2022	4.04	2.94	0.94	74	50	1.1	0.118	NT	NT	NT	38.6	154	28	87/56	> 95%
October 7, 2022	3.67	2.78	0.68	77	50	1.79	NT	NT	NT	NT	37.8	120	16	97/69	> 95%
October 8, 2022	3.73	2.99	0.55	75	50	1.37	NT	3.44	NT	384.5	37.6	136	22	75/51	> 95%
October 9, 2022	3.53	2.36	0.92	105	50	0.92	NT	NT	NT	NT	37.6	105	23	108/76	> 95%
October 10, 2022	3.98	3.05	0.69	93	48	0.9	NT	NT	NT	332.5	37.6	95	24	111/77	> 95%
October 11, 2022	4.78	3.64	0.88	99	56	1.3	0.096	NT	NT	NT	37.3	131	20	128/84	> 95%
October 12, 2022	5.89	4.78	0.73	98	54	1.08	NT	NT	1.11	NT	37.2	104	26	84/59	> 95%

October 14, 2022	5.1	4.05	0.66	97	56	1.14	NT	NT	NT	NT	37.2	117	22	97/60	> 95%
October 15, 2022	6.06	4.82	0.77	99	63	0.41	NT	NT	NT	NT	36.3	105	20	90/62	> 95%
October 16, 2022	7.05	5.69	0.88	101	74	0.41	NT	NT	NT	346	36.5	120	23	97/67	> 95%

ALC: Absolute lymphocyte count; ANC: Absolute neutrophil count; BP: Blood pressure; CRP: C-reactive protein; Fib: Fibrinogen; Hb: Hemoglobin; HR: Heart rate; NT: Not tested; PCT: Procalcitonin; PLT: Platelet count; RR: Respiratory rate; SF: Serum ferritin; SpO2: Pulse oxygen saturation; T: Temperature; TG: Triglyceride; WBC: White blood cell count.

TREATMENT

From September 25, 2022 to September 26, 2022, this patient received meropenem and linezolid anti-infection therapy. From September 26, 2022 to September 28, 2022, the patient received meropenem and high-dose methylprednisolone therapy (180 mg/d, body weight of 18.8 kg). From September 28, 2022 to October 11, 2022, the patient received cefoperazone/sulbactam as anti-infection therapy, and *S. typhimurium* was sensitive to the treatment. During the inpatient period, this boy experienced two episodes of shock, one on September 25, 2022 and one on October 3, 2022, during which time his blood pressure decreased to 78/40 mmHg and 72/44 mmHg, respectively. Both episodes of shock occurred after the patient developed a fever, and his body temperature eventually returned to normal. After antishock therapy, his vital signs stabilized. From October 11, 2022 to October 17, 2022, this patient received meropenem therapy again.

OUTCOME AND FOLLOW-UP

After careful evaluation, the patient did not receive HLH chemotherapy during the whole disease course and was discharged on October 17, 2022. During the nonhospitalization period, he was followed up by telephone for more than 1 year and recovered very well.

DISCUSSION

Currently, dexamethasone, etoposide, cyclosporine A, and ruxolitinib are the main choices for HLH treatment[15]. Reliable laboratory markers that can differentiate subtypes of HLH at an early stage would provide tremendous help for treatment. Several researchers have shown that elevated IL-10 levels are associated with a poor prognosis in HLH[16,17]. In this study, we examined 8 children infected with *S. typhimurium*, and only 1 of them fulfilled the diagnostic criteria for HLH. The IL-10 levels in this *S. typhimurium*-HLH patient and the 7 controls with *S. typhimurium* infection were lower than 10.0 pg/mL, while the levels of IL-10 in the 3 EBV-HLH patients were all greater than 10.0 pg/mL. In our clinical practice, different cytokine patterns for differentiating various HLH subtypes can be obtained within 5 h, and 88 patients with IFN-γ levels ≤ 225 pg/mL and a ratio of IL-10 to IFN-γ ≤ 1.33 have the best outcome, showing that this subtype has

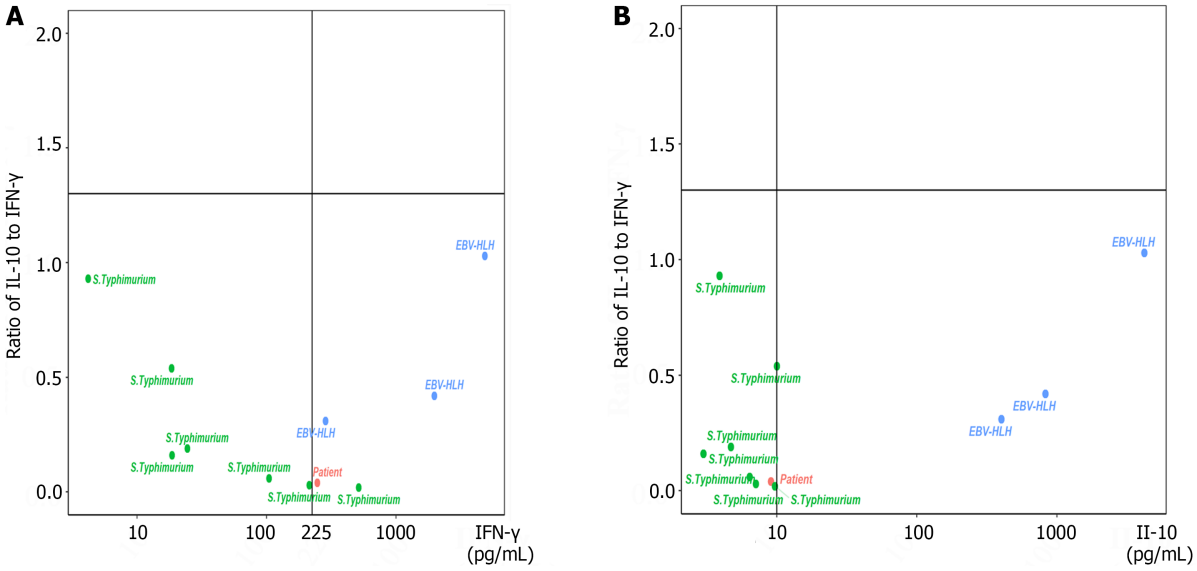

Figure 2 Four-quadrant models for differentiating secondary hemophagocytic lymphohistiocytosis patients with different features. A: Distribution of the patients, 7 controls infected with *Salmonella enteric* serovar *typhimurium* (*S. typhimurium*), and 3 Epstein-Barr virus-hemophagocytic lymphohistiocytosis (EBV-HLH) patients according to a four-quadrant diagram based on the ratio of interleukin-10 (IL-10) to interferon gamma (IFN-γ) > 1.33 or ≤ 1.33 and IFN-γ level > 225 pg/mL or ≤ 225 pg/mL; B: Distribution of the patients, 7 controls infected with *S. typhimurium*, and 3 EBV-HLH patients according to a four-quadrant diagram based on the ratio of IL-10 to IFN-γ > 1.33 or ≤ 1.33 and IL-10 level > 10 pg/mL or ≤ 10 pg/mL.

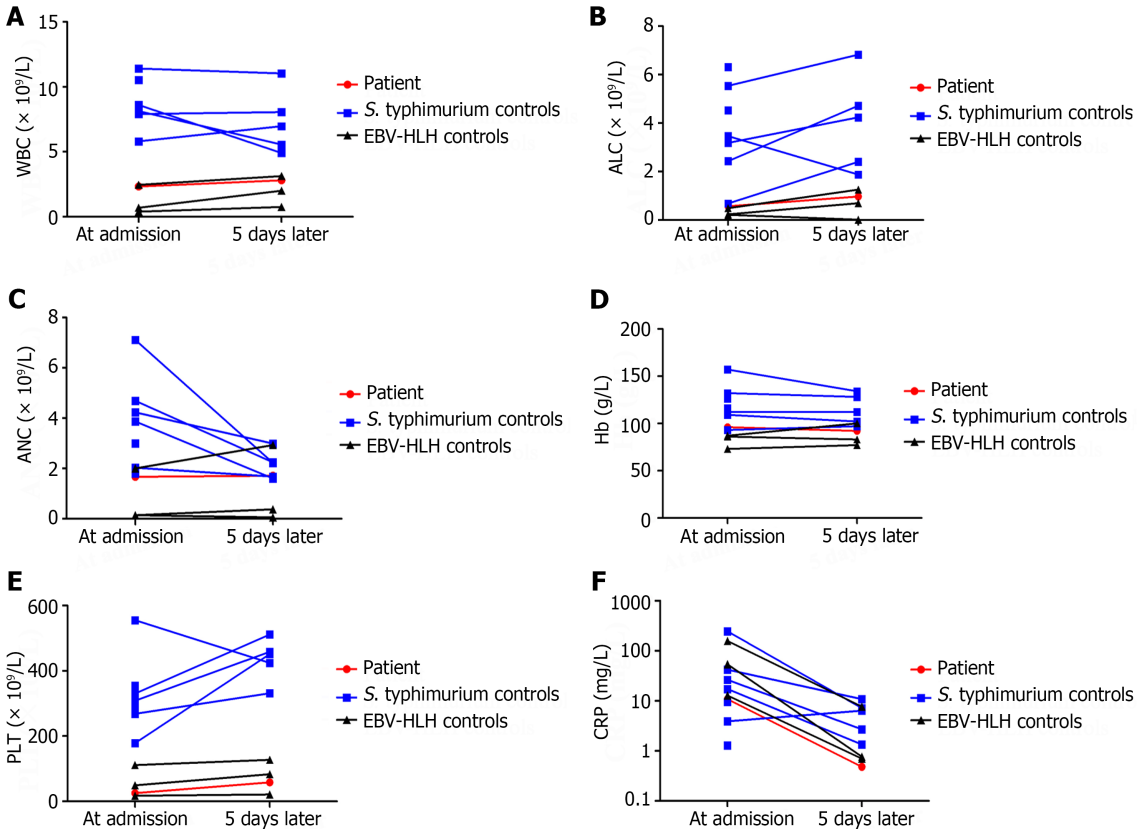

Figure 3 Complete blood count at admission and 5 d later. A: White blood cell (WBC) count of the patient, 7 *Salmonella enteric* serovar *typhimurium* (*S. typhimurium*)-infected controls, and 3 Epstein-Barr virus-hemophagocytic lymphohistiocytosis (EBV-HLH) controls; B: Absolute lymphocyte count (ALC) of the patient and controls; C: Absolute neutrophil count (ANC) of the patient and controls; D: Hemoglobin (Hb) of the patient and controls; E: Platelet (PLT) count of the patient and controls; F: C-reactive protein (CRP) of the patient and controls.

Table 2 Results of laboratory examinations after admission

Testing date	Laboratory examination items	Results
September 26, 2022	Nucleic acid detection of 13 pathogens from nasopharyngeal swab	Human Rhino Virus and Mycoplasma Pneumoniae were positive, and others were all negative
September 26, 2022	T-cell spot of tuberculosis assay	Negative
September 26, 2022	EBV antibodies	EBVCA-IgM was 1.26 U/mL, EBVCA-IgG was 10.9 U/mL, EBNA-IgG was more than 600 U/mL, EBEA-IgG was negative, and EBEA-IgM was 0.06 COI
September 26, 2022	EBV-DNA	0 copies/mL
September 28, 2022	Blood culture	*S. typhimurium* was positive
September 30, 2022	Widal test	FDSO, FDSH, FDSA, FDSB, and FDSC were all less than 1:40
October 1, 2022	Stool culture	Negative
October 1, 2022	Cerebrospinal fluid culture	Negative
October 4, 2022	Blood culture for the second time	Negative
October 7, 2022	Urine culture	Negative
October 7, 2022	Sputum culture	Negative
October 11, 2022	Bone marrow culture	Negative
October 17, 2022	Widal test for the second time	FDSO and FDSH were both 1:40, while FDSA, FDSB, and FDSC were less than 1:40

COI: Cut-off index; EBEA: EBV early antigen; EBNA: EBV nuclear antigen; EBV: Epstein-Barr virus; EBVCA: EBV viral capsid antigen; FDSB: Antigen of *Salmonella paratyphi* B; FDSC: Antigen of *Salmonella paratyphi* C; FDSO: O-antigen of *S. typhimurium*; FDSH: H-antigen of *S. typhimurium*; FDSA: Antigen of *Salmonella paratyphi* A; IgG: Immunoglobulin G; IgM: Immunoglobulin M.

the best outcome of all HLH subtypes[13], which was verified by this study.

There is no consensus on how to treat *S. typhimurium*-triggered sHLH, and early intervention is needed to improve outcomes in patients with HLH[18]. Most of the current research is empirical, and the decision-making process is relevant to the time point at which positive culture results are obtained and based on the clinician's experience. Several researchers have shown that antimicrobial and supportive treatment alone are effective[5,19-23]. However, many researchers have used both antimicrobial treatment and the HLH protocol to treat sHLH triggered by *Salmonella* infections[6,10,24]. In this study, after careful evaluation, our patient did not receive HLH chemotherapy during the whole disease course. After receiving meropenem, linezolid, and cefoperazone/sulbactam for anti-infection therapy combined with high-dose methylprednisolone therapy, the patient recovered very well.

This study had several limitations. First, it was impossible to precisely distinguish pHLH from sHLH, as this patient did not undergo pHLH-related gene examinations during the study period. Second, the 7 controls infected with *S. typhimurium* recovered well, and only some agreed to undergo a second recheck of their cytokines and CBC, which led to missing data. Finally, only 1 patient infected with *S. typhimurium* progressed to sHLH, and we could not perform a cohort analysis of specific cytokine patterns.

CONCLUSION

In summary, if a *Salmonella*-triggered sHLH patient has a ratio of IL-10 to IFN-γ ≤ 1.33, an IL-10 concentration ≤ 10.0 pg/mL, and/or an IFN-γ concentration ≤ 225 pg/mL at admission, early antimicrobial and supportive treatment may be sufficient. Eight weeks of dexamethasone treatment and the HLH-94/2004 protocol are not necessary under these conditions.

FOOTNOTES

Author contributions: Xu XJ was the principal investigator and takes primary responsibility for the manuscript; Chen YY and Xu XZ acquired and analyzed the data; Chen YY drafted the manuscript; Xu XJ and Chen YY revised the manuscript; All authors approved the final version to be published.

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accompanying images.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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Country/Territory of origin: China

ORCID number: Yuan-Yuan Chen 0000-0002-8206-1979; Xiang-Zhi Xu 0009-0004-1727-9068; Xiao-Jun Xu 0000-0003-1388-2535.

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CASE REPORT

Multi-systemic melioidosis in a patient with type 2 diabetes in non-endemic areas: A case report and review of literature

Huan-Yu Ni, Ying Zhang, Dong-Hai Huang, Feng Zhou

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Huan-Yu Ni, Feng Zhou, Department of Endocrinology, Puren Hospital, Wuhan University of Science and Technology, Wuhan 430080, Hubei Province, China

Huan-Yu Ni, School of Medicine, Wuhan University of Science and Technology, Wuhan 430080, Hubei Province, China

Ying Zhang, Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan 430071, Hubei Province, China

Dong-Hai Huang, Department of Rheumatology and Immunology, Puren Hospital, Wuhan University of Science and Technology, Wuhan 430080, Hubei Province, China

Corresponding author: Feng Zhou, MD, Doctor, Department of Endocrinology, Puren Hospital, Wuhan University of Science and Technology, No. 1 Benxi Road, Qianshan District, Wuhan 430080, Hubei Province, China. przhoufeng@sina.com

Abstract

BACKGROUND

Melioidosis, an infectious disease caused by *Burkholderia pseudomallei* (*B. pseudomallei*), occurs endemically in Southeast Asia and Northern Australia and is a serious opportunistic infection associated with a high mortality rate.

CASE SUMMARY

A 58-year-old woman presented with scattered erythema on the skin of her limbs, followed by fever and seizures. *B. pseudomallei* was isolated successively from the patient's urine, blood, and pus. Magnetic resonance imaging showed abscess formation involving the right forehead and the right frontal region. Subsequently, abscess resection and drainage were performed. The patient showed no signs of relapse after 4 months of follow-up visits post-treatment.

CONCLUSION

We present here a unique case of multi-systemic melioidosis that occurs in non-endemic regions in a patient who had no recent travel history. Hence, it is critical to enhance awareness of melioidosis in non-endemic regions.

Key Words: Melioidosis; *Burkholderia pseudomallei*; Endemic; Diabetes; Case report

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Core Tip: This case describes a patient with no history of travel to melioidosis-endemic areas, who accidentally contracted *Burkholderia pseudomallei* (*B. pseudomallei*) due to trauma caused by a fall in a non-endemic area, leading to a multi-system melioidosis. This case is beneficial in enhancing the understanding of melioidosis, and suggests that *B. pseudomallei* could emerge in other non-endemic regions with climate change.

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INTRODUCTION

Melioidosis is an endemic disease caused by *Burkholderia pseudomallei* (*B. pseudomallei*), which is mainly in tropical and sub-tropical areas, such as Southeast Asia, Northern Australia, and India, and is extremely rare in temperate regions[1-3]. *B. pseudomallei* is an environmental saprophyte found in soil, surface water, and groundwater[4]. Humans are likely infected through contaminated scratches and abrasions or the occasional aspiration of fresh water. Infections typically occur in the epidemic areas; sporadic cases are very rare, and melioidosis reported in other areas is essentially from imported cases of travelers or immigrants[5]. The most significant risk factors of melioidosis include diabetes, excessive alcohol use, chronic lung disease, chronic renal disease, thalassemia, immunosuppressive therapy, and cancer[6,7]. Melioidosis has been dubbed "the Great Imitator" given the absence of specific clinical features. Clinical and laboratory diagnoses of melioidosis are challenging[7,8]. Although melioidosis is a serious opportunistic infection, the mortality rate is very high [7,9,10]. Timely diagnosis and treatment are key to reducing the mortality rate.

Herein, we report the clinical details of a patient with multi-systemic melioidosis caused by *B. pseudomallei* in Wuhan, Hubei Province of China, which is a non-endemic region.

CASE PRESENTATION

Chief complaints

The patient was admitted due to a 6-d history of fever.

History of present illness

Twenty days after the incident, the patient experienced painful erythematous swelling of the bilateral lesser thenar and erythema on her limbs (Figure 1). She was diagnosed with undifferentiated connective tissue disease because of limb skin erythema, left knee joint pain, and positive Sjogren's syndrome antigen B antibody. She began taking 30 mg prednisone daily for treatment. About 3 wk after prednisone therapy, the patient presented with chills, fever, headaches, frequent mic-turition, and other uncomfortable symptoms, with the highest temperature reaching 39.2 °C. Despite oral antibiotic therapy with 0.5 g amoxicillin (Amoxil) three times daily, the fever and headache did not subside.

History of past illness

She has had type 2 diabetes for more than 5 years, with no chronic kidney dysfunction or blood system diseases, among other conditions.

Physical examination

Upon examination, the patient was apyretic (body temperature: 36.5 °C), but generally unwell. The patient had a small erythematous patch with tenderness on the right forehead. Pathological examination revealed a frontal lobe abscess of brain (Figure 2). She was hemodynamically stable, and the results of her respiratory and cardiovascular examinations were perfectly normal. Her abdomen was soft, with no hepatosplenomegaly. She had scattered skin rashes on her limbs. The result of her neurological examination was normal.

Laboratory examinations

Blood biochemistry revealed elevated C-reactive protein (CRP) and erythrocyte sedimentation rate and normal white cell count and neutrophils. However, the red and white blood cell counts were positive in urine sediment analysis (Table 1).

Imaging examinations

Head computed tomography (CT) measurements were normal (Figure 3A). Brain magnetic resonance imaging (MRI) showed a T2-weighted-fluid-attenuated inversion recovery (Figure 3B) signal that was slightly hyperintense, involving the right frontal region with a 7.6 mm × 33 mm strip, suggesting subdural hematoma. The right frontal skin showed swelling (Figure 3C). A second brain MRI was performed 1 wk after the first one and showed that the subdural hema-

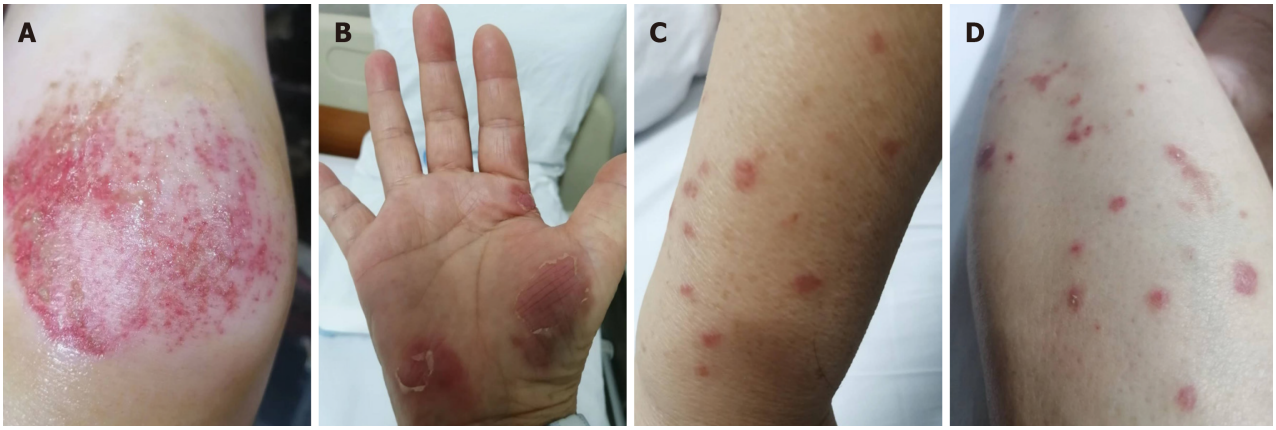

Figure 1 The patient developed dry asymmetric lesions on her limbs. A: Knee joint; B: Bilateral lesser thenar; C and D: Limbs.

toma and subcutaneous swelling at the right frontal region worsened (Figure 3).

FINAL DIAGNOSIS

Multi-systemic melioidosis; type 2 diabetes.

TREATMENT

Blood and urine cultures were performed on the 2nd day of admission. On the 3rd day of admission, the patient presented with sudden loss of consciousness and generalized seizure for a few seconds. The patient was diagnosed with epileptic seizure and treated with diazepam. On the 5th day of admission, blood and urine cultures revealed a gram-negative bacillus, *B. pseudomallei*, which is sensitive to ceftazidime, levofloxacin, cotrimoxazole, and meropenem. Ceftazidime (2 g every 8 h) was given according to the drug sensitivity test. The patient's fever resolved, and the rashes gradually subsided after therapy. After 1 wk of ceftazidime treatment, the patient again developed high fever (highest recorded temperature: 39.0 °C). Ceftazidime was discontinued and replaced with meropenem. The patient was treated with incision and drainage of the subcutaneous abscess in the right frontal region (Figure 4).

OUTCOME AND FOLLOW-UP

The patient showed no signs of relapse at the 4-month follow-up visit.

DISCUSSION

Melioidosis is regarded endemic to Southeast Asia and Northern Australia. In China, melioidosis often occurs in the southern areas, namely Hainan, Guangdong, Guangxi, and Fujian[11], and is very rare in other parts of China. Most of the sporadic cases reported in other parts of China are of patients with a travel history of endemic melioidosis. Although it is an endemic disease, melioidosis is a life-threatening disease caused by *B. pseudomallei*. Our patient presented multi-systemic involvement including the skin and soft tissue, genitourinary system, and central nervous system (CNS).

Cutaneous melioidosis (CM) has rarely been described compared with other systemic melioidosis[12]. CM may be a primary cutaneous infection or a disseminated secondary skin infection[13]. The common presentations of CM include ulcers, skin abscesses, single pustules, crusted erythematous lesions, and dry asymmetric erythematous flat lesions[13,14]. CM is often misdiagnosed as other diseases in non-endemic areas, because the skin manifestations and histologic results of CM are non-specific[15,16]. The dry asymmetric erythematous flat lesions in this patient were considered the main evidence for the diagnosis of undifferentiated tissue disease. The risk factors of melioidosis includes diabetes mellitus, excessive alcohol consumption, liver disease, chronic lung disease, chronic kidney disease, and steroid use[5,7,17-19]. Melioidosis patients with known diabetes have poor diabetic control and show a stunted *B. pseudomallei*-specific cellular response during acute illness compared with those without diabetes[20]. Uncontrolled blood sugar and steroid therapy are also important risk factors for the spread of melioidosis[19]. This patient showed typical melioidosis skin lesions such as painful erythematous swelling of the bilateral lesser thenar and erythema on the limbs, but the patient's condition was aggravated by misdiagnosis, diabetes, and steroid therapy.

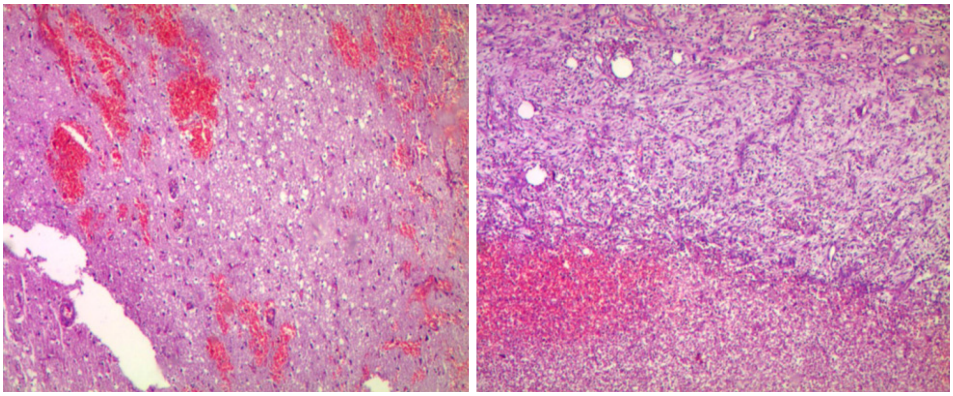

Figure 2 Pathological results of the patient's frontal lobe brain abscess.

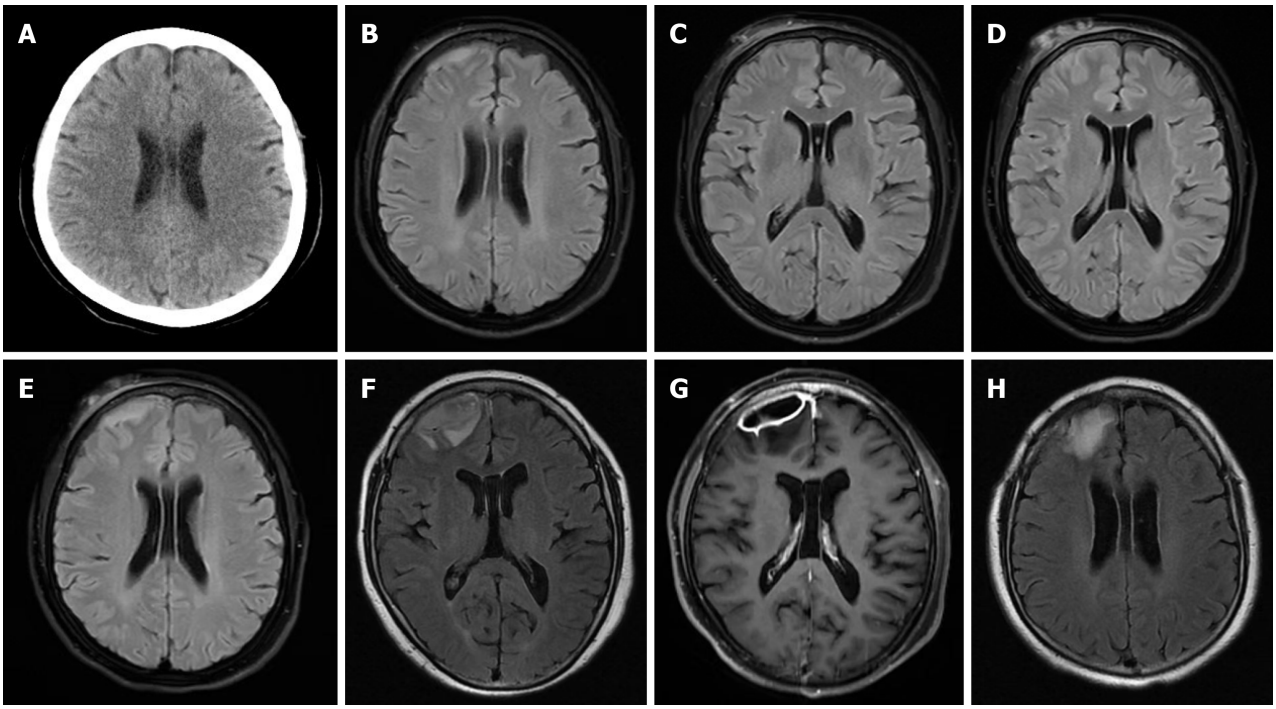

Figure 3 The patient presented radiographic features of neurological melioidosis. A: Head computed tomography measurements were normal; B: Brain magnetic resonance imaging (MRI) suggesting subdural hematoma; C: The right frontal skin showed swelling; D and E: A second brain MRI showed that the subdural hematoma and subcutaneous swelling at the right frontal region worsened; F: The third brain MRI showed an exacerbation of the subdural lesion in the right frontal lobe, with unclear demarcation between the lesion and the right frontal lobe, suggesting an intracranial infection; G: Enhanced MRI indicated the formation of a subdural abscess in the right frontal lobe; H: Two months post-surgery for an intracranial abscess, brain MRI showed gliosis at the surgical excision site.

Genitourinary melioidosis is common, accounting for 3.2%-14% of all melioidosis cases[7,21]. Genitourinary melioidosis occurs more frequently in male patients with complications such as prostatitis, prostatic abscess, renal abscess, epididymo-orchitis, and sepsis[7,22]. The clinical manifestations are mainly urinary frequency, dysuria, urinary retention, and swelling of the scrotum[22,23], and some patients may present septic shock[24]. Many white and red blood cells can be observed in urine[25]. Genitourinary melioidosis can be ruled out if the patient has no urinary symptoms or a negative urine test[26]. This patient also presented with urinary frequency and white and red blood cells in the urinalysis.

Neurological melioidosis is rare but has a high mortality rate[27,28]. In a patient series of 540 melioidosis, neuro-melioidosis accounts for only 3%-5%, but accounts for 21% of mortalities[7]. The neurological manifestations of melioidosis often include meningoencephalitis, myelitis, and spinal epidural abscess but rarely brain abscess[29,30]. Although the radiographic features of neurological melioidosis are not specific, CNS imaging is essential for locating lesions and identifying those that can be treated with surgery or biopsy so that appropriate treatment can be initiated in a timely manner[31,32]. In this case, head CT presented no abnormalities, and cerebral hemorrhage was misdiagnosed on head MRI. However, the subsequent head MRI revealed the progression of melioidosis and recorded the evolution of the patient's intracranial abscess. MRI is more sensitive for diagnosing neurological melioidosis than CT[33]. Therefore, serial head MRI is one of the important methods of diagnosing neurological melioidosis.

Table 1 Laboratory test results of the patient

Laboratory parameters	Day 1	Day 10	Day 21	Day 30	Day 38	Normal range
WBC (× 10^9/L)	6.96	4.52	4.15	6.73	4.05	3.5-9.5
Neutrophils (× 10^9/L)	4.81	2.88	1.51	3.69	2.88	1.8-6.3
RBC (× 10^{12}/L)	4.21	3.28	3.55	4.21	3.28	3.8-5.1
Platelets (× 10^9/L)	183.0	178.0	274.0	290.0	178.0	125-350
Alanine aminotransferase (U/L)	56.7	135.7	40.3	16.5	25.1	7-40
Aspartate aminotransferase (U/L)	22.1	138	21.1	18.5	56.0	13-35
Total protein (g/L)	69.4	70.5	71.8	78.8	64.8	65-85
Albumin (g/L)	36.1	35.1	36.0	36.6	39.0	40-55
Globulin (g/L)	33.3	35.2	35.8	35.8	25.8	20-40
Total bilirubin (μmol/L)	9.70	8.35	7.88	12.86	5.7	0-21
DBIL (μmol/L)	3.90	3.94	2.80	3.76	3.0	0-8
Blood urea nitrogen (mmol/L)	8.53	3.20	5.73	4.75	1.68	2.6-7.5
Creatinine (μmol/L)	57.8	63.4	54.4	71	55.7	41-73
Fasting blood glucose (mmol/L)	9.5	4.8	7.6	7.2	7.9	3.7-6.1
Creatine kinase (U/L)	16	-	-	30	-	40-200
Creatine kinase-MB (ng/mL)	1.0	-	-	1.6	-	0-5
Potassium (mmol/L)	3.66	5.11	4.2	4.58	4.23	3.5-5.3
Sodium (mmol/L)	131.2	137.5	130.3	136.2	138.6	137-147
Chloride (mmol/L)	94.3	97.9	93.3	102.0	105.	99-110
Calcium (mmol/L)	2.09	2.33	2.29	2.43	2.20	2.11-2.52
CRP (mg/L)	85.460	128.9	45.67	3.46	-	0-3
ESR (mm/h)	41	60	71	19	-	0-20
Hemoglobin A1c (%)	10.90		-	-	-	3-6.5
Urine WBC (cell/μL)	Positive	Negative	-	Negative	-	-
Urine RBC (cell/μL)	Positive	Negative	-	Negative	-	-

CRP: C-reactive protein; DBIL: Direct bilirubin; ESR: Erythrocyte sedimentation rate; RBC: Red blood cell; WBC: White blood cell.

The isolation of *B. pseudomallei* from clinical specimens is the gold standard for the diagnosis of melioidosis. However, *B. pseudomallei* can be easily thought of as a contaminant or confused with other bacteria[5], resulting in the misdiagnosis or delayed diagnosis of melioidosis. Blood cultures are the most important, but the positive rate of *B. pseudomallei* is only 50%-70% in blood culture[34,35]. In one series, only 29% of the brain tissue or 19% of the cerebrospinal fluid (CSF) samples were culture-positive[29]. *B. pseudomallei* was isolated from the samples of this patient's blood, urine, and right frontal subcutaneous abscesses, but not from CSF and intracranial abscess samples.

The laboratory markers associated with poor prognosis include leucopenia (especially lymphopenia), a normal or only slightly raised CRP, raised transaminases, bilirubin, urea, and creatinine, hypoglycemia, and acidosis[36,37]. CRP estimations may be helpful in ascertaining active infection in patients with low serum levels of specific immunoglobulin M antibody[38]; however, a normal level of CRP cannot be used to exclude acute, chronic, or relapsed melioidosis in febrile patients in endemic regions[39]. In this case, the level of CRP gradually decreased with the improvement of the patient's disease, and no serious increase in transaminases, bilirubin, and creatinine was noted. Because melioidosis is a serious threat to patients' health, the patient should immediately begin treatment instead of waiting until the culture results. The treatment of melioidosis consists of an intensive phase of at least 10-14 d of intravenous administration of ceftazidime, meropenem, or imipenem, followed by oral eradication therapy, usually with trimethoprim-sulfamethoxazole for 3-6 months[40,41]. Attention should also be paid to the risks of long-term antibiotic treatment. *B. pseudomallei* is resistant to penicillin, ampicillin, first-generation and second-generation cephalosporins, gentamicin, tobramycin, streptomycin, macrolides, and polymyxins[42,43], Thus, no therapeutic effect was noted when the patient first took amoxicillin. This patient was initially given ceftazidime according to the susceptibility testing upon admission, which was switched to meropenem because of fever during treatment with ceftazidime. The failure of ceftazidime treatment may be related to suppression of the immune system by steroid therapy and poor blood glucose control. Festic *et al*[44] showed that

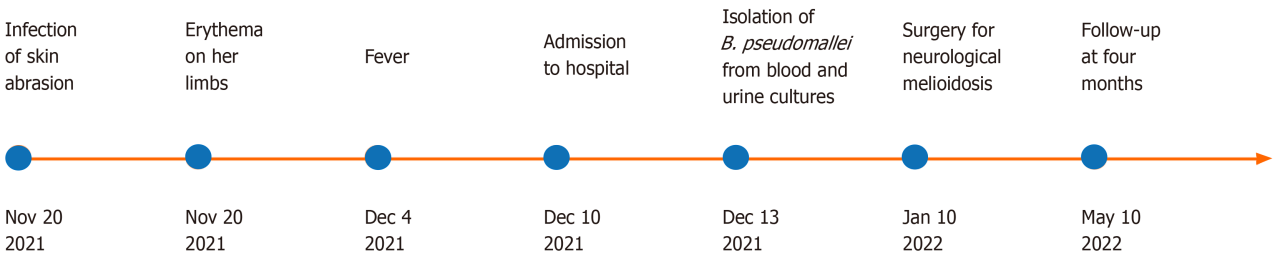

Figure 4 Timeline of the case.

glucocorticosteroids impact biofilm formation and antibiotic tolerance. Physicians who are unfamiliar with the treatment of melioidosis should follow the course of treatment recommended by the guidelines[45,46]. Although antibiotics are preferred for the treatment of multiple intracranial abscesses in melioidosis[47]. Adjunctive abscess drainage was performed in 58% cases. After treatment, 37% patients with CNS melioidosis recovered completely or nearly completely, 31% had moderate neurological improvement, while 13% did not recover and suffered neurological disability[48]. In our patient, the intracranial abscess gradually increased during the course of antibiotic treatment, so intracranial abscess drainage was performed, resulting in no further adverse neurological prognosis.

CONCLUSION

We present here a rare case of multi-systemic melioidosis in a female patient without a travel history in a non-endemic area. In this case, cutaneous and genitourinary melioidosis infection as well as intracranial melioidosis infection occurred. For melioidosis with poor response to antibiotics, the aggravation of infection leads to intracranial abscess for which abscess excision and drainage are an effective measure. We believe that this report will help improve the traditional understanding of melioidosis among the medical staff in non-endemic areas and provide an account of the clinical experience for the diagnosis and treatment of multi-systemic melioidosis.

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FOOTNOTES

Co-first authors: Huan-Yu Ni and Ying Zhang.

Author contributions: Ni HY, Zhang Y, Huang DH, and Zhou F have conducted many works in treatment and post-operative follow-up; Ni HY and Zhang Y sorted out all of the materials and wrote the manuscript; Zhou F and Huang DH revised the manuscript. Ni HY and Zhang Y contributed equally to this work as co-first authors; All authors approved the final version of the manuscript.

Informed consent statement: The patient provided written informed consent to participate in this study.

Conflict-of-interest statement: The authors have no conflicts of interests to declare.

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ORCID number: Ying Zhang 0000-0003-1422-3558; Feng Zhou 0000-0001-7678-556X.

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CASE REPORT

Endoscopic ultrasound-guided tissue sampling induced pancreatic duct leak resolved by the placement of a pancreatic stent: A case report

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

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Ki-Hyun Kim, Eunae Cho, Yohan Lee, Department of Internal Medicine, Chonnam National University Hospital, Gwangju 61469, South Korea

Chang Hwan Park, Department of Gastroenterology, Chonnam National University Hospital, Gwangju 61469, South Korea

Corresponding author: Chang Hwan Park, MD, PhD, Professor, Department of Gastroenterology, Chonnam National University Hospital, No. 42 Jebong-ro Donggu, Gwangju 61469, South Korea. p1052ccy@hanmail.net

Abstract

BACKGROUND

Pancreatic ductal leaks complicated by endoscopic ultrasonography-guided tissue sampling (EUS-TS) can manifest as acute pancreatitis.

CASE SUMMARY

A 63-year-old man presented with persistent abdominal pain and weight loss. Diagnosis: Laboratory findings revealed elevated carbohydrate antigen 19-9 (5920 U/mL) and carcinoembryonic antigen (23.7 ng/mL) levels. Magnetic resonance imaging of the pancreas revealed an approximately 3 cm ill-defined space-occupying lesion in the inferior aspect of the head, with severe encasement of the superior mesenteric artery. Pancreatic ductal adenocarcinoma was confirmed after pathological examination of specimens obtained by EUS-TS using the fanning method. Interventions and outcomes: The following day, the patient experienced severe abdominal pain with high amylase (265 U/L) and lipase (1173 U/L) levels. Computed tomography of the abdomen revealed edematous wall thickening of the second portion of the duodenum with adjacent fluid collections and a suspicious leak from either the distal common bile duct or the main pancreatic duct in the head. Endoscopic retrograde cholangiopancreatography revealed dye leakage in the head of the main pancreatic duct. Therefore, a 5F 7 cm linear plastic stent was deployed into the pancreatic duct to divert the pancreatic juice. The patient's abdominal pain improved immediately after pancreatic stent insertion, and amylase and lipase levels normalized within a week. Neoadjuvant chemotherapy was then initiated.

CONCLUSION

Using the fanning method in EUS-TS can inadvertently cause damage to the pan-

creatic duct and may lead to clinically significant pancreatitis. Placing a pancreatic stent may immediately resolve acute pancreatitis and shorten the waiting time for curative therapy. When using the fanning method during EUS-TS, ductal structures should be excluded to prevent pancreatic ductal leakage.

Key Words: Endoscopic ultrasound-guided tissue sampling; Pancreatitis; Pancreatic duct leak; Pancreatic stent; Case report

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Core Tip: Endoscopic ultrasound guided tissue sampling is a crucial procedure for histological diagnosis of pancreatic lesions, but it may occasionally be accompanied by unforeseen complications. The Fanning method is a technique that can enhance diagnostic accuracy, but it also carries the risk of unintended ductal injury. Here, we report a case where the use of the Fanning method during endoscopic ultrasound guided tissue sampling resulted in leakage of the pancreatic duct. We successfully managed this complication by performing pancreatic duct stent *via* endoscopic retrograde cholangiopancreatography.

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INTRODUCTION

Endoscopic ultrasound-guided tissue sampling (EUS-TS) has become the gold standard for histological diagnosis of solid pancreatic lesions[1,2]. Although EUS-TS is considered relatively safe, unexpected complications inevitably arise. Acute pancreatitis is one of the more severe complications of EUS-TS, as it can delay the surgical schedule of resectable lesions and can even make curative treatment impossible[3]. Pancreatic ductal leaks often complicate the situation, while recent treatment guidelines for acute pancreatitis, such as early feeding, can be counterproductive. EUS-TS puts patients at risk of developing pancreatic ductal leaks if normal pancreatic ducts are damaged during the procedure[4]. Fortunately, pancreatic ductal leaks can be adequately treated by placing a pancreatic stent to divert the leaking pancreatic juice into the duodenal lumen[5]. According to our review of English-language scientific literature, this is the first recorded case of a pancreatic ductal leak developing after timely EUS-TS treatment with pancreatic stent placement. Therefore, clinical suspicion is key to promptly diagnosing and treating pancreatic ductal leaks in patients who present with acute pancreatitis after EUS-TS. Herein, we present a case of acute pancreatitis caused by a pancreatic ductal leak after EUS-TS that was treated with a pancreatic stent.

CASE PRESENTATION

Chief complaints

A 63-year-old man visited the outpatient department with a weight loss.

History of present illness

The weight loss has been significant, with a decrease of 14 kg over the past two months, and upper abdominal pain was occurred 10 d ago.

History of past illness

He had been diagnosed with hypertension and diabetes mellitus four years earlier.

Personal and family history

He was a chronic alcoholic and a current smoker.

Physical examination

The physical examination showed tenderness in the epigastric area without rebound tenderness.

Laboratory examinations

His white blood cell count was 3500/mm^3 (reference value: 6000–10000/mm^3), lipase level was 120 U/L (reference value: 7–60 U/L), carbohydrate antigen 19-9 level was 5920 U/mL (reference value: < 37 U/mL), and carcinoembryonic antigen level was 23.7 ng/mL (reference value: 0–4.7 ng/mL). All other laboratory test results were within the normal ranges.

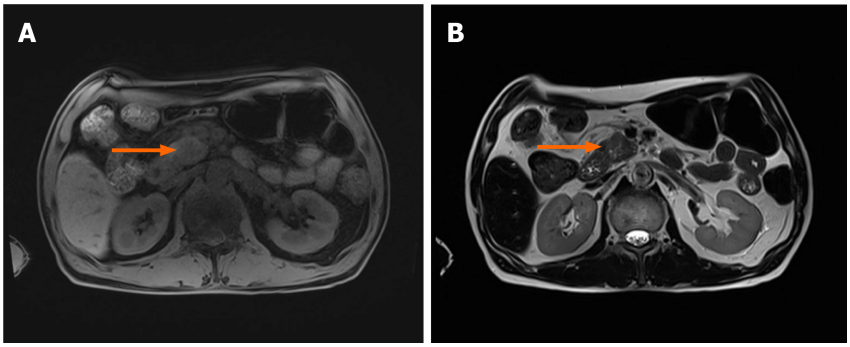

Figure 1 Magnetic resonance imaging. A and B: An approximately 3 cm, ill-defined, space-occupying lesion in the inferior aspect of the head with high signal intensity on T1- and T2-weighted imaging (orange arrows).

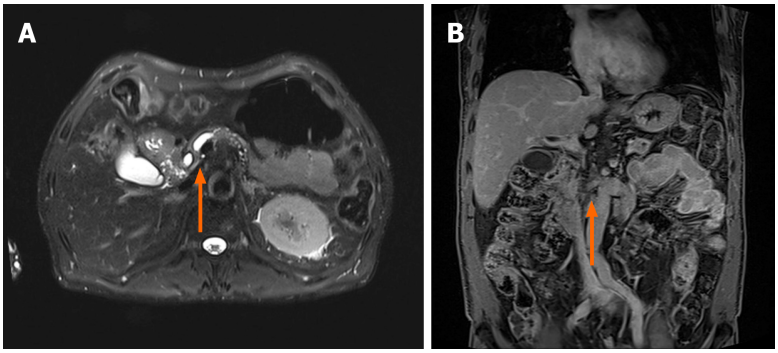

Figure 2 Magnetic resonance imaging. A: An ill-defined space-occupying lesion invading the distal common bile duct and main pancreatic duct, both of which were narrowed, and the upstream main pancreatic duct dilated (orange arrow); B: The lesion severely encased the superior mesenteric artery (orange arrow).

Imaging examinations

Magnetic resonance imaging of the pancreas showed an approximately 3 cm-sized, ill-defined space-occupying lesion in the inferior aspect of the head, with high signal intensity on T1- and T2-weighted imaging (Figure 1). The distal common bile duct and main pancreatic duct adjacent to the lesion were narrowed, the upstream main pancreatic duct was dilated, and the superior mesenteric artery was severely encased (Figure 2).

FINAL DIAGNOSIS

EUS-TS was performed for pathologic diagnosis, which demonstrated a 36.0 mm × 32.9 mm sized ill-defined, relatively heterogeneous, hypoechoic mass in the pancreatic head. EUS-TS was performed with a 22-gauge EZ shot (EZ shot 3 plus; Olympus, Tokyo, Japan) using the fanning method (Figure 3). Pathological examination confirmed a pancreatic ductal adenocarcinoma. The day after the procedure, the patient experienced severe abdominal pain in the right upper quadrant and epigastric areas. His follow-up amylase, lipase, and C-reactive protein levels were 265 U/L (reference range: 43–116 U/L), 1173 U/L (reference range: 7–60 U/L), and 27.7 mg/dL (reference range: 0–3 mg/dL), respectively. Computed tomography (CT) of the abdomen two days after EUS-TS revealed edematous wall thickening of the second portion of the duodenum with adjacent fluid collections and a suspicious leak from either the distal common bile duct or the main pancreatic duct in the head (Figure 4).

TREATMENT

During the initial endoscopic retrograde cholangiopancreatography (ERCP), selective biliary cannulation could only be achieved through the ampulla of Vater. Although no definitive dye leak from the distal CBD was observed, a 7F 7 cm double pigtail plastic stent (ZSO-7-7; Cook Medical, Indiana, United States) was deployed over the stricture to allow for effective biliary drainage (Figure 5). Selective pancreatic cannulation was attempted several times without success. Despite biliary diversion, the patient continued to experience severe abdominal pain for four days. Follow-up abdominal CT showed no resolution of the suspected leak, suggesting a pancreatic ductal leak. During the second ERCP, a separate orifice was observed below the biliary orifice, which was not observed in the first ERCP. Selective pancreatic cannulation was easily achieved through the orifice (Figure 6). As the pancreatogram showed a dye leak in the head portion of the

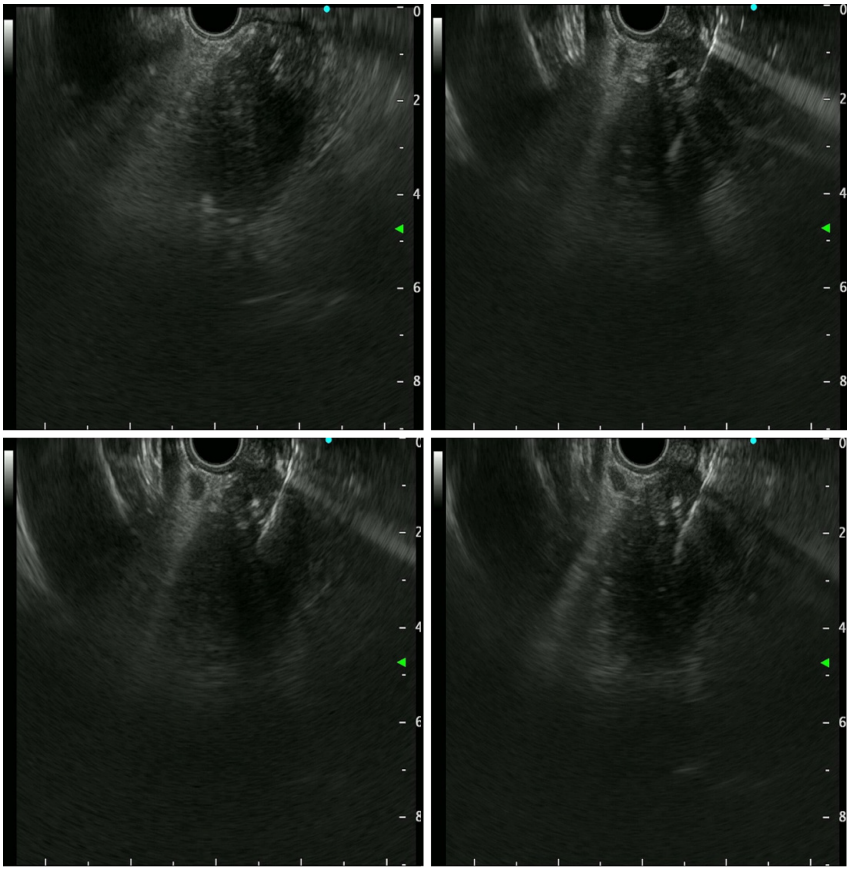

Figure 3 Endoscopic ultrasound-guided tissue sampling. Endoscopic ultrasound (EUS) showed a 36.0 mm × 32.9 mm sized ill-defined relative heterogeneous hypoechoic mass in the pancreatic head. EUS-guided tissue sampling (EUS-TS) was performed using a 22-gauge EZ Shot (EZ Shot 3 Plus; Olympus, Tokyo, Japan) using the fanning method.

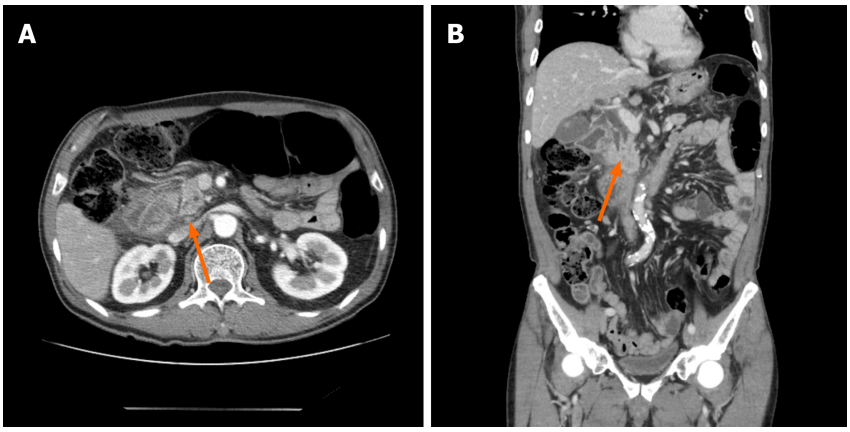

Figure 4 Computed tomography of the abdomen two days after endoscopic ultrasound-guided tissue sampling. A and B: Edematous wall thickening of the second portion of the duodenum with adjacent fluid collection was detected and a leak was suspected (orange arrows).

main pancreatic duct, a 5F 7 cm linear plastic stent was deployed to divert the pancreatic juice (Figure 7).

OUTCOME AND FOLLOW-UP

Immediately after insertion of the pancreatic stent, his abdominal pain markedly improved, and amylase and lipase levels normalized within a week. Two weeks after the pancreatic stent insertion procedure, follow-up abdominal CT imaging revealed the disappearance of adjacent fluid collection and edematous change of head of pancreas findings and healing of the duct leakage site (Figure 8). Based on these observations, neoadjuvant chemotherapy was initiated.

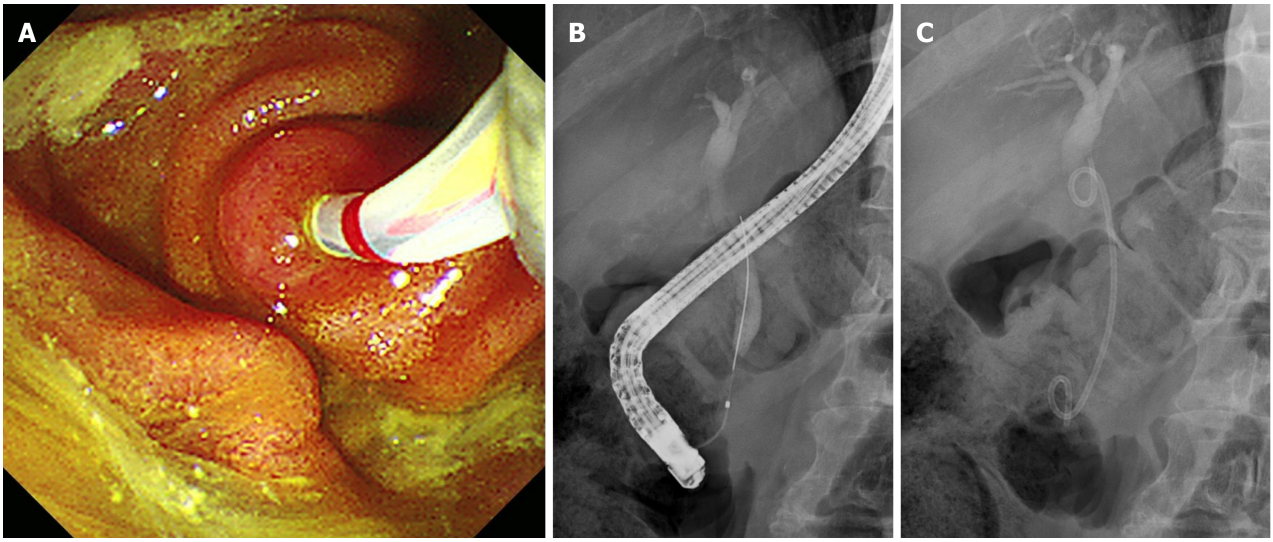

Figure 5 First endoscopic retrograde cholangiopancreatography. A: Selective biliary cannulation was achieved only through the ampulla of Vater; B: There is no definitive dye leakage from the distal common bile duct; C: A 7F 7 cm-sized double pigtail plastic stent was deployed for effective biliary drainage.

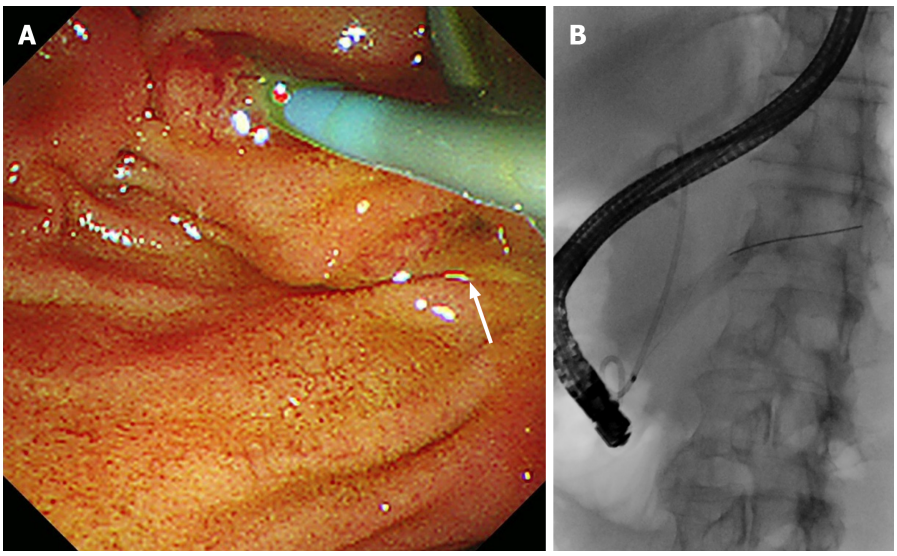

Figure 6 Second endoscopic retrograde cholangiopancreatography. A: A separate orifice below the biliary orifice that had not been observed during the first endoscopic retrograde cholangiopancreatography is noted (white arrow); B: Selective pancreatic cannulation was easily achieved through a separate orifice.

DISCUSSION

EUS-TS is a revolutionary technique that shifts the narrative surrounding the diagnosis of pancreatic lesions, such as cysts and solid lesions, and can target small pancreatic tumors. Before the advent of EUS-TS, ultrasonography-guided percutaneous transabdominal TS played a major role in significant seeding risk[5]. However, despite the many benefits of EUS-TS, it can also cause adverse side effects such as bleeding, pancreatitis, infection, duodenal perforation, abscesses, and sepsis[6]. Pancreatic ductal leaks are also a rare complication of EUS-TS, with only two cases reported thus far in the English-language scientific literature[1,7]. Unlike the current case, these cases involved pancreatic juice collected as a pseudocyst or as pancreatic ascites.

The patient in this case study was diagnosed with acute pancreatitis as he had suffered persistent severe pain over 24 h and had amylase and lipase levels more than three times the upper normal limit immediately after EUS-TS. Sequential abdominal CT imaging studies suggested a pancreatic ductal leak from the dilated main pancreatic duct, which a second ERCP confirmed. The patient recovered immediately after pancreatic stent placement to divert the leaking pancreatic juice from the intraperitoneal cavity to the duodenal lumen.

Acute pancreatitis (AP) is a rare EUS-TS complication. Recent research has demonstrated that a recent history of acute pancreatitis and undertaking EUS-TS through more than 5 mm of the normal parenchyma can lead to a much greater risk of acute pancreatitis[3]. However, a history of acute pancreatitis was not found in the current case, and the EUS-TS fine needle passed through less than 5 mm of the normal parenchyma. Another study reported that patients with a branch

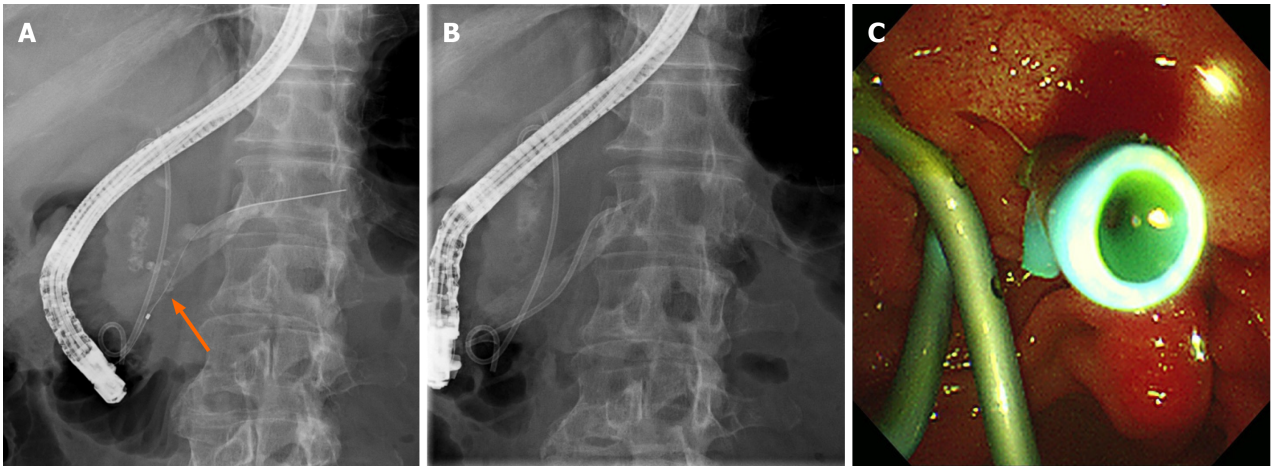

Figure 7 Second endoscopic retrograde cholangiopancreatography. A: A pancreatogram showing dye leakage in the head of the main pancreatic duct (orange arrow); B and C: A 5F 7 cm linear plastic stent was deployed to divert the pancreatic juice.

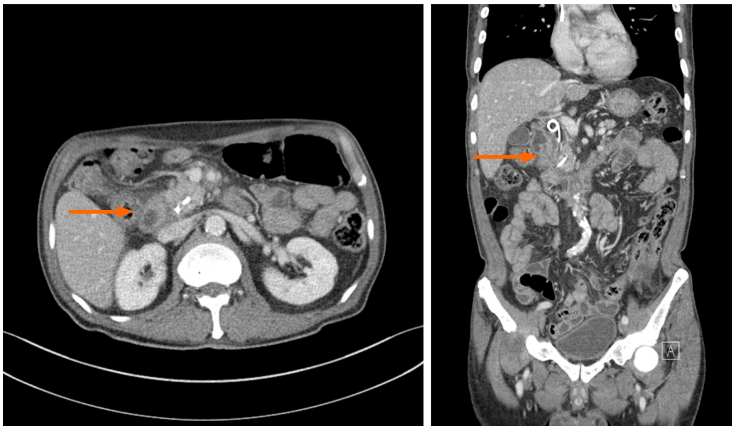

Figure 8 Computed tomography of the abdomen two weeks after pancreatic stent placement. Disappearance of adjacent fluid collection and edematous change of head of pancreas, and healing of the duct leakage site finding were seen.

duct-type intraductal papillary mucin-secreting neoplasm are at risk of developing acute pancreatitis after EUS-TS[2]. However, unlike that study, the current case involved pancreatic ductal adenocarcinoma (PDAC).

In the present case, the fanning method was used to achieve a high diagnostic accuracy. The fanning method in EUS-TS involves sampling by cycles of in-and-out needle passes addressed in multiple directions within a solid lesion to obtain more target tissue[8]. While blood vessels were visualized and excluded by color Doppler during EUS-TS in the current case, pancreatic ductal structures without color Doppler might have a greater chance of being damaged by the fanning technique than the standard technique. A retrospective analysis of the EUS images in the current case revealed a suspicious ductal structure within the target fanning area (Figure 9). When using the fanning method during EUS-TS, ductal structures without color Doppler imaging should be excluded to prevent pancreatic ductal leaks. To avoid pancreatic ductal injury, a thorough evaluation of the ductal structures should be performed before EUS-TS with Doppler imaging in the pancreatic mass, and the fanning method range should be limited in the field without suspicious ductal structures.

Although PDAC generally has a poor prognosis because it is frequently detected at an advanced stage, recent studies demonstrate that innovations in neoadjuvant chemotherapy have provided opportunities to proceed to curative surgery, thereby improving long-term outcomes in patients with borderline resectable and locally advanced PDAC[9]. Therefore, prompt treatment with neoadjuvant chemotherapy is critical for improving prognosis, while a delay in treatment could cause borderline resectable and locally advanced PDAC to become distant and metastatic. Acute pancreatitis initiates a hypercatabolic state caused by elevated protein catabolism and an inflammatory cytokine storm[10]. Recent guidelines dictate that patients with acute pancreatitis may benefit from early oral or enteral nutrition, which is in contrast to managing pancreatic ductal leaks as they require prolonged fasting and parenteral nutrition[4]. The hypercatabolic state and prolonged fasting in acute pancreatitis due to pancreatic ductal leaks could make PDAC patients unsuitable for toxic chemotherapy. In the current case, placement of the pancreatic stent helped to reduce the waiting interval for neoadjuvant chemotherapy, as the patient's acute pancreatitis was immediately resolved.

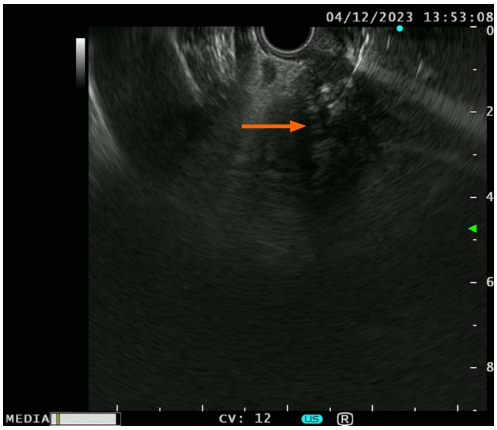

Figure 9 Retrospective analysis of endoscopic ultrasound imaging in the current case. Suspected ductal structure within the fanning area of the target (orange arrow).

CONCLUSION

In conclusion, pancreatic ductal leakage caused by EUS-TS can lead to acute pancreatitis. Therefore, imaging studies should be immediately performed after EUS-TS to rule out pancreatic ductal leaks in patients with clinical signs and symptoms of AP. If a pancreatic ductal leak is suspected, ERCP must confirm the leak. Pancreatic stent placement may allow patients to immediately recover from acute pancreatitis and shorten the waiting time for curative therapy. When using the fanning method during EUS-TS, ductal structures without color Doppler imaging should be excluded to prevent pancreatic ductal leaks.

FOOTNOTES

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Country/Territory of origin: South Korea

ORCID number: Ki-Hyun Kim 0009-0007-8558-0540; Chang Hwan Park 0000-0002-2995-8779; Eunae Cho 0000-0001-5931-4643; Yohan Lee 0000-0002-0643-3304.

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CASE REPORT

Upadacitinib for refractory ulcerative colitis with primary nonresponse to infliximab and vedolizumab: A case report

Xuan Xu, Jing-Wen Jiang, Bing-Yun Lu, Xia-Xi Li

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Xuan Xu, Jing-Wen Jiang, Bing-Yun Lu, Xia-Xi Li, Department of Gastroenterology, Shenzhen Hospital, Southern Medical University, Shenzhen 518100, Guangdong Province, China

Xuan Xu, Jing-Wen Jiang, The First Clinical Medical School, Southern Medical University, Guangzhou 510515, Guangdong Province, China

Corresponding author: Xia-Xi Li, PhD, Chief Doctor, Department of Gastroenterology, Shenzhen Hospital, Southern Medical University, No. 1333 Xinhu Road, Shenzhen 518100, Guangdong Province, China. xiaxi_li@foxmail.com

Abstract

BACKGROUND

Many patients with ulcerative colitis (UC) do not respond well to, or tolerate conventional and biological therapies. There is currently no consensus on the treatment of refractory UC. Studies have demonstrated that the selective Janus kinase 1 inhibitor upadacitinib, a small-molecule drug, is effective and safe for treating UC. However, no studies have revealed that upadacitinib is effective in treating refractory UC with primary nonresponse to infliximab and vedolizumab.

CASE SUMMARY

We report the case of a 44-year-old male patient with a chief complaint of bloody diarrhoea with mucus and pus, in addition to dizziness. The patient had recurrent disease after receiving mesalazine, prednisone, azathioprine, infliximab and vedolizumab over four years. Based on the endoscopic findings and pathological biopsy, the patient was diagnosed with refractory UC. In particular, the patient showed primary nonresponse to infliximab and vedolizumab. Based on the patient's history and recurrent disease, we decided to administer upadacitinib. During hospitalisation, the patient was received upadacitinib under our guidance. Eight weeks after the initiation of upadacitinib treatment, the patient's symptoms and endoscopic findings improved significantly. No notable adverse reactions have been reported to date.

CONCLUSION

Our case report suggests that upadacitinib may represent a valuable strategy for treating refractory UC with primary nonresponse.

Key Words: Upadacitinib; Refractory ulcerative colitis; Primary nonresponse; Infliximab; Vedolizumab; Case report

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Core Tip: Ulcerative colitis (UC) is a major type of inflammatory bowel disease. Many patients do not respond well to the current therapies. We report the case of a patient diagnosed with refractory UC, with primary nonresponse to infliximab and vedolizumab. The patient experienced recurrent symptoms after receiving mesalazine, prednisone, azathioprine, infliximab, and vedolizumab for more than four years. After optimising the upadacitinib treatment, UC remission was achieved. Our report suggests that the small-molecule upadacitinib may be a new treatment option that deserves to be reported and studied.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) caused by multiple factors. However, its aetiology and pathogenesis are not completely understood. The disease often relapses and remits.

For UC treatment, 5-aminosalicylic acid preparations (5-ASA), glucocorticoids, and immunosuppressants are used. In recent years, various biological agents such as infliximab have shown good efficacy in treating IBD. However, many patients with UC do not respond well at all, or cannot tolerate conventional or biological therapies. Therefore, additional treatment options are needed for patients with refractory UC.

Here, we report a case of refractory UC successfully treated with upadacitinib, a small-molecule drug that inhibits Janus kinase (JAK) signalling. The patient failed to respond to infliximab and vedolizumab, two biological agents commonly used to treat IBD. We also reviewed the relevant literature on the use of JAK inhibitors for IBD and discussed the advantages of its oral administration and low immunogenicity.

CASE PRESENTATION

Chief complaints

The patient was a 44-year-old caucasian male with a body mass index of 26.5 (height, 178 cm; weight, 84 kg). He presented to the hospital on December 15, 2022, with a chief complaint of haematochezia and dizziness.

History of present illness

The patient had experienced frequent episodes of bloody diarrhoea with mucus and pus for more than 10 d.

History of past illness

He had a history of chronic intermittent small volume hematochezia for 5 years, with a frequency of more than 10 episodes per day.

The patient underwent colonoscopy at another hospital and was diagnosed with UC (left-sided active phase) (Figure 1).

Despite receiving mesalazine and other symptomatic treatments, the patient experienced recurrent flare-ups. In November 2019, the patient received induction therapy with mesalazine (4 g) and prednisone (64 mg), which resulted in significant symptom relief, reduced the erythrocyte sedimentation rate (ESR) to 37 mm/h, and normalised stool frequency and quality (no mucus, pus, or blood). A follow-up colonoscopy performed in February 2021 revealed complete mucosal healing (Figure 2).

Mesalazine was maintained at 4 g/d after initial treatment. In January 2022, the patient again experienced recurrent symptoms of abdominal pain and bloody stool, ranging from two to five times a day and investigations revealed an elevated ESR of 93 mm/h. The symptoms were alleviated with oral methylprednisolone (64 mg), azathioprine (100 mg), and metronidazole. However, the symptoms recurred as bloody stools increased to 2–10 times a day. The patient was therefore, treated with infliximab (400 mg) and azathioprine (100 mg) in July 2022.

The patient experienced recurrent symptoms after the second infliximab infusion, such as passing > 10 stools per day with mucus, pus, or blood. The infliximab dose was increased to 500 mg at the fourth dose. However, there was no improvement in colonoscopic findings, which showed chronic relapsing UC involving the entire colon (Ulcerative Colitis Endoscopic Index of Severity score 6).

The patient exhibited primary nonresponse to infliximab and continued to experience symptoms.

Personal and family history

The patient denied any family history of malignant tumours.

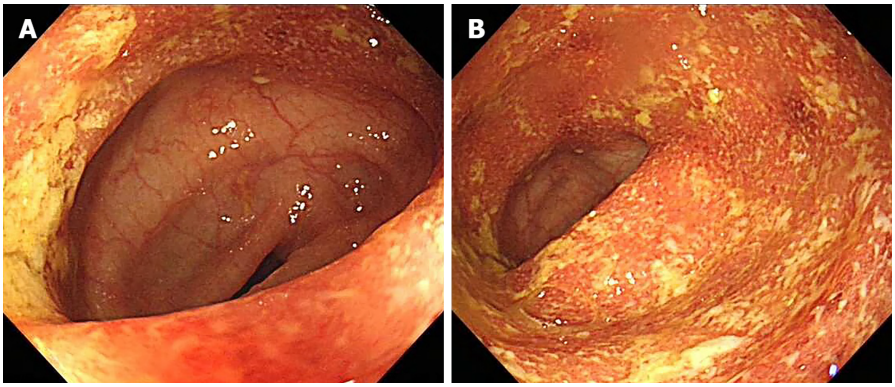

Figure 1 Colonoscopy on November 26, 2019. A: Continuous mucosal erosions can be seen in the junction of the descending colon and sigmoid colon with more pus attached to the surface; B: Persistent mucosal erosion is observed in the sigmoid colon, covered with more pus.

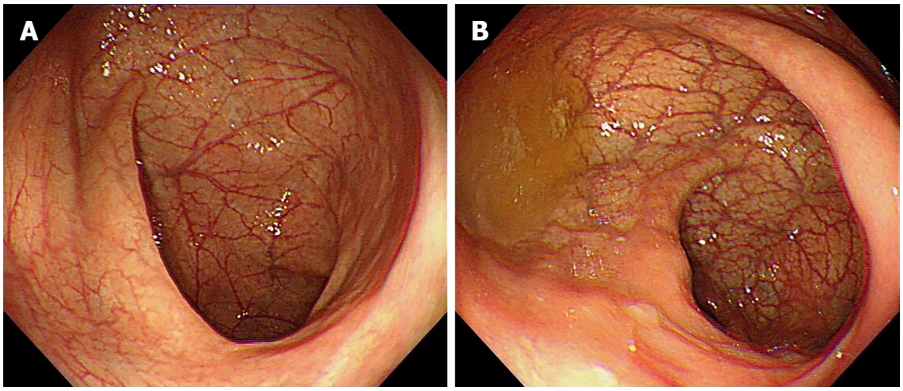

Figure 2 Colonoscopy on February 17, 2021. A: The wrinkled wall of the sigmoid colon is smooth; B: The folded shape of the lower sigmoid colon is regular and the mucosa was smooth; the submucosal vascular texture is clear. No erosion or ulceration is observed in both images.

Physical examination
There were no obvious abnormalities except tenderness in the left lower abdomen.

Laboratory examinations
Epstein-Barr virus DNA quantization was 1.28E+3 copies/mL. Haemoglobin level was 123 g/L, and ESR was 33 mm/h. Albumin 38.4g/L, and hepatorenal function was normal. Faecal erythrocyte count 4+, occult blood test +. Faecal and C. difficile cultures were negative. C-reactive protein, anti-neutrophil cytoplasmic antibodies, antinuclear antibodies, cytomegalovirus antibody, T-SPOT, thyroid function, tumour markers, eight infectious diseases [hepatitis B surface antigen, anti- hepatitis C virus, antigen-human immunodeficiency virus (HIV)/antibody-HIV, antibody-syphilis], coagulation function, D-dimers, and tuberculosis T-SPOT were all within the normal ranges.

Imaging examinations
Computed tomography showed that the mucosa of the rectum and sigmoid intestinal wall were uniformly thickened and significantly strengthened, indicating UC-related alterations. Pelvic magnetic resonance imaging revealed colorectal wall thickening.

Further diagnostic work-up
In December 2022, colonoscopy revealed extensive ulceration of both the sigmoid colon and rectum, and the diagnosis was of UC (E2, Ulcerative Colitis Endoscopic Index of Severity score 5–6, Mayo endoscopic score 2–3) (Figure 3).

The Pathology Department of our hospital confirmed UC on the patient's biopsy specimens obtained from another hospital.

FINAL DIAGNOSIS
The final diagnosis was UC (chronic recurrent type, total colon type, active, moderate, Mayo score 6).

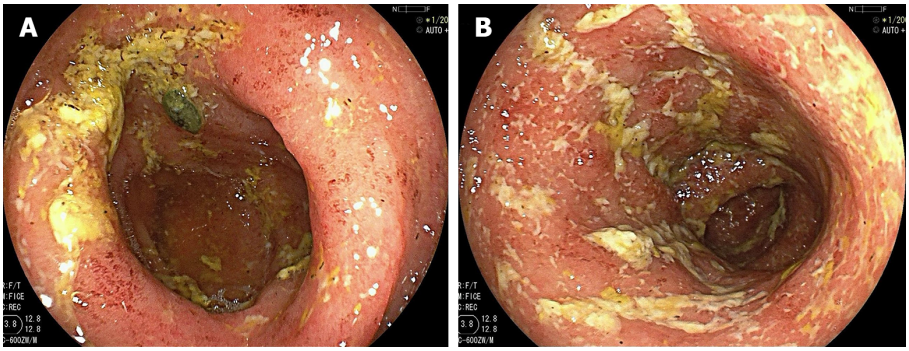

Figure 3 Colonoscopy on December 17, 2022. A: The mucosa in the sigmoid colon is extensively hyperaemic and oedematous, scattered with multiple irregular shallow ulcers and patchy erosions; B: The hyperaemia and oedema also can be observed in the junction of descending colon and sigmoid colon; and the submucosal vascular texture has disappeared. All the lesions are distributed throughout the mucosa and are covered with a large number of yellow and white secretions.

TREATMENT

The patient declined glucocorticoid therapy after admission and received vedolizumab and azathioprine 100 mg/d, along with two daily enemas of Brinider suspension, starting on December 20, 2022. However, the symptoms persisted, with 5–10 stools per day, consisting mostly of pus and blood. The ESR was 42 mm/h after five days. The patient then received oral mesalazine, mesalazine enemas, faecal microbiota transplantation (FMT), and a second dose of vedolizumab.

Despite receiving a FMT on February 17-19, 2023, and a third dose of vedolizumab on February 18, 2023, the patient did not experience symptom relief. The patient received a fourth dose of vedolizumab on April 1, 2023, and a fifth dose on May 10, 2023, with no improvement in clinical outcomes.

The patient experienced recurrent symptoms of mucus, pus, and bloody stools 2–5 times per day on May 12, 2023, suggesting primary nonresponse to vedolizumab. The patient was then commenced on upadacitinib 45 mg/d on May 14, 2023.

OUTCOME AND FOLLOW-UP

On June 9, 2023, the patient reported significant improvement in haematochezia symptoms, with no other discomfort. Follow-up colonoscopy after 8 wk (Figure 4) showed that the UC was in remission and the Mayo endoscopic score was 0. The patient is currently receiving upadacitinib (30 mg/d). We plan to review him in six months and reduce the dose to 15 mg/d, as appropriate.

DISCUSSION

UC is a major type of inflammatory bowel disease that was first described in 1895[1]. The main clinical feature of UC is bloody diarrhoea. Many patients experience left-sided abdominal pain, particularly if the inflammation is limited to the left colon. Patients with pancolitis, or inflammation of the entire colon, often experience diffuse abdominal pain and tenesmus[2]. Endoscopic examination reveals continuous inflammation of the colonic mucosa, starting from the rectum and extending proximally to the ileocecal valve[1].

Currently, the available treatments for UC include conventional drugs (such as 5-ASA, glucocorticoids and immunosuppressants), biologics (such as infliximab, vedolizumab and ustekinumab), JAK inhibitors and S1P receptor modulators. 5-ASA is the standard first-line therapy for mild to moderately active UC[3]. Glucocorticoids are indicated for patients with moderate-to-severe disease or those with symptoms that are refractory to standard therapies.

However, many patients with UC do not respond adequately, lose their response to conventional or biological therapies, or experience adverse effects from these treatments[4]. Previous studies have shown that even after switching to new biological agents, only one-third of patients achieve or maintain clinical remission at one year[5]. Patients who depend on glucocorticoids or are unresponsive or intolerant to at least one of 5-ASA, corticosteroids or immunosuppressants are considered to have refractory UC[6].

This patient had recurrent disease despite multiple courses of mesalazine, prednisone, azathioprine, and vedolizumab over four years, and showed primary nonresponse to infliximab and vedolizumab. These features met the criteria for refractory UC. The evidence for the efficacy of optimising vedolizumab or combining it with azathioprine is inconsistent across studies[7,8]. However, the patient's symptoms did not improve significantly after optimising the vedolizumab treatment.

Upadacitinib is a selective small-molecule JAK1 inhibitor. In clinical trials, upadacitinib was shown to be highly effective in achieving remission in patients with moderate-to-severe UC[5].

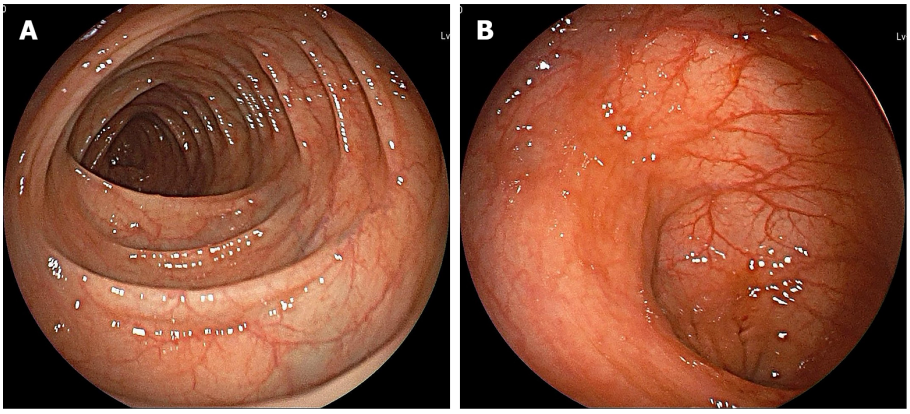

Figure 4 Colonoscopy on July 10, 2023. A: The mucousa of the descending colon is rough, and the vascular texture is unclear; B: There are extensive cicatricial changes in the sigmoid colon; scattered mucous hyperaemia is observed between the scars. No obvious erosion and ulcers are observed in both figures.

We reviewed the relevant literature and found a few studies on upadacitinib treatment for intractable UC. A retrospective cohort study reported that most patients achieved steroid-free clinical remission and clinical response within 8-16 wk of starting upadacitinib and that most of them had previously received anti-tumor necrosis factors and vedolizumab[9]. Phase II and III trials demonstrated that a selective JAK1 inhibitor for UC was effective and safe.

The patients in this study previously failed to respond adequately, lost response to, or experienced adverse effects from, at least one conventional or biologic therapy[4].

The two previous studies did not specify the type of nonresponse (primary or secondary) of the patients included. In contrast, our patient showed primary nonresponse to vedulizumab and infliximab as well as an inadequate response to other drugs. His condition was more complex and severe than that of the patients in the two previous studies. Considering the patient's lack of response to multiple therapies, and the efficacy of upadacitinib in phase II and III trials, we decided to administer upadacitinib only after obtaining informed consent.

We administered upadacitinib at a dose of 45 mg/d. Colonoscopy revealed that the patient achieved remission eight weeks later. The patient continued to receive a maintenance dose of 30 mg/d of upadacitinib monotherapy and remained in remission, demonstrating the efficacy of upadacitinib in this case.

CONCLUSION

In summary, our patient experienced recurrence of symptoms after receiving mesalazine and prednisone, and showed primary nonresponse to infliximab and vedolizumab. This case demonstrates that upadacitinib is effective in treating refractory UC, in a patient who failed to respond to infliximab and vedolizumab, with significant improvement in symptoms and endoscopic findings, and no notable adverse reactions have been observed to date. This provides an alternative option for patients with refractory UC and primary nonresponse. Moreover, small-molecule drugs may have advantages such as reduced immunogenicity and enhanced patient adherence. However, this was a single-case report. The efficacy of upadacitinib in refractory UC patients with primary nonresponse needs to be verified in further clinical studies.

FOOTNOTES

Co-first authors: Xuan Xu and Jing-Wen Jiang.

Author contributions: Xu X and Jiang JW drafted the original report; Li XX was involved in the revision of the report and supervised the report and provided the required resources; Xu X, Jiang JW and Li XX acquired data; Xu X interpreted images; Lu BY was involved in the patient's care. All authors have read and agreed to the published version of the manuscript.

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Country/Territory of origin: China

ORCID number: Xia-Xi Li 0000-0003-4731-3170.

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CASE REPORT

Exogenous insulin autoimmune syndrome: A case report and review of literature

Ling-Ling Xu, Jia-Xin Chen, Jing-Ping Cheng, Ni Luo

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Ling-Ling Xu, Jia-Xin Chen, Medical College, School of Medicine, Wuhan University of Science and Technology, Wuhan 430065, Hubei Province, China

Jing-Ping Cheng, Ni Luo, Department of Gerontology, CR & WISCO General Hospital Affiliated to Wuhan University of Science and Technology, Wuhan 430080, Hubei Province, China

Corresponding author: Jing-Ping Cheng, Doctor, Chief Doctor, Department of Gerontology, CR & WISCO General Hospital Affiliated to Wuhan University of Science and Technology, No. 29 Metallurgy Avenue, Qingshan District, Wuhan 430080, Hubei Province, China.
404178516@qq.com

Abstract

BACKGROUND

Insulin autoimmune syndrome (IAS) is a severe manifestation of spontaneous hypoglycemia. It is characterized by elevated levels of immune-reactive insulin and highly potent insulin autoantibodies (IAAs), which are induced by endogenous insulin circulating in the bloodstream. It is distinguished by recurring instances of spontaneous hypoglycemia, the presence of IAA within the body, a substantial elevation in serum insulin levels, and an absence of prior exogenous insulin administration. Nevertheless, recent studies show that both conventional insulin and its analogs can induce IAS episodes, giving rise to the notion of non-classical IAS. Therefore, more attention should be paid to these diseases.

CASE SUMMARY

In this case report, we present a rare case of non-classical IAS in an 83-year-old male patient who present with symptoms of a psychiatric disorder. Upon symptom onset, the patient exhibited Whipple's triad (including hypoglycemia, blood glucose level less than 2.8 mmol/L during onset, and rapid relief of hypoglycemic symptoms after glucose administration). Concurrently, his serum insulin level was significantly elevated, which contradicted his C-peptide levels. After a comprehensive examination, the patient was diagnosed with exogenous insulin autoimmune syndrome. Considering that the patient had type 2 diabetes mellitus and a history of exogenous insulin use before disease onset, it was presumed that non classical IAS was induced by this condition. The PubMed database was used to search for previous cases of IAS and non-classical IAS to analyze their characteristics and treatment approaches.

CONCLUSION

The occurrence of non-classical IAS is associated with exogenous insulin or its analogs, as well as with sulfhydryl drugs. Symptoms can be effectively alleviated through the discontinuation of relevant medications, administration of hormones or immunosuppressants, plasma exchange, and lifestyle adjustments.

Key Words: Insulin autoimmune syndrome; Type 2 diabetes; Exogenous insulin; Insulin autoantibodies; Hypoglycemia; Case report

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Core Tip: Exogenous insulin autoimmune syndrome (EIAS), also known as non-classical insulin autoimmune syndrome, occurs in individuals with type 2 diabetes who use exogenous insulin, resulting in the production of insulin autoantibodies and the subsequent development of hyperinsulinemia. This condition is characterized by significant fluctuations in blood glucose levels and insulin resistance. In patients with type 2 diabetes receiving treatment with oral medications or insulin therapy, episodes of hypoglycemia are often attributed to drug-related causes. Consequently, EIAS tends to be overlooked in clinical practice, particularly among elderly patients. Herein, we report a case of EIAS in an elderly person. Based on an analysis of PubMed cases, it has been observed that the disease tends to be self-limiting with a favorable prognosis.

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INTRODUCTION

The insulin autoimmune syndrome (IAS) is a rare clinical condition that often leads to misdiagnosis or missed diagnosis. Although its exact etiology remains unclear, several studies have suggested a strong association between genetic susceptibility and the use of sulfhydryl-containing drugs or exogenous insulin. In clinical practice, both IAS and exogenous insulin autoimmune syndrome (EIAS) present with hypoglycemic symptoms and positive insulin antibodies[1]; however, they differ in terms of the inducing factors and characteristics of the insulin antibody[2]. The prognoses for both IAS and EIAS are generally favorable, with treatment goals focused on correcting hypoglycemia, addressing underlying causes, and reducing insulin antibody titers[3].

CASE PRESENTATION

Chief complaints

The patient, an 83-year-old man, was admitted to the hospital due to episodic nocturnal gibberish for 3 d and worsening for 1 d.

History of present illness

A member of his family acted as a proxy and provided an account of the patient's symptoms during the episodes which included: incoherent speech, slurred words, bilateral drooling, and impaired recognition of family members, lasting for approximately 20 min. The symptoms ameliorated following sleep, and partial recollection was observed upon awakening. At approximately 4:00 on the same day, the above symptoms recurred.

History of past illness

The patient had a medical history of hypertension, managed through the long-term use of sustained-release nifedipine and candesartan tablets for treatment. He was diagnosed with type 2 diabetes over 20 years ago. Initially, oral hypoglycemic drugs were prescribed to manage blood glucose levels. However, 3 months ago, owing to inadequate glycemic control, the patient was initiated on insulin aspart injections before meals at a dose of 8 units in the morning, 10 units at noon, and 10 units in the evening. The subcutaneous administration of insulin glargine was initiated at a dose of 10 units at 20:00. Unfortunately, specific details regarding blood glucose control are unavailable as the patient did not monitor their blood glucose levels at home. Moreover, the patient's medical history included chronic bronchitis, old cerebral infarction, hepatitis B, benign prostatic hyperplasia, and left knee arthritis.

Personal and family history

The patient denied any specific family history.

Physical examination

Physical examination revealed a body temperature of 36.3 ℃, respiratory rate of 19 times/minute, pulse rate of 76 times/min, blood pressure of 130/75 mmHg, SPO2 level of 99% (with oxygen supplementation), height of 170 cm, weight of 70 kg, and body mass index of 24.22 kg/m^2. His random blood glucose level on admission was 13 mmol/L. No significant abnormalities were detected during cardiovascular or abdominal examinations, and no edema was observed in either lower limb. Neurological examinations did not reveal any apparent abnormalities.

Laboratory examinations

Complete blood count, thyroid function test, plasma ammonia, coagulation profile, liver and kidney function tests, electrolytes, B-type natriuretic peptide, cardiac enzyme spectrum, three indicators of myocardial infarction urinalysis and routine stool examination, glomerular filtration rate, rheumatoid factor test, and autoimmune liver disease antibody levels were within normal ranges. Serum cortisol levels at 8:00 and 16:00 were also within normal limits. Tumor markers including alpha-fetoprotein, carbohydrate antigen 125, carbohydrate antigen 19-9, total prostate-specific antigen, neuron-specific enolase, cytokeratin fragment 19 and cancer antigen 72-4 were all normal except for carcinoembryonic antigen which was elevated (6.15 ng/mL, reference value: 0-4.00 ng/mL). His glycated hemoglobin level was 7.0%.

Imaging examinations

The patient's electrocardiogram showed normal sinus rhythm. Enhanced computed tomography of the pancreas revealed pancreatic atrophy, bilateral renal cystic lesions, and kidney stones in the right kidney. Brain diffuse-weighted magnetic resonance imaging demonstrated multiple lacunar infarctions in the brainstem, bilateral basal ganglia, and frontal and parietal lobes. There was also evidence of cerebral atrophy, white matter degeneration, and cerebral arteriosclerosis. Abdominal ultrasound indicated fatty liver and slightly increased echogenicity of the bilateral renal parenchyma with bilateral cystic lesions. The bladder wall appeared rough, with diverticulum formation. Additionally, an enlarged prostate with stones or calcified spots was identified.

Further diagnostic work-up

Around 2:00 on the day of admission, the patient presented with delirium, palpitations, and fatigue. His finger blood glucose measurement revealed a level of 2.6 mmol/L. Consequently, 20 mL glucose solution was orally administered and 10% glucose solution was intravenously infused. Hence, the blood glucose levels increased to 9.4 mmol/L. After the gradual relief of symptoms, the insulin dosage were reduced. On the second night after admission, the patient experienced another episode of palpitations and discomfort. Immediate venous blood glucose measurement showed a level of 2.7 mmol/L (reference range: 3.9-6.1 mmol/L), an insulin level of more than 600 mU/L (reference range: 8.5-22.70 mU/L), and a C-peptide level of 3.40 ng/mL (reference range: 0.78-5.19 ng/mL). This indicated an insulin-C-peptide dissociation phenomenon. The insulin and C-peptide release tests of the patient (Table 1) yielded results consistent with previous reports, suggesting an association between hypoglycemia in the patient and high serum insulin concentrations. Therefore, immediate discontinuation of insulin was implemented. Dynamic blood glucose monitoring in the patient revealed fluctuations ranging from 2.4 to 18.0 mmol/L, with episodes of low blood sugar predominantly occurring between 2:00 to 5:00, where blood sugar levels fluctuated within the range of 2.4 to 3.3 mmol/L; hence, hypoglycemia occurred intermittently. The insulin antibody (Table 2) and gene tests were completed. The human leukocyte antigen (HLA) alleles were HLA-DRB1*0803/1202, HLA-DQB1*0601/0301, HLA-DPB1*0501/0501.

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was EIAS.

TREATMENT

Upon confirmation of the diagnosis, the patient was advised to discontinue insulin therapy, modify their dietary regimen to include frequent smaller meals throughout the day, and initiate oral linagliptin administration at a dose of 5 mg once daily.

OUTCOME AND FOLLOW-UP

After treatment initiation, no recurrent episodes of hypoglycemic attacks were observed in the patient; their blood glucose levels remained stable without any recurrence of psychiatric symptoms. No hypoglycemic events occurred during the 3-month follow-up.

Table 1 Findings from insulin release test and C-peptide release test

Project	0 h	2 h	After 10 d of insulin withdrawal	0 h	2 h
Insulin release test	> 600 mU/L	> 600 mU/L		> 600 mU/L	> 600 mU/L
C-peptide release test	3.60 ng/mL	4.90 ng/mL		4.90 ng/mL	6.62 ng/mL

Table 2 Insulin antibody test

Project		After 10 d of insulin withdrawal		Reference value
Islet cell antibody	0.05		0.05	< 0.9 COI
Serum anti-glutamic acid decarboxylase antibody	0.96		0.99	< 10 IU/mL
Insulin autoantibody	12.6		13.3	< 0.9 COI

DISCUSSION

IAS or Hirata's disease, was initially documented by Japanese scholars[4] and is widely recognized as a significant etiology of spontaneous hypoglycemia. IAS is a relatively uncommon condition encountered in clinical practice, with a pathogenesis characterized primarily by elevated levels of insulin autoantibodies (IAAs) and excessive endogenous insulin secretion[5]. The diagnosis of IAS can generally be confirmed if the following conditions are met[6]: Hyperinsulinemic hypoglycemia; during hypoglycemic episodes, blood glucose levels decrease below 3.0 mmol/L; increased IAA concentrations; no exogenous insulin administration was employed; and no observable pancreatic pathological abnormalities.

Research suggests that approximately half of the patients with IAS have previously been exposed to relevant medications. These medications are classified into two categories: Those containing thiol-based compounds, such as methimazole, propylthiouracil, lipoic acid, imipenem, glutathione, captopril, sulfasalazine, amphotericin B, and N-acetylcysteine, with methimazole being the most prevalent; and those not inherently containing thiol groups but with the ability to produce thiol-based compounds through metabolism, including clopidogrel, pantoprazole, rabeprazole, levofloxacin and isoniazid[7]. Thiols possess the ability to interact with disulfide bonds within insulin molecules, inducing conformational alterations in endogenous insulin and eliciting an immune response that leads to the production of IAA. These antibodies are characterized by a high binding capacity and low affinity[2], suggesting that a large amount of insulin binds to form complexes; however, this easily dissociates, resulting in increased free insulin in the circulation [8], consequently resulting in the manifestation of IAS[9].

Genetic susceptibility also plays an important role in IAS[10]. Studies have found a strong correlation between IAS and the HLA phenotype[11,12]. However, different ethnic groups carry different HLA types, among which the HLA-DR4 allele is the most common[13]. Approximately 96% of Japanese patients with IAS express HLA-DR4[14], mainly including DRB1*0406, with a few including DRB1*0403 and DRB1*0407[15]. The main HLA types in Korean population are DRB1*0803 and DRB1*1602[16], and those in European and American populations are DRB1*0403[17]. At present, there are few HLA samples for IAS gene detection in China, those that exist mainly include DRB1*0406[18] and DRB1*0406/0409[19], most of which are detected in patients with hyperthyroidism taking methimazole. The possible mechanism is that HLA-DRB1*0406 encodes serine, and when exposed to reducing substances such as methimazole, specific fragments of the insulin A chain have a high affinity for their polypeptide-binding sites, thereby stimulating the proliferation of T cell lines and resulting in increased IAA production[20]. However, in recent years, some scholars have also reported that HLA-DRB1*0415, HLA-DRB1*0404, and other genes may also be susceptibility genes for IAS[21,22]. However, there is still a lack of large-scale research data.

Furthermore, in recent years, the symptoms of hypoglycemia induced by exogenous insulin in patients with diabetes have become similar to those of IAS, leading scholars to designate this condition as EIAS, which is a non-classical form of IAS[23].

EIAS denotes that the autoimmune response is induced by exogenous insulin, resulting in the production of the immunoreactive antigen IAA. This is characterized by low insulin binding capacity and relatively high insulin affinity[2], suggesting that the amount of insulin binding to form complexes is small, and it does not easily to dissociate, resulting in islet resistance[24], and elevation of serum immunoreactive insulin concentrations. These features instigate recurrent episodes of spontaneous hypoglycemia[25]. Almost all types of insulin can contribute to the occurrence of EIAS in individuals with diabetes[26,27]. Furthermore, the time interval between insulin administration and recurrent hypoglycemia can exhibit irregularities ranging from a few days to several years[26]. Owing to the adverse effects of insulin-induced hypoglycemia, EIAS is easily missed or misdiagnosed in patients with diabetes, and numerous domestic and international studies have consistently reported a wide range of detection rates for IAA in patients using exogenous insulin, varying from 21.5% to 78.0%[28]. In patients with type 2 diabetes receiving exogenous insulin therapy, if the fasting insulin/C-peptide ratio exceeds 8.6 or the postprandial 2-hour insulin/C-peptide ratio surpasses 17.8, it indicates the potential presence of IAAs in the body. A higher ratio corresponds to an increased likelihood of a positive result, thereby necessitating prompt testing for IAAs[29]. In clinical practice, when patients with type 2 diabetes undergoing

insulin therapy experience recurrent episodes of hypoglycemia, it is important to consider the possibility of EIAS. A diagnosis of EIAS can be made if there is a significant increase in serum insulin levels accompanied by a dissociation between insulin and C-peptide, along with positive results for islet cell autoantibodies, after ruling out other potential causes such as medication usage, tumors, deficiency in insulin counter-regulatory hormones, and autoimmune diseases.

Although the incidence of EIAS in clinical practice is rare, it has been progressively increasing over the years due to the escalating number of patients with diabetes and widespread utilization of insulin preparations[30]. Because of the potential for severe hypoglycemia, EIAS can be easily misdiagnosed in clinical practice; therefore, clinicians should be aware of this condition. In patients receiving insulin therapy with poor blood sugar control and frequent episodes of hypoglycemia, apart from considering factors such as insulin dosage, formulation, administration method, and dietary rhythm, it is also crucial to consider performing pancreatic islet-related antibody and glucose tolerance tests to assess insulin and C-peptide levels. Special attention should be paid to the presence of dissociation between insulin and C-peptide to promptly detect EIAS.

Currently, there is no standardized treatment protocol for EIAS. The primary focus is on the correction of hypoglycemia and the conversion of IAAs to a negative status. Measures primarily encompass discontinuation of insulin therapy, administration of glucocorticoids, immunosuppressants, and plasma exchange, among others. Furthermore, patients are encouraged to implement nutritional interventions, such as adjusting dietary structure to include smaller and more frequent meals, and selecting carbohydrates with a low glycemic index, as well as enhancing lifestyle by engaging in mild aerobic exercise and avoiding excessive physical exertion or exercising on an empty stomach. These measures exhibit a certain efficacy in alleviating symptoms[31]. The course of EIAS is typically self-limiting and has a favorable prognosis. In most patients, hypoglycemic episodes can gradually be alleviated by discontinuing insulin therapy or in combination with oral antidiabetic medications and the implementation of lifestyle modifications.

CONCLUSION

In conclusion, both classic IAS and EIAS present with hypoglycemia and elevated serum levels of IAA. However, EIAS specifically manifests as a confirmed history of exogenous insulin therapy and no history of thiol-based drug use. Our understanding of the pathogenesis and progression of both classic IAS and EIAS remains incomplete, necessitating active exploration in clinical settings to enable accurate diagnosis and targeted treatments and avoid misdiagnosis or delayed illness. Larger sample sizes are required to enhance our understanding of this disease subtype. Furthermore, evidence-based medicine should guide further diagnosis and treatment.

FOOTNOTES

Co-first authors: Ling-Ling Xu and Jia-Xin Chen.

Co-corresponding authors: Jing-Ping Cheng and Ni Luo.

Author contributions: Xu LL wrote the manuscript; Chen JX proofread and verified the data in the manuscript; Cheng JP and Luo N screened patients and obtained clinical data and final reviewed the manuscript; All authors have read and approve the final manuscript. Xu LL summarized the data and wrote the first draft. Chen JX proof-collated the data and optimized the manuscript. Both authors have made crucial and indispensable contributions towards the completion of the project and thus qualified as the co-first authors of the paper. Both Cheng JP and Luo N have played important and indispensable roles in data interpretation and manuscript preparation as the co-corresponding authors. Cheng JP conceptualized, designed, and supervised the whole process of the project. Luo N was responsible for data re-analysis and re-interpretation, table drawing and ideas refining. This collaboration between Cheng JP and Luo N is crucial for the publication of this manuscript and other manuscripts still in preparation.

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Country/Territory of origin: China

ORCID number: Ling-Ling Xu 0009-0005-1047-0246; Jing-Ping Cheng 0009-0005-2251-6977; Ni Luo 0009-0007-7635-2247.

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CASE REPORT

Unexplained fetal tachycardia: A case report

Hui Wang, Run-Zi Duan, Xin-Jiu Bai, Bing-Ting Zhang, Jie Wang, Wen-Xia Song

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Hui Wang, Department of Nutrition, Changzhi Maternal and Child Health Care Hospital Affiliated to Changzhi Medical College, Changzhi 046000, Shanxi Province, China

Run-Zi Duan, Bing-Ting Zhang, Jie Wang, Department of Obstetrics, Changzhi Maternal and Child Health Care Hospital Affiliated to Changzhi Medical College, Changzhi 046000, Shanxi Province, China

Xin-Jiu Bai, Department of Gynaecology, Changzhi Maternal and Child Health Care Hospital Affiliated to Changzhi Medical College, Changzhi 046000, Shanxi Province, China

Wen-Xia Song, Department of Medical Genetic, Changzhi Maternal and Child Health Care Hospital Affiliated to Changzhi Medical College, Changzhi 046011, Shanxi Province, China

Corresponding author: Wen-Xia Song, MD, Chief Physician, Department of Medical Genetic, Changzhi Maternal and Child Health Care Hospital Affiliated to Changzhi Medical College, No. 48 Weiyuanmen Middle Road, Luzhou District, Changzhi 046011, Shanxi Province, China. songwenxia.love@163.com

Abstract

BACKGROUND

This study aimed to explore the possible etiology and treatment of severe fetal tachycardia in the absence of organic disease and provide a reference for clinical management of severe fetal tachycardia.

CASE SUMMARY

A 29-year-old pregnant woman, with a gravidity 1 parity 0, presented with a fetal heart rate (FHR) of 243 beats per minute during a routine antenatal examination at 31 + 2 wk of gestation. Before termination of pregnancy at 38 wk of gestation, the FHR repeatedly showed serious abnormalities, lasting more than 30 min. However, the pregnant woman and the fetus had no clinical symptoms, and repeated examination revealed no organic lesions. The mother and the baby were regularly followed up.

CONCLUSION

This was a case of severe fetal tachycardia with no organic lesions and management based on clinical experience.

Key Words: Fetal heart rate disorder; Fetal tachycardia; Severe tachycardia; Case report

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Core Tip: Clinical manifestations and obstetric management of this case demonstrated that the abnormal fetal heart rate (FHR) of unknown etiology could be transiently controlled by varying doses of sotalol hydrochloride tablets. However, not all pregnant women experience favorable outcomes. Therefore, the treatment and obstetric management strategies for unexplained FHR abnormalities need investigation.

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INTRODUCTION

Fetal arrhythmias are not common in clinical practice, and the probability of their detection during pregnancy is 0.6%–2%, especially unexplained fetal tachycardia. However, once sustained tachycardia occurs in the fetus during pregnancy, it may lead to fetal death, unexplained edema, and premature delivery, seriously threatening the health of the fetus and pregnant woman and requiring active identification and treatment by clinicians. We reported this case of fetal tachycardia (200 beats per minute) and positive outcomes of the mother and the infant after receiving placental therapy. Also, we comprehensively compared various treatment methods for fetal tachycardia in recent years to provide the basis for standardized diagnosis and treatment in the future.

CASE PRESENTATION

Chief complaints

The chief complaints were menopause for 31 + 2 wk and an abnormal fetal heart rate (FHR) for 1 d.

History of present illness

This was a 29-year-old patient with a gravidity 1 parity 0 (G1P0). The patient had regular menstrual cycles, with the last menstrual period on July 11, 2022. The expected date of confinement was April 18, 2023. The patient had no apparent signs of early pregnancy complications. Also, she had no history of radiation exposure or adverse medication use during early pregnancy to protect the fetus. Throughout the pregnancy, no significant abnormalities were observed in nuchal translucency value measurements, Down's screening results, or four-dimensional color ultrasounds. The oral glucose tolerance test results indicated higher fasting blood glucose levels than normal, leading to a diagnosis of gestational diabetes. Symptomatic treatment was provided through dietary adjustments and appropriate exercise; however, blood glucose monitoring in later stages was not reported. The patient had no complaints of dizziness, blurred vision, or palpitations during pregnancy. At 31 + 2 wk of gestation, the fluctuations in FHR were detected during an outpatient visit. The patient was mentally and emotionally stable throughout her pregnancy without any sleep disturbances or changes in appetite. She did not experience fever or chills nor exhibited symptoms such as coughing or production of sputum. The weight gain was approximately 20 kg while maintaining normal bowel movements and urine output without discomfort related to excessive drinking/eating/urination patterns observed by the patient herself. The blood pressure readings were within normal range throughout this period.

History of past illness

The patient was previously healthy. She had normal body temperature and no history of pregnancy anemia, abnormal thyroid function, or arrhythmia.

Personal and family history

The patient denied any family history of malignancy.

Physical examination

On physical examination, the vital signs were as follows: Body temperature: 36 °C; blood pressure: 152/88 mmHg; heart rate: 100 bpm; and respiratory rate: 20 breaths per minute. The other system examinations revealed no abnormalities.

Laboratory examinations

No abnormality was detected in routine blood and urine analyses.

Imaging examinations

The obstetric ultrasound (February 25, 2023) revealed the following: (1) Intrauterine pregnancy single live fetus (cephalic, ultrasound gestational age about 32 WLD); (2) anterior placenta; (3) appropriate amniotic fluid; and (4) fetal tachycardia.

Further examination was recommended. The obstetrical color ultrasound detected the FHR of 243 bpm. The fetal heart color ultrasound further confirmed the FHR of 243 bpm, and fetal cardiac structure showed no obvious abnormalities (Figure 1).

FINAL DIAGNOSIS

The final diagnosis was as follows: Abnormal fetal heart monitoring (fetal distress?), 31 + 2 wk G1P0, gestational diabetes, surgical history of teratoma, and pregnancy combined with obesity.

TREATMENT

The possibility of fetal distress could not be ruled out. The patient was admitted to the hospital to receive symptomatic treatment such as oxygen inhalation, continuous fetal heart monitoring, fetal lung maturity promotion, and labetalol 100 mg po q8h. During hospitalization, the FHR reached 230–270 bpm. The patient's vital signs were stable, without palpitation, abdominal distension, and vaginal water and bleeding. After referral to a higher-level hospital, sotalol hydrochloride tablets were given at a dose of 80 mg twice a day first, which was increased to 160 mg twice a day 3 d later. The patient was pregnant (33 + 6 wk), and the FHR was 133 bpm. The obstetric color ultrasound was performed at 34 + 6 wk of gestation, and the FHR was 213 bpm. The fetal heart color ultrasound was performed, revealing fetal tachycardia (FHR 231 bpm). No obvious abnormalities were found in the fetal cardiac structure (Figure 2). The dose of sotalol hydrochloride tablets was adjusted to 240 mg twice a day. The FHR was 143 bpm at 35 + 6 wk.

OUTCOME AND FOLLOW-UP

The pregnancy was terminated at 38 wk of gestation. The newborn weighed 3300 g. No arrhythmia was found in the pregnant woman or the newborn until 4 wk after delivery.

DISCUSSION

If fetal tachycardia occurs, the cause should be actively sought. Most cases of fetal tachycardia have a heart rate of less than 200 bpm, which usually does not require treatment but requires close follow-up[1,2]. Approximately 10%–20% of cases of fetal tachycardia require referral to a fetal cardiologist for further evaluation, and persistent fetal tachycardia with congestive cardiac dysfunction or fetal edema requires intrauterine or postpartum treatment[3,4]. One report of FHR > 224 bpm indicated that the persistence of fetal tachycardia was not necessarily caused by fetal hypoxia, and the heart rate was controlled by metoprolol treatment after transfer to a higher-grade hospital[5]. Another study indicated that fetuses without sustained tachycardia and without edema were usually treated with expectation, and the natural course of development was good. The fetus with nonedematous persistent tachycardia had a good effect of drug therapy on conversion, whereas the fetus with severe edema had a poor effect of drug therapy[6]. However, Strasburger *et al*[7] pointed out that fetal arrhythmias were usually managed during the second or third trimester of pregnancy, and it was emphasized that fetal echocardiography and magnetocardiography were the two primary means of diagnosing fetal arrhythmias. Transient or hidden arrhythmias, such as bundle branch block, long QT syndrome, and tip torsion, may lead to cardiomyopathy and sudden unexplained fetal death, and may also require medications. Therefore, no matter whether fetal tachycardia is benign or not, it may cause fetal edema or cardiac insufficiency. Recent studies have reported that prenatal maternal administration of digoxin, flucaine, sotalol, and amiodarone can control fetal tachycardia, but these drugs may cause serious adverse reactions. Therefore, currently, the standardized treatment for fetal tachyarrhythmia has not been established in clinical practice. It requires multi-institutional evaluation and follow-up, followed by determination and adjustment of initial treatment and dose, while considering pharmacokinetic factors, and close monitoring of maternal adverse reactions. A study on the prenatal treatment of supraventricular fetal arrhythmias indicated that tachyarrhythmia might still recur in the first 2 wk after birth[8].

Fetal tachycardia is a type of fetal arrhythmia. The FHR in the present case was severely abnormal, with intermittent repeated attacks of 230–270 bpm, lasting from several hours to several days. This was an extremely rare and severe fetal tachycardia. The case was actively referred to a higher-level hospital after discovery. After the oral administration of sotalol (32–38 wk of gestation), FHR was initially controlled. Despite an occasional increase in FHR, the fetal outcome was good. In recent years, the diagnosis of fetal tachycardia basically relies on continuous fetal heart monitoring chart and fetal heart color ultrasound to preliminarily exclude fetal organic lesions, and the management of fetal tachycardia is still in the stage of empirical research. Li Xiulan reported a case of FHR of 227–242 bpm, with biphase blood flow in the foramen ovale. Oral digoxin treatment was given considering the possibility of abnormal cardiac conduction in the fetus. The FHR returned to normal on the fourth day of medication, and the foramen ovale returned to normal after treatment [9]. Munoz *et al*[10] provided a unique treatment method: Intrauterine intramuscular injection of digoxin alleviated refractory fetal supraventricular tachycardia accompanied by fetal edema, which could be completely resolved by one-time injection. Yuan *et al*[11] administered sotalol orally to 10 mothers with fetal tachycardia (atrial fibrillation) for 7 d.

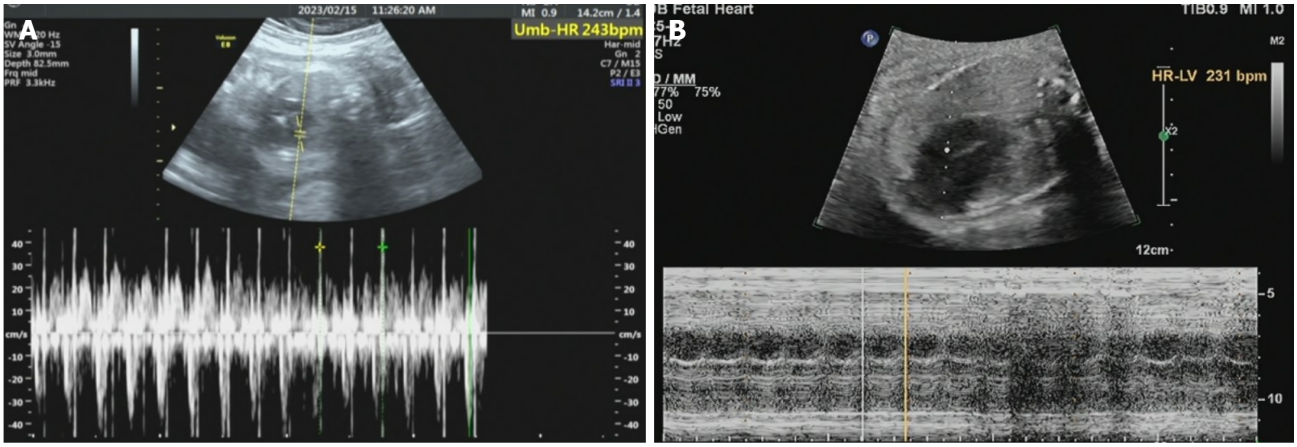

Figure 1 February 15, 2023, 31 + 2 B-mode ultrasonography images obstetric color ultrasound and fetal heart color ultrasound. A: B-mode ultrasonography images obstetric color ultrasound; B: Fetal heart color ultrasound.

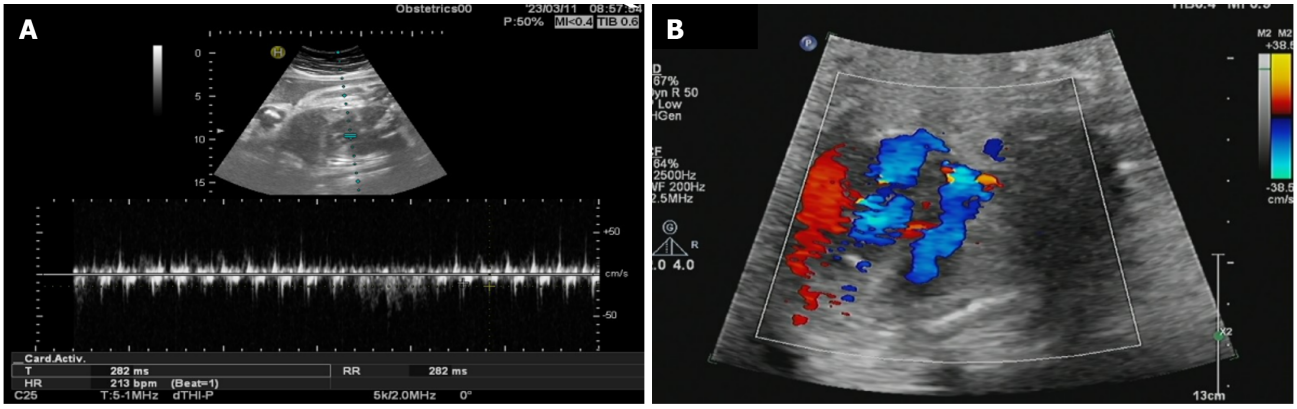

Figure 2 March 11, 2023, 34 + 6 B-mode ultrasonography images obstetric color ultrasound and fetal heart color ultrasound. A: B-mode ultrasonography image obstetric color ultrasound; B: Fetal heart color ultrasound.

Eight of these mothers had a conversion back to normal sinus rhythm, and one died after the dosage was increased. This indicated that sotalol was more efficient in treating fetal atrial fibrillation but less effective for other arrhythmias, especially for the fetus with supraventricular tachycardia, where the fatality rate was higher[12]. However, Purkayastha *et al*[13] pointed out that the management of fetal supraventricular tachycardia with flucanide or sotalol as monotherapy or in combination with digoxin might be the main approach, but this needs to be further evaluated in a practical setting. O'Leary *et al*[14] examined 57 cases of fetal persistent tachycardia at 13–37 wk under the control of digoxin, flucanide, sotalol, and amiodarone. They showed that the risk of fetal death in the uterus was minimal after placental therapy for persistent fetal tachycardia with normal cardiac structure. In another multicenter analysis of the prenatal treatment of 49 cases of supraventricular tachycardia, 44 cases of fetal tachyarrhythmias were controlled after treatment with digoxin, sotalol, and flucanide. One mother and four fetuses experienced severe adverse events (two of which were fetal death mainly due to heart failure), and tachyarrhythmia occurred in 15 neonates within 2 wk after birth[15]. Refaat *et al*[15] reported two cases of persistent fetal supraventricular tachycardia: One case was treated with flucanica–sotalol and the other with sotalol–digoxin, which effectively controlled fetal tachycardia, laying a foundation for the empirical treatment of first and second-line drugs. In the present case, severe fetal tachycardia was detected in a routine birth examination. No obvious abnormality was found in fetal cardiac color Doppler ultrasound, maternal electrocardiogram, maternal cardiac color Doppler ultrasound, and other examination results. Subsequent birth examination revealed multiple fetal tachycardia, and the maternal fetal outcome was good after sotalol treatment. In this case, although the fetus had no organic disease, the long-term rapid heart rate of the fetus increased the risk of fetal heart failure, intrauterine distress, and even intrauterine death. The symptoms were relieved after systematic treatment, and no obvious complications were found after the outcome of childbirth. When similar cases are encountered clinically, we should actively intervene and follow up closely. This approach holds positive significance for the health of both pregnant women and fetuses. However, the limitation of the present case was that the choice of drugs, initial dosing, and so forth for the management of unexplained fetal arrhythmia remained unclear.

CONCLUSION

The management of FHR abnormalities aims at reducing fetal hypoxia and improving fetal prognosis. When the cause of the abnormal FHR cannot be determined or no significant improvement is found in the FHR after conservative treatment, preparation for pregnancy termination should be done at the same time. For unexplained severe fetal tachycardia, only maternal factors can be excluded in clinical practice. At the same time, fetal heart color ultrasound is used to evaluate fetal heart structure abnormalities, edema, and fetal movement. During this period, only fetal heart monitoring is performed, and the mother and the child are observed to determine the next treatment. This case report discussed the clinical diagnosis and treatment of severe fetal tachycardia without organic lesions to provide a relevant basis for the standardized treatment of severe fetal tachycardia, ultimately reducing the perinatal adverse outcome rate for infants.

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FOOTNOTES

Co-first authors: Hui Wang and Run-Zi Duan.

Author contributions: Wang H and Duan RZ contributed equally to this work; Wang H and Duan RZ collected cases, recorded data and write review; Bai XJ processed the image; Zhang BT followed up patients; Wang J reeded and searched for paper; Song WX planed overall, wrote and modified review. All authors have read and approve the final manuscript.

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CASE REPORT

Challenging anticoagulation therapy for multiple primary malignant tumors combined with thrombosis: A case report and review of literature

Jia-Xin Chen, Ling-Ling Xu, Jing-Ping Cheng, Xun-Hua Xu

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Jia-Xin Chen, Ling-Ling Xu, Department of Gerontology, China Resources and Wisco General Hospital, Wuhan University of Science and Technology, Wuhan 430080, Hubei Province, China

Jia-Xin Chen, Ling-Ling Xu, Medical College, Wuhan University of Science and Technology, Wuhan 430065, Hubei Province, China

Jing-Ping Cheng, Department of Gerontology, China Resources and Wisco General Hospital, Wuhan 430080, Hubei Province, China

Xun-Hua Xu, Department of Radiology, China Resources and Wisco General Hospital, Wuhan 430080, Hubei Province, China

Corresponding author: Jing-Ping Cheng, Doctor, DPhil, Chief Doctor, China Resources and Wisco General Hospital, China Resources and Wisco General Hospital, No. 29 Metallurgical Avenue, Qingshan District, Wuhan 430080, Hubei Province, China. 404178516@qq.com

Abstract

BACKGROUND

Venous thromboembolism significantly contributes to patient deterioration and mortality. Management of its etiology and anticoagulation treatment is intricate, necessitating a comprehensive consideration of various factors, including the bleeding risk, dosage, specific anticoagulant medications, and duration of therapy. Herein, a case of lower extremity thrombosis with multiple primary malignant tumors and high risk of bleeding was reviewed to summarize the shortcomings of treatment and prudent anticoagulation experience.

CASE SUMMARY

An 83-year-old female patient was admitted to the hospital due to a 2-wk history of left lower extremity edema that had worsened over 2 d. Considering her medical history and relevant post-admission investigations, it was determined that the development of left lower extremity venous thrombosis and pulmonary embolism in this case could be attributed to a combination of factors, including multiple primary malignant tumors, iliac venous compression syndrome, previous novel coronavirus infection, and inadequate treatment for prior thrombotic events. However, the selection of appropriate anticoagulant medications, determination of optimal drug dosages, and establishment of an appropriate duration

of anticoagulation therapy were important because of concurrent thrombocytopenia, decreased quantitative fibrinogen levels, and renal insufficiency.

CONCLUSION
Anticoagulant prophylaxis should be promptly initiated in cases of high-risk thrombosis. Individualized anticoagulation therapy is required for complex thrombosis.

Key Words: Venous thromboembolism; Cancer-associated thrombosis; Anticoagulation therapy; iliac vein compression syndrome; COVID-19; Thrombocytopenia; Case report

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Core Tip: Lung cancer and pancreatic cancer form a rare combination of multiple primary malignant tumors. This patient had a rare lower extremity venous thrombosis complicated by pulmonary embolism. Its causes included a history of various malignant tumors, recent novel coronavirus infection, insufficient anticoagulant therapy for previous lower extremity thrombosis, and iliac vein compression syndrome. Anticoagulant therapy poses challenges to patients with active cancer and reduced fibrinogen levels; abnormally elevated D-dimer levels; and decreased platelet counts. This article provides a comprehensive overview of the therapeutic options for anticoagulation.

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INTRODUCTION

Venous thromboembolism is a leading cause of patient deterioration and mortality. The management of anticoagulant therapy for this condition is inherently complex, requiring careful consideration of various factors including bleeding risk, dosage and type of anticoagulants, and duration of treatment. Patients at high risk of thrombosis should receive prompt anticoagulation prophylaxis.

We present a case of venous thrombosis in the lower extremities and pulmonary embolism caused by an active tumor, iliac vein compression syndrome, history of novel coronavirus infection, and previous thrombosis that was inadequately treated. This case poses challenges for anticoagulation treatment, and we have provided a review of the relevant literature.

CASE PRESENTATION

Chief complaints

An 83-year-old female patient complained of edema in her left lower extremity for the 2 wk, which had worsened over the last 2 d.

History of present illness

A 2-wk history of swelling in the left lower extremity, which worsened in the last 2 d without dyspnea or chest pain.

History of past illness

The patient had a history of novel coronavirus infection 6 months prior and venous thrombosis in the right lower extremity (administered oral edoxaban tablets for 2 months but discontinued on her own). No blood clots were observed on ultrasound examination of either lower limb after treatment discontinuation. Two months prior, she was diagnosed with non-small cell lung cancer, pancreatic ductal adenocarcinoma, and metastasis to the liver and right inguinal lymph node. Her current treatments included oral tegafur, gimeracil, and oteracil potassium + almonertinib mesilate tablets. Routine blood tests, liver function tests, renal function tests, and coagulation results were normal.

Personal and family history

The patient denied any relevant family history.

Physical examination

Severe swelling in the left lower extremity. A few scattered petechiae were observed in the skin and mucosa.

Laboratory examinations

The patient's platelet count was 75×10^9/L↓, D-dimer (DD) 80.55 mg/LFEU↑, fibrinogen (FIB) 1.86 g/L↓, creatinine 84.9 μmol/L↑, and her liver function was within normal limits.

Imaging examinations

Double lower extremity vascular ultrasound indicated venous thrombosis in the left iliac, femoral, and popliteal veins. The patient underwent inferior vena cava venography, pulmonary arteriography, and lower extremity venography (Figure 1A).

FINAL DIAGNOSIS

Pulmonary artery embolism, left lower extremity venous thrombosis, left iliac vein compression syndrome, thrombocytopenia, renal insufficiency, non-small cell lung cancer, and pancreatic ductal adenocarcinoma.

TREATMENT

The patient discontinued her current treatment (oral tegafur, gimeracil, and oteracil tablets) and underwent percutaneous transcatheter pulmonary artery aspiration thrombectomy, inferior vena cava filter placement, percutaneous transcatheter lower extremity vein aspiration thrombectomy, venous balloon dilation angioplasty of the lower extremity, and stenting of the iliac vein (Figure 1). The patient declined edoxaban tablets due to palpitations and elevated blood pressure. Consequently, she was prescribed apixaban tablets (2.5 mg/dose, Q12h, orally) as anticoagulation therapy following surgery.

OUTCOME AND FOLLOW-UP

Following postoperative re-examination, lower extremity vascular ultrasound revealed venous thrombosis in the distal end of the left femoral and popliteal veins. Additionally, the platelet count was 79×10^9/L, CA199 2.40 U/mL, and DD 8.67 mg/LFEU. The dose of apixaban was adjusted to 5 mg Q12h, and tegafur, gimeracil, and oteracil were continue discontinued. DD and FIB after 4 months were re-examined (Table 1).

DISCUSSION

Coronavirus disease 2019 and venous thrombotic events

Both coronavirus disease 2019 (COVID-19) and long COVID-19 (also known as "acute sequelae of COVID-19") patients are susceptible to thrombotic disease due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis[1-4]. Thromboembolic complications resulting from COVID-19 have been extensively documented as primary contributors to sudden deterioration and mortality[5], highlighting the significance of prevention and early detection of thrombosis. The risk of thrombosis can be assessed by dynamically monitoring DD levels using various thrombus scoring tools, such as Caprini, Padua, and Improve[1,5,6]. Existing guidelines recommend that all COVID-19 patients who are not at a high risk of bleeding should receive anticoagulant prophylaxis[7-11]. The minimum duration of anticoagulant therapy for patients with venous thrombosis is 3 months[12].

In this case, the patient had COVID-19 infection 6 months prior. Anticoagulation prophylaxis was not administered during the infection period, and venous thrombosis of the lower extremities was identified within 1 month of recovery. The patient was prescribed anticoagulant therapy but discontinued after 2 months, which may have contributed to the occurrence of recurrent lower extremity venous thrombosis.

Iliac vein compression syndrome and venous thrombotic event

Iliac vein compression syndrome, also known as May-Thurner syndrome (MTS) or Cockett syndrome, is an anatomical variation resulting from compression of the left common iliac vein (LCIV) between the right common iliac artery and vertebrae[13]. While most cases are asymptomatic, compromised venous return and endothelial injury caused by chronic pulsatile compression of the LCIV by the right common iliac artery can occur, leading to subsequent obstruction and extensive deep vein thrombosis[14,15]. Venography is considered the gold standard for diagnosing MTS. MTS management involves alleviating LCIV compression and restoring normal blood flow through endovascular surgical intervention complemented by anticoagulation therapy[14,16]; this combination has been demonstrated to be an efficacious treatment for MTS[17]. The present patient was treated with this combination therapy.

Multiple primary malignant tumors and venous thrombotic event

Individuals with malignant tumors frequently have hypercoagulable blood and are prone to venous thrombotic events (VTEs). The incidence of VTEs varies across different cancers, with notably higher rates observed in pancreatic, gastric,

Table 1 The changes of indexes before and after operation were examined

Date	May 30, 2023, 13:00	May 30, 2023, 23:53	May 31, 2023	Operation	June 1, 2023	June 2, 2023	June 3, 2023	June 5, 2023	June 6, 2023	…	October 27, 2023
D-dimer (mg/L)	80.55	64.91	53.64	Operation	30.89	19.55	13.67	9.02	8.67	…	3.00
Fibrinogen quantification (g/L)	1.86	1.76	2.08	Operation	2.14	1.87	1.92	1.79	1.96	…	2.57

A notable reduction in the patient's postoperative D-dimer level was observed in comparison to the preoperative period.

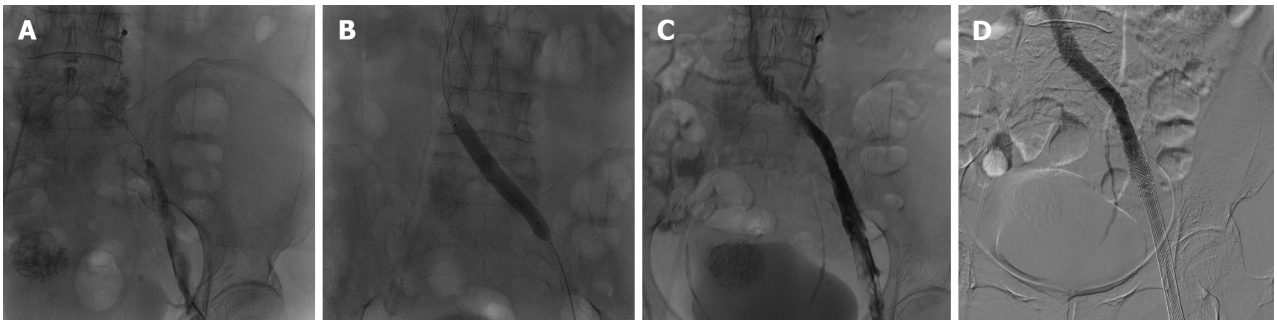

Figure 1 Contrast examination. A: Imaging *via* the left femoral vein. Contrast return into the inferior vena cava is obstructed. A filling defect (thrombus) is seen in the external iliac vein, the common iliac vein is thinned by compression, and the left lumbar ascending vein is visualized; B: Angiography after balloon dilation of the left common iliac vein; C: Post-balloon dilatation angioplasty imaging of the left common iliac vein. The contrast is seen to drain back into the inferior vena cava, but the common iliac vein is still markedly compressed. The external iliac vein and femoral vein are filled with defects (thrombi); D: Imaging after left common iliac vein-femoral vein stenting, with contrast converging into the inferior vena cava patently.

and lung cancers[18]. Furthermore, chemotherapy, radiation, and surgical interventions all elevate the risk of deep vein thrombosis (DVT)[19]. Specifically, the use of systemic chemotherapy has been associated with an 18-19-fold increase in VTE risk[20]. Moreover, cancer patients are at a higher risk of complications, including VTE recurrence and bleeding during VTE treatment, than those without cancer[19,21]. The absolute risk of developing subsequent VTE in patients with cancer with a history of VTE is 6-7-fold higher than that in patients without prior thromboembolic events[18]. The prevalence of DVT accompanied by pulmonary embolism has been documented to be relatively low, ranging from 29 to 78 cases per 100000 individuals annually. This prevalence increases with the presence of active tumors[22,23].

Venous thromboembolism ranks as the second leading cause of mortality among individuals with cancer[18,20]. It is advisable to provide thromboprophylaxis to all hospitalized cancer patients and high-risk outpatients, as determined by risk assessment models and computerized tools, in a timely and targeted manner. This approach aims to reduce the incidence of thrombotic events, enhance the prognosis of cancer patients, and ultimately improve survival. A recent article deliberating on the appropriateness of thromboprophylaxis for cancer outpatients suggested that barring a high risk of bleeding, initial thromboprophylaxis is recommended for individuals with pancreatic cancer and lung cancer who may harbor anaplastic lymphoma kinase/ROS proto-oncogene 1, receptor tyrosine kinase translocations. Patients with upper gastrointestinal cancers are at a higher risk of VTE; however, a thorough evaluation of bleeding risk should precede decisions regarding antithrombotic prophylaxis. Notably, for cancer patients with a heightened risk of bleeding, such as those with brain cancer, moderate-to-severe thrombocytopenia, or severe renal impairment, it is not advisable to pursue primary prevention of VTE. In cases where patients present with absolute contraindications for anticoagulation therapy, such as active bleeding or severe long-term thrombocytopenia, inferior vena cava filter implantation may be considered based on specific circumstances[24].

Substantial evidence has accumulated regarding the advantages of anticoagulant therapy in individuals with highly thromboembolic tumors[25,26]. The Prospective Randomized Trial of Enoxaparin and Chemotherapy Concurrently for Pancreatic Cancer was formulated to assess the effectiveness of enoxaparin in patients with locally advanced or metastatic pancreatic cancer undergoing systemic chemotherapy. The findings indicated a reduction in the prevalence of VTEs from 87.1% to 25.3% at 9 months, and from 13.5% to 12% at 15 months[25]. The administration of anticoagulant intervention in patients with pancreatic cancer resulted in a significant reduction in the incidence of VTE, from 23% to 3.4%[26].

A review of multiple clinical guidelines from American society of clinical oncology (ASCO), European society for medical oncology (ESMO), and national comprehensive cancer network (NCCN) states that low molecular weight heparin (LMWH) or normal heparin is the recommended standard of care for the prevention and treatment of cancer-associated thrombosis (CAT)[19,27-29]. LMWH is the preferred choice due to its lower risk of heparin-induced thrombocytopenia and convenient administration[27,30,31]. However, patients may experience an injection burden after hospital discharge, and direct oral anticoagulants are approved as alternatives to LMWH for the treatment of CAT[21,29]. According to the 2023 ASCO guidelines, apixaban is effective in reducing the risk of recurrent VTE and has a lower risk of

Table 2 Anticoagulation regimens in different situations

	Mode of administration	Initial therapeutic dose	Maintenance of therapeutic dose	Extended treatment dose
Unfractionated heparin	Intravenous	Maintain APTT 1.5 times the upper limit of normal	/	/
Low molecular heparin	Subcutaneous	200 IU/kg/d for 1 month	150 IU/kg	/
Rivaroxaban	Oral	15 mg each time, twice a day for 3 wk	20 mg each time, once a day	20 mg each time, once a day
Apixaban	Oral	10 mg each time, twice a day for 1 wk	5 mg each time, twice a day	2.5 mg each time Twice a day
Eldosaban	Oral	At least 5 d of heparin introduction is required, with dose reduction after LMWH introduction, *i.e.* 30 mg each time, once a day	60 mg each time, once a day	60 mg each time, once a day

LMWH: Low molecular weight heparin; APTT: Activated partial thromboplastin time.

major bleeding. Additionally, a panel of experts agreed that apixaban could be recommended as an alternative treatment for CAT[19]. However, the CHEST guidelines update article published in 2021 indicated that oral Xa inhibitors (apixaban, edoxaban, and rivaroxaban) are more strongly recommended than LMWH for treatment initiation in patients with acute VTE and cancer-associated thrombosis (strong recommendation, moderate quality evidence)[32].

However, an article published in 2016 in *Lancet* suggested that direct oral anticoagulants should not be the first choice for VTE in patients with active cancer, although there are no contraindications[33]. The use of LMWH or oral anticoagulants in the acute phase remains controversial; further large-scale clinical trials are needed. In this case, an oral anticoagulant was used immediately after interventional therapy. However, the dose of anticoagulant was insufficient; the therapeutic effect on CAT could not achieve the ideal effect in theory.

Thrombocytopenia frequently leads to the discontinuation of anticoagulation therapy in cancer patients. Therefore, the guidelines recommend that patients with platelet counts ≥ 50×10^9/L receive full-dose anticoagulation (whether with using LMWH or an oral anticoagulant) without concomitant platelet transfusions[34-36]. CAT therapy typically consists of three phases: acute (occurring 5-10 d after diagnosis), maintenance (lasting 3-6 months), and extended phase (lasting > 6 months). In patients with active cancer undergoing cancer therapy, where the risk of recurrence outweighs bleeding complications, an extension of anticoagulation therapy for > 6 months may be considered. The recommended anticoagulation therapies for each period are presented in Table 2 Unfractionated heparin is recommended for patients with severe renal insufficiency (CrCl < 30 mL/min) because of the elevated risk of hemorrhage and recurrent venous thrombosis associated with anticoagulant therapy[29].

In conclusion, the patient was in the acute stage of thrombosis at present. However, considering advanced age; thrombocytopenia; renal insufficiency; presence of a few scattered petechial dots on the skin and mucosa; and the slightly higher risk of anticoagulant bleeding in this patient, interventional therapy and apixaban (2.5 mg twice a day) were initially administered. After observation, petechiae in the skin and mucosa did not progress; the DD was 13.67 mg/L; and there was still thrombus on the reexamination using color Doppler ultrasound. The effect of anticoagulant therapy was considered to be unsatisfactory. Therefore, the dose of apixaban tablets was adjusted to 5 mg twice a day. The deficiencies in the treatment of the low-risk thrombocytopenia in this patient include: Receiving no anticoagulant prophylaxis. In addition, the dose of anticoagulant therapy was slightly lower than the recommended dose according to the guidelines. After follow-up, DD in the patient was significantly decreased. Furthermore, no more serious bleeding events occurred, which also indicated that the combined treatment scheme in this case was feasible; anticoagulant therapy was safe and effective.

Paradoxical manifestation of DD and FIB

FIB plays a crucial role as a reactive substrate in thrombosis and is implicated in critical stages[37]. DD, a small protein fragment resulting from fibrin breakdown, has been the subject of research as a predictive biomarker for VTE in cancer [18,38]. Elevated DD and FIB levels are commonly observed in patients with COVID-19 and those with malignancy[5]. The decrease in FIB is common in patients with primary and secondary hyperfibrinolysis, such as DIC. Additionally, impairment in liver cell function leads to the decrease in liver synthesis, snake venom therapy, and thrombolytic therapy. In conjunction with the present case, the patient in question had a tumor and experienced VTEs. In such cases, DD and FIB should be theoretically elevated; however, this patient exhibited abnormally elevated DD, low FIB levels, and a decreased platelet count. When considering the patient's history of a normal coagulation phase, it is reasonable to suspect the presence of DIC and a reduction in FIB due to the substantial consumption of FIB within the body.

CONCLUSION

In summary, patients with active cancer, chemotherapy, novel coronavirus infection, and iliac vein compression syndrome should be on high alert for venous thrombosis. This requires dynamic assessment of anticoagulation and bleeding risks; comprehensive management; reduction in thrombotic events; preventing bleeding complications and recurrence; and improvement in prognosis.

FOOTNOTES

Co-first authors: Jia-Xin Chen and Ling-Ling Xu.

Co-corresponding authors: Jing-Ping Cheng and Xun-Hua Xu.

Author contributions: Chen JX and Xu LL contributed to manuscript writing and editing, and data collection; Cheng JP and Xu XH were responsible for conceptualization, supervision and communication contacts. All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. The reasons for designating Cheng JP and Xu XH as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding 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-corresponding authors best reflects 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, Cheng JP and Xu XH contributed efforts of equal substance throughout the research process. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Cheng JP and Xu XH as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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Country/Territory of origin: China

ORCID number: Jia-Xin Chen 0009-0005-5419-7229; Ling-Ling Xu 0009-0005-1047-0246; Jing-Ping Cheng 0009-0005-2251-6977; Xun-Hua Xu 0000-0002-8364-1393.

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LETTER TO THE EDITOR

Epinephrine also acts on beta cells and insulin secretion

Lina Zabuliene, Ioannis Ilias

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Lina Zabuliene, Faculty of Medicine, Vilnius University, Vilnius LT-03101, Lithuania

Ioannis Ilias, Department of Endocrinology, "Hippokration" General Hospital, Athens GR-11527, Greece

Corresponding author: Ioannis Ilias, MD, PhD, Director, Department of Endocrinology, "Hippokration" General Hospital, No. 63 Evrou Street, Athens GR-11527, Greece. iiliasmd@yahoo.com

Abstract

In a recent review examining neurotransmitter modulation of insulin secretion, the significant impact of epinephrine was not addressed. Its primary action involves inhibiting insulin release *via* alpha-adrenergic receptors, thereby reducing the response to insulin secretion stimulators, through the activation of K+ channels and resulting in membrane hyperpolarization in beta cells.

Key Words: Epinephrine; Insulin; Islets; Glucose; Human

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Core Tip: Among the neurotransmitters influencing insulin secretion, the role of epinephrine (EPI) might be underestimated. EPI mainly inhibits insulin release through alpha-adrenergic receptors, thereby attenuating the response to insulin secretion stimulators.

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TO THE EDITOR

We have reviewed with interest the concise examination by Kong *et al*[1] of neurotransmitter influence on insulin secretion. While the authors extensively cover norepinephrine (NEPI), the role of epinephrine (EPI) is overlooked. Both EPI and NEPI, acting as neurotransmitters and hormones, are synthesized and released in the central

and peripheral nervous systems and the adrenal medulla[2]. Despite NEPI's primary role as a neurotransmitter, the significance of EPI, which also functions as a hormone, should not be disregarded for its neurotransmitter functions. Hence, EPI's impact closely parallels that of NEPI, though with more pronounced peripheral effects[2].

EPI can prompt insulin release *via* beta-adrenergic receptor activation, involving adenylate cyclase, cAMP generation, and the cAMP Response Element-Binding Protein pathway[3]. However, its primary effect, mediated by alpha-adrenergic receptor activation, inhibits insulin secretion through the Protein kinase A pathway. This inhibition significantly moderates the response to insulin's strongest stimulants[4]. EPI achieves this by activating K+ channels, leading to hyperpolarization of pancreatic beta cell membranes[5,6].

The above concise overview of EPI's impact on insulin secretion complements the excellent and comprehensive review of neurotransmitter effects on insulin secretion[1].

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Lina Zabuliene 0000-0002-7889-0862; Ioannis Ilias 0000-0001-5718-7441.

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