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ABOUT COVER

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EDITORIAL

Efficacy of probiotics supplementation in amelioration of celiac disease symptoms and enhancement of immune system

Mostafa Hossam-Eldin Moawad, Ibraheem M Alkhawaldeh, Abdulqadir J Naswhan

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Abstract

Patients with celiac disease (CD) have a mucosal layer that is unable to regulate the gut microbiota, leaving the host vulnerable to dangerous infections and antigens. When compared to healthy people, this dysbiosis is marked by a decrease in intra- and intergeneric biodiversity, which demonstrates an imbalance between helpful bacteria and possibly harmful or proinflammatory species. The early gut microbiota is influenced by the genotype of newborns with the HLA-DQ2 haplotypes, and this may modify how gluten is handled in the intestinal lumen, polarize innate or adaptive immune responses, and result in gluten-sensitive enteropathy. The outcome of gluten digestion can vary depending on the composition of the intestinal gut bacteria and the partial conversion of gluten into peptides larger than ten amino acids in the small intestines, which can be immunogenic. In the small intestine, 114 different bacterial strains belonging to 32 different species have 27 of them exhibiting peptidolytic activity. Thus, the individual risk of developing a gluten-related illness is further influenced by microbial composition and gluten degrading capacity. The conclusion that *lactobacilli* and *Bifidobacterium* spp. may be used as a probiotic supplement in CD patients is based on their shared possession of the most extensive peptidolytic and proteolytic activity thought to be engaged in the breakdown of gluten among all potential bacterial genera present in the gut microbiota. In children with CD autoimmunity, daily oral dose of *Lactobacillus. plantarum* HEAL9 and *Lactobacillus. paracasei* 8700:2 was found to modify the peripheral immune response. *Bifidobacterium. breve* strains have demonstrated a beneficial effect on reducing pro-inflammatory cytokine TNF- production in CD children on gluten-free diets.

Key Words: Celiac disease; Gut microbiota; Probiotics; Probiotics supplementation; Efficacy; Immune system

Core Tip: In the context of celiac disease (CD), probiotics emerge as a multifaceted therapeutic approach with promising implications. Clinical trials demonstrate their potential to modulate immune responses, alleviate gastrointestinal symptoms, and reshape the gut microbiota in CD patients. Notably, specific probiotic strains have shown the ability to enzymatically break down immunotoxic gluten peptides, addressing a central challenge in CD pathogenesis. This dual-pronged role positions probiotics as a holistic means of CD management, offering immunomodulation and symptom relief to patients while potentially mitigating the toxicity of gluten peptides. Probiotics thus represent an encouraging avenue for enhancing the quality of life for individuals living with CD, underscoring their significance in the evolving landscape of CD treatment.

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INTRODUCTION

The small intestine is primarily affected by celiac disease (CD), an autoimmune ailment that develops in those with a hereditary predisposition to gluten and is characterized by symptoms on both the intestinal and extraintestinal levels. The increasing body of research provides support for the hypothesis that changes in the composition and functionality of the gut microbiome are associated with various chronic inflammatory conditions such as inflammatory bowel disease, cancer, and Crohn's disease[1].

The gut microbiota plays a crucial role in promoting tolerance in normal physiological conditions. However, any disruption in the microbiota, known as dysbiosis, can disturb the balance between immune responses that promote tolerance and those that induce inflammation. This imbalance can contribute to the development of diseases such as Crohn's disease, which is characterized by an overactive Th1 immune response. The small intestine of people who have CD makes partial metabolism (due to dysbiosis) to gluten leading to its breakage into large chains of more than 10 amino acids which is immunogenic. The principal probiotic bacteria are *Lactobacillus* and *Bifidobacterium* species, which are found in the intestinal environment. *Bifidobacteria* produce exopolysaccharides that serve as fermentable substrates for additional human intestinal bacteria, whereas *lactobacilli* can secrete mucins, reinforce the epithelial barrier, improve tight-junction activities, and inhibit the epithelial cells death . It was discovered that microbiota composed of *Bifidobacterium* and *lactobacilli* can produce more active peptidases to break down those long chain amino acids, thus protecting the intestine from severe immunological reaction when ingesting gluten[2].

Increased interferon (IFN)-γ synthesis in CD causes TNF-α secretion, which is crucial for causing intestinal mucosal injury and inflammation. Increased production of TNF-α is also associated with lower *Firmicutes/Bacteroidetes* ratio which is considered a major dysbiosis in CD patients. Klemenak *et al*[3] and Quagliariello *et al*[4] demonstrated a decline in TNF-α and the increase of the *Firmicutes/Bacteroidetes* ratio, respectively, after treatment with *B.breve* which is in line with Primec *et al*[5] who showed that after 3 mo of *B.breve* treatment, TNF-α was reduced with parallel increase in *Firmicutes*.

Khorzoghi *et al*[6] studied how probiotic administration affected the composition of the intestinal microbiota and how clinical symptoms in CD patients improved as a result. In this investigation, the ingestion of a probiotic combination containing *Bifidobacterium* spp., *Lactobacillus* spp., and *S. thermophilus* resulted in a reduction in the intensity of clinical symptoms (fatigue, muscle discomfort, bloating, and a gassy feeling) compared to placebo. The relative levels of *Lactobacillus*, *Bacteroidetes*spp., *Bifidobacterium* spp., *Clostridium* cluster I, *Enterobacteriaceae*, and *Firmicutes* were higher in the probiotics group than they were in the control group, with the exception of *Staphylococcus* spp. In light of this, a 12-week probiotic multi-strain treatment plan could alter the make-up of the intestinal microbiota and lessen gastrointestinal symptoms in CD patients. According to Klemenak *et al*[3] and Quagliariello *et al*[4], *B. breve* strains combined with GFD act on a decrease in TNF- α production, which may have an impact on preventing a pro-inflammatory milieu in children with CD. The effects of this probiotic pill, however, only last while being consumed. Three months following the end of the intervention, Klemenak *et al*[3] discovered that TNF-α levels have nearly completely returned to baseline levels. Therefore, further trials are required to investigate a long-lasting effect of probiotic pills and control the microbiota environment of the CD patients.

Håkansson *et al*[7] conducted a randomized, double-blind, placebo-controlled clinical trial for children with CD. The main result was the steady alteration in the peripheral immune response; demonstrated by T cells regulation and decreased their concentration and responses in the probiotic group compared to placebo group indicating that *L. paracasei* 8700:2 and *L. plantarum* HEAL9 were capable of modulating the peripheral immune response in CD autoimmunity. The median levels of IgA-tTG also decreased as a result of the probiotic therapy (P = 0.013).

In a major prospective, randomized study, Francavilla *et al*[8] combined five strains of lactic acid bacteria and *bifidobacteria*: *L. casei* LMG 101/37 P-17504, *L. plantarum* CECT 4528, *B. animalis* subsp. lactis Bi1 LMG P-17502, *B. breve* Bbr8 LMG P-17501, and B. breve Bl10 LMG P-17500. They recruited 109 CD patients who strictly adhered to a GFD and had signs and symptoms of irritable bowel syndrome (IBS). They were randomly assigned for six weeks to receive

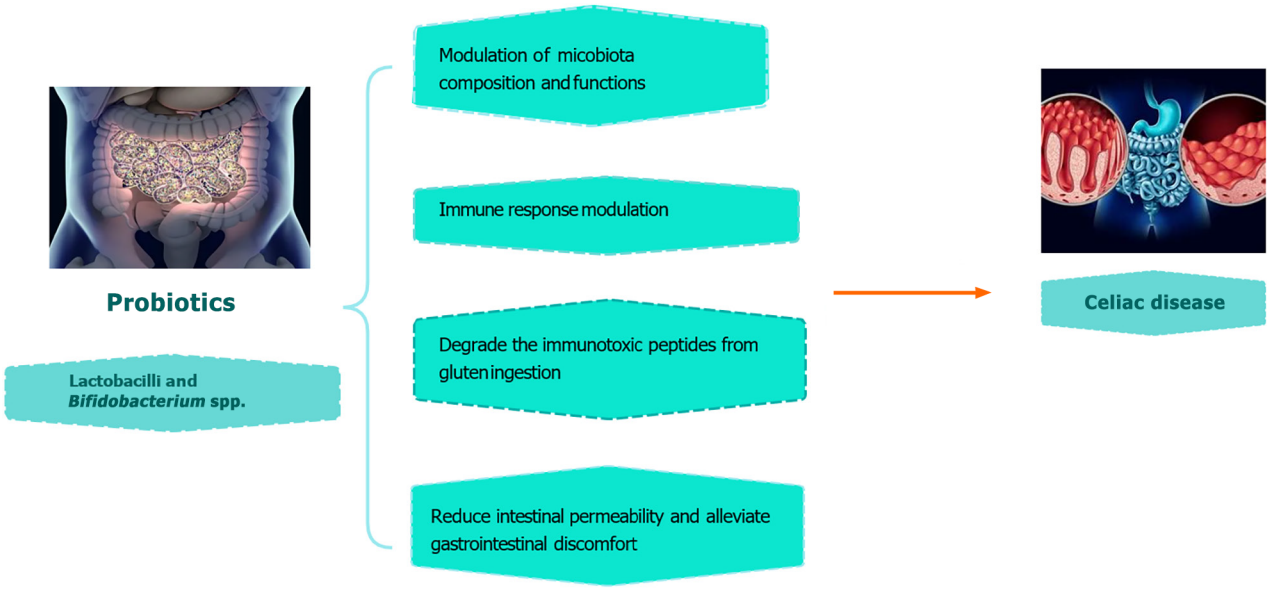

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Figure 1 The possible advantages of using probiotics in celiac disease patients.

probiotics or a placebo, and then were monitored for another six weeks. The findings showed that this probiotic mixture was effective in reducing the severity of gastrointestinal symptoms, with a decreased feeling of pain on various clinical assessments and a significantly greater percentage of treatment success (defined as at least a 50% decrease in the symptom scores). With a rise in lactic acid bacteria, *Bifidobacterium*, and *Staphylococcus* that was remained observable six weeks after the withdrawal of probiotics, they were able to demonstrate a favorable modification of the gut microbiota (Figure 1).

In a different trial[9], 20 CD patients received hydrolyzed wheat gluten bread with *L. alimentaris*, *L. brevis*, *L. sanfranciscenis*, and *L. hilgardi* for six days. In comparison to healthy controls, the findings revealed no substantial rise in IFN-γ. Thus, clinical trials have recently produced growing and positive outcomes. Serological, histological, and immunohistochemical characteristics were unaffected when CD patients were fed a diet of baked goods with less than 10 ppm of gluten prepared from fermented wheat flour. Similar outcomes were attained when CD patients in remission were exposed to *lactobacilli* that had already digested gluten for 60 d[10]. Patients' symptoms, intestinal permeability, or serological markers did not worsen, indicating that lactobacilli-derived endopeptidases may be capable of completely breaking down gluten and reducing gluten toxicity in CD patients[10].

CONCLUSION

Due to this findings, present research aims to identify probiotic strains that can totally degrade the immunotoxic peptides from gluten ingestion. Therefore, probiotics are the uprising mainstay of treatment of CD patients whether by their administration to them or by their effect of gluten peptides that cause autoimmune reactions.

FOOTNOTES

Author contributions: Ibraheem M Alkhawaldeh, Mostafa Hossam-Eldin Moawad and Abdulqadir J Nashwan contributed to this paper; Ibraheem M Alkhawaldeh and Mostafa Hossam-Eldin Moawad designed the overall concept and outline of the manuscript; Ibraheem M Alkhawaldeh, Mostafa Hossam-Eldin Moawad, and Abdulqadir J Nashwan contributed to the writing, and editing the manuscript, illustrations, and review of the literature.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Effect of enhanced recovery after surgery with multidisciplinary collaboration on nursing outcomes after total knee arthroplasty

Jing Liu, Qian-Qian Zheng, Yang-Tao Wu

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Abstract

BACKGROUND

There is a lack of studies on the effects of enhanced recovery after surgery (ERAS) with multidisciplinary collaboration on the nursing outcomes of total knee arthroplasty (TKA).

AIM

To explore the effect of ERAS with multidisciplinary collaboration on nursing outcomes after TKA.

METHODS

We retrospectively analyzed the clinical data of 80 patients who underwent TKA at a tertiary hospital between January 2021 and December 2022. The patients were divided into two groups according to the nursing mode: the ERAS group (n = 40) received ERAS with multidisciplinary collaboration, and the conventional group (n = 40) received routine nursing. The following indicators were compared between the two groups: length of hospital stay, hospitalization cost, intraoperative blood loss, hemoglobin level 24 h after surgery, visual analog scale (VAS) score for pain, range of motion (ROM) of the knee joint, Hospital for Special Surgery (HSS) knee score, and postoperative complications.

RESULTS

The ERAS group had a significantly shorter length of hospital stay, lower hospitalization cost, less intraoperative blood loss, higher hemoglobin level 24 h after surgery, lower VAS score for pain, higher knee joint ROM, and higher HSS knee score than the conventional group (all $P < 0.05$). There was no significant difference in the incidence of postoperative complications between the two groups ($P > 0.05$).

CONCLUSION

Multidisciplinary collaboration with ERAS can reduce blood loss, shorten hospital stay, and improve knee function in patients undergoing TKA.

Key Words: Arthroplasty, replacement, knee; Retrospective studies; Range of motion, articular; Length of stay; Blood loss, surgical; Hemoglobins

Core Tip: Enhanced recovery after surgery (ERAS) with multidisciplinary collaboration improves nursing outcomes in total knee arthroplasty (TKA). Compared to conventional nursing, ERAS leads to shorter hospital stays, lower costs, reduced blood loss, higher hemoglobin levels, decreased pain as per visual analog scale scores, improved knee joint range of motion, and higher Hospital for Special Surgery knee scores. There is no significant difference in postoperative complications. Multidisciplinary collaboration with ERAS enhances TKA patient outcomes by reducing blood loss, shortening hospital stays, and improving knee function.

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INTRODUCTION

Knee osteoarthritis is a degenerative joint disease that affects millions of people worldwide, causing pain, disability, and a reduced quality of life[1]. It is a major public health problem that imposes a heavy burden on healthcare systems and society[2]. The prevalence of knee osteoarthritis increases with age, obesity, and physical inactivity and is expected to rise due to the aging population and the obesity epidemic[3].

Total knee arthroplasty (TKA) is a surgical procedure that replaces the damaged articular surfaces of the knee joint with artificial implants to relieve pain and restore function[4]. It is one of the most successful and cost-effective interventions for end-stage knee osteoarthritis[5]. However, TKA is a major surgery that involves significant trauma, blood loss, and pain and requires a long recovery period[6]. Conventional perioperative care for patients undergoing TKA is often suboptimal, resulting in delayed mobilization, prolonged hospital stay, high hospitalization costs, and an increased risk of complications[7].

Enhanced recovery after surgery (ERAS) is a novel perioperative care model that integrates evidence-based interventions to optimize recovery in surgical patients[8,9]. It was first developed for colorectal surgery in the 1990s by Kehlet *et al*[10] in Denmark and has since been applied in various surgical specialties, including orthopedic surgery. ERAS aims to reduce the surgical stress response, enhance physiological function, and minimize postoperative morbidity and mortality in patients[11]. ERAS has been shown to improve the outcomes of patients with TKA by reducing blood loss, pain, opioid consumption, hospital stay, and complications and improving patient satisfaction and functional recovery[12-14].

Multidisciplinary collaboration is an essential element of ERAS that requires the involvement and coordination of different health professionals throughout the perioperative period[15]. This ensures that patients receive standardized and individualized care based on the best available evidence and their specific needs[16]. Multidisciplinary collaboration also facilitates communication and education among health professionals, patients, and their families, which can improve the quality and safety of care and the satisfaction and compliance of all parties[17].

However, there is a lack of studies on the effects of ERAS with multidisciplinary collaboration on the nursing outcomes of TKA. Nursing outcomes are defined as "the effects or results of nursing interventions on individuals or groups"[18]. They reflect the quality and effectiveness of nursing care and the impact of nursing care on patient outcomes. Nursing outcomes are important indicators for evaluating and improving nursing practice, as well as for demonstrating the value and contribution of nursing to health care[18].

Therefore, this study aimed to explore the effects of ERAS with multidisciplinary collaboration on the nursing outcomes of TKA.

MATERIALS AND METHODS

Study design and ethical approval

This retrospective cohort study used the electronic medical records of 80 patients who underwent TKA at a tertiary hospital between January 2021 and December 2022. The study was approved by the ethics committee of the hospital, and the requirement for informed consent was waived because of the retrospective nature of the study.

Patient allocation

The patients were divided into two groups according to the nursing mode: the ERAS group (n = 40) received ERAS with multidisciplinary collaboration, and the conventional group (n = 40) received routine nursing. The allocation of patients to the groups was based on the availability of ERAS protocols and the hospital's multidisciplinary team. The ERAS protocols and multidisciplinary team were implemented in the hospital in July 2021. All patients who underwent TKA thereafter were assigned to the ERAS group. Patients who had undergone TKA before that date were assigned to the conventional group.

ERAS group protocol

The ERAS group followed the ERAS protocols developed by our hospital based on a literature review and expert consensus[19,20]. The main components of the ERAS protocol were as follows:

Preoperative education: The patients received a booklet and video on the TKA procedure, anesthesia options, pain management, wound care, mobilization exercises, and discharge criteria. Patients were also invited to attend a preoperative education session led by a nurse educator in which they could ask questions and clarify their doubts. Patients were encouraged to bring their family members or caregivers to the sessions.

Anesthesia: The patients received spinal anesthesia with intrathecal morphine, which provided adequate analgesia and minimized blood loss and opioid consumption. Patients also received a femoral nerve block with ropivacaine, which enhanced postoperative analgesia and facilitated early mobilization.

Analgesia: The patients received multimodal analgesia, including oral acetaminophen, celecoxib, tramadol, intravenous ketorolac, and dexmedetomidine. Patients did not undergo patient-controlled analgesia (PCA) with morphine because it was associated with more side effects and delayed recovery. Patients rated their pain on a visual analog scale (VAS) every 4 h, and the analgesics were adjusted accordingly.

Fluid management: The patients received restrictive fluid therapy to maintain a near-normal fluid balance and avoid fluid overload. Patients received intravenous crystalloids at a rate of 2 mL/kg/h during surgery, and oral fluids were tolerated after surgery. The patients did not receive colloids or blood transfusions unless indicated by hemodynamic instability or severe anemia.

Nutrition: The patient resumed oral intake within 6 h after surgery and received a high-protein diet thereafter. The patients did not receive a nasogastric tube or parenteral nutrition unless indicated by gastrointestinal dysfunction or malnutrition.

Mobilization: Patients started passive range-of-motion (ROM) exercises of the knee joint within 2 h after surgery and active ROM exercises within 6 h. The patients were assisted in getting out of bed and walking with a walker within 12 h. The patients also received daily physiotherapy until discharge.

Discharge criteria: The patients were discharged when they met the following criteria: (1) Stable vital signs; (2) adequate pain control; (3) wound healing without infection; (4) independent walking with assistive devices; (5) ROM of the knee joint ≥ 90°; and (6) Hospital for Special Surgery (HSS) knee score ≥ 85.

Conventional group protocol

The conventional group received routine nursing care according to hospital guidelines, mainly comprising preoperative education and a brief introduction to the TKA procedure and postoperative care from nurses.

Anesthesia: The patients received general or spinal anesthesia according to their preference and the anesthesiologist's decision.

Analgesia: The patients received intravenous PCA with morphine for 48 h after surgery, followed by oral analgesics as needed.

Fluid management: The patients received intravenous fluids for 24 h after surgery, followed by oral fluids as tolerated.

Nutrition: The patients resumed oral intake on the first day after surgery and received a regular diet thereafter.

Mobilization: The patients started passive ROM exercises of the knee joint on the first day after surgery and active ROM exercises on the second day. The patients were assisted in getting out of bed and walking with a walker on the third day.

Discharge criteria: These were the same as for the ERAS group.

Comparisons and indicators

The following indicators were compared between the two groups:

Length of hospital stay – the number of days from the day of surgery to the day of discharge.

Hospitalization cost – the total cost of hospitalization, including surgery, anesthesia, medication, laboratory tests, imaging examinations, nursing care, and rehabilitation.

Intraoperative blood loss – the amount of blood loss during surgery, measured by weighing the gauze and suction bottles.

Hemoglobin level 24 h after surgery – the hemoglobin level in the blood sample taken 24 h after surgery.

VAS score for pain – the intensity of pain rated by the patients on a scale from 0 (no pain) to 10 (worst pain imaginable), measured 24, 48, and 72 h after surgery.

ROM of the knee joint – the degree of flexion and extension of the knee joint, measured by a goniometer at 24, 48, and 72 h after surgery.

HSS knee score – the functional status of the knee joint, evaluated by a standardized questionnaire that includes pain, function, ROM, muscle strength, stability, deformity, and walking distance, measured before surgery and at discharge, with the score ranging from 0 (worst) to 100 (best).

Postoperative complications – the occurrence of adverse events after surgery, such as infection, bleeding, hematoma, wound dehiscence, deep vein thrombosis, pulmonary embolism, nerve injury, or implant failure.

Data collection and analysis

Data were collected by two trained nurses who were blinded to the group allocation. Data were analyzed using SPSS software version 22.0. The measurement data were expressed as mean ± SD or median (interquartile range) and compared by *t*-test or Mann-Whitney U test. Count data are expressed as frequencies (percentages) and were compared using the chi-square or Fisher's exact test. Statistical significance was set at $P < 0.05$ significant.

RESULTS

Demographic and clinical characteristics

The demographic and clinical characteristics of the two groups are presented in Table 1. There were no significant differences in age, sex, body mass index, ASA physical status, or preoperative HSS knee score between the two groups (all $P > 0.05$).

Nursing outcomes

The nursing outcomes of the two groups are presented in Table 2. The ERAS group had a significantly shorter length of hospital stay, lower hospitalization cost, less intraoperative blood loss, higher hemoglobin level 24 h after surgery, lower VAS score for pain, higher ROM of the knee joint, and higher HSS knee score than the conventional group (all $P < 0.05$). There was no significant difference in the incidence of postoperative complications between the two groups ($P > 0.05$).

DISCUSSION

This study showed that ERAS with multidisciplinary collaboration can improve nursing outcomes after TKA, such as reducing blood loss, shortening hospital stay, and enhancing knee function. These results are consistent with those of previous studies that reported the benefits of ERAS in patients[21-23]. The possible mechanisms of ERAS are as follows. Preoperative education can increase patients' knowledge and confidence about TKA, reduce their anxiety and stress, and enhance their compliance with and participation in perioperative care[24]. Anesthesia can affect surgical stress response, blood loss, postoperative pain, and recovery. Regional anesthesia, such as spinal anesthesia or nerve blocks, can provide better analgesia, reduce blood loss, and facilitate early mobilization than general anesthesia[25]. Analgesia is essential to reduce postoperative pain, improve patient satisfaction, and promote recovery. Multimodal analgesia, which combines different analgesics such as opioids, NSAIDs, and local anesthetics, can provide effective pain relief with minimal side effects[26]. Fluid management can affect hemodynamic stability, tissue perfusion, wound healing, and edema. Restrictive fluid therapy, which aims to maintain a near-normal fluid balance, can reduce blood loss, transfusion rate, and complications compared to liberal fluid therapy[27]. Nutrition influences wound healing, immune function, and patient recovery. Early oral intake can stimulate gastrointestinal motility, prevent malnutrition, and reduce complications[28]. Mobilization can improve blood circulation, muscle strength, and joint and respiratory function. Early mobilization can prevent joint stiffness, muscle atrophy, deep vein thrombosis, pulmonary embolism, and pneumonia[29]. Discharge criteria can ensure the safety and quality of patient care. Standardized discharge criteria can help evaluate patients' readiness for discharge and avoid unnecessary hospital stay[30].

Multidisciplinary collaboration is a key factor in the success of ERAS. Coordination and communication among different health professionals are required to provide individualized and comprehensive patient care. We established a multidisciplinary team of surgeons, anesthesiologists, nurses, physiotherapists, nutritionists, and pharmacists. The team members held regular meetings to discuss ERAS protocols, patient assessments, care plans, and outcome evaluations. The team members also communicated with patients and their families to provide education, counseling, and support. Multidisciplinary collaboration can ensure qualitative and continuous patient care and improve patient satisfaction and compliance[31].

This study had some limitations. First, it was a retrospective study with a small sample size conducted at a single center. Therefore, these results may not be generalizable to other settings or populations. Second, the study did not include the long-term follow-up of the patients. Therefore, the effect of ERAS with a multidisciplinary collaboration on patients' functional recovery and quality of life remains unclear. Third, the satisfaction and compliance of patients and

Table 1 Demographic and clinical characteristics of the two groups

Indicator	ERAS group (*n* = 40)	Conventional group (*n* = 40)	*P* value
Age (yr)	64.3 ± 7.8	65.1 ± 8.2	0.58
Sex (male/female)	16/24	18/22	0.67
Body mass index (kg/m^2)	26.5 ± 3.2	27.1 ± 3.6	0.42
ASA physical status (I/II/III)	12/24/4	10/26/4	0.77
Preoperative HSS knee score	54.8 ± 6.7	55.2 ± 7.1	0.79

ERAS: Enhanced recovery after surgery; ASA: American Society of Anesthesiologists; HSS: Hospital for Special Surgery.

Table 2 Nursing outcomes of the two groups

Indicator	ERAS group (*n* = 40)	Conventional group (*n* = 40)	*P* value
Length of hospital stay (d)	5 (4-6)	7 (6-8)	< 0.01
Hospitalization cost (USD)	12345 ± 1234	14567 ± 1456	< 0.01
Intraoperative blood loss (ml)	150 ± 50	250 ± 75	< 0.01
Hemoglobin level 24 h after surgery (g/L)	120 ± 10	110 ± 15	< 0.01
VAS score for pain 24 h after surgery	3 ± 1	5 ± 2	< 0.01
VAS score for pain 48 h after surgery	2 ± 1	4 ± 2	< 0.01
VAS score for pain 72 h after surgery	1 ± 1	3 ± 2	< 0.01
ROM of the knee joint 24 h after surgery (°)	60 ± 10	40 ± 15	< 0.01
ROM of the knee joint 48 h after surgery (°)	80 ± 10	60 ± 15	< 0.01
ROM of the knee joint 72 h after surgery (°)	90 ± 10	70 ± 15	< 0.01
HSS knee score at discharge	90 ± 5	85 ± 5	< 0.01
Postoperative complications (yes/no)	2/38	3/37	0.64

ERAS: Enhanced recovery after surgery; VAS: Visual analog scale; ROM: Range of motion; HSS: Hospital for Special Surgery.

health professionals were not measured. Therefore, the acceptability and feasibility of the ERAS in multidisciplinary collaborations are unknown.

CONCLUSION

ERAS with multidisciplinary collaboration can improve nursing outcomes after TKA, such as reduced blood loss, shortened hospital stay, and enhanced knee function. ERAS is a safe and effective perioperative care model for patients undergoing TKA. It also had a positive effect on the perceptions and experiences of both patients and health professionals. However, some challenges and barriers need to be addressed to improve ERAS through multidisciplinary collaboration. Further studies with multidisciplinary collaborations are required to confirm the long-term benefits and cost-effectiveness of ERAS in patients undergoing TKA.

ARTICLE HIGHLIGHTS

Research background

Total knee arthroplasty (TKA) is a common surgical procedure for patients with knee joint degeneration. However, there is a lack of research investigating the effects of enhanced recovery after surgery (ERAS) with multidisciplinary collaboration on nursing outcomes in TKA patients. Understanding the background and present status of this research gap is crucial.

Research motivation

The motivation behind this study arises from the lack of research investigating the effects of ERAS with multidisciplinary collaboration on nursing outcomes in patients undergoing TKA. This research gap highlights the need to explore the potential benefits and effectiveness of ERAS in improving the nursing outcomes of TKA patients.

Research objectives

The main objectives of this study were to explore the effects of ERAS with multidisciplinary collaboration on nursing outcomes in patients undergoing TKA. The specific objectives included assessing the impact of ERAS on length of hospital stay, hospitalization cost, intraoperative blood loss, postoperative hemoglobin levels, pain management, knee joint ROM, Hospital for Special Surgery (HSS) knee score, and postoperative complications.

Research methods

This study utilized a retrospective analysis of clinical data to explore the impact of ERAS with multidisciplinary collaboration on nursing outcomes in TKA patients. By comparing the ERAS group to the conventional group, significant improvements were observed in various indicators such as hospital stay, blood loss, pain scores, and knee function. These findings highlight the importance of implementing ERAS protocols and multidisciplinary collaboration in TKA care.

Research results

The study found that implementing ERAS with multidisciplinary collaboration in TKA patients led to significant improvements in nursing outcomes, including shorter hospital stays, reduced blood loss, improved knee function, and lower pain scores. However, no significant difference was observed in postoperative complications. These findings contribute to the understanding of ERAS benefits, but further research is needed to explore its impact on complication rates and long-term effects of TKA nursing care protocols.

Research conclusions

The study concludes that multidisciplinary collaboration with ERAS can significantly improve nursing outcomes in patients undergoing TKA. Compared to routine nursing care, implementing ERAS protocols resulted in a shorter length of hospital stay, reduced hospitalization costs, decreased intraoperative blood loss, higher postoperative hemoglobin levels, lower pain scores, improved knee joint ROM, and higher HSS knee scores. These findings highlight the effectiveness of ERAS strategies in reducing blood loss, enhancing postoperative recovery, and improving knee function in TKA patients.

Research perspectives

Future research in the field of ERAS and multidisciplinary collaboration in TKA nursing care should focus on investigating long-term outcomes, conducting cost-effectiveness analyses, optimizing multidisciplinary collaboration, and performing comparative studies. These areas can lead to advancements in optimizing ERAS implementation, improving nursing outcomes, and enhancing overall care quality for TKA patients.

FOOTNOTES

Author contributions: Liu J proposed the concept of this study; Zheng QQ has made contributions to data collection; Wu YT contributes to formal analysis; Liu J, Zheng QQ, Wu YT participated in the research; Wu YT has contributed to these methods; Liu J guided the research; Wu YT validated the effectiveness of this study; Zheng QQ and Wu YT contributed to the visualization of this study; Liu J drafted the first draft; Liu J, Zheng QQ, and Wu YT jointly reviewed and edited the manuscript.

Institutional review board statement: This study has passed the ethical review and approval of Shangrao People's Hospital.

Informed consent statement: The patient's informed consent form is not suitable for this study.

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ORIGINAL ARTICLE

Retrospective Study

Appropriate leucine-rich α-2 glycoprotein cut-off value for Japanese patients with ulcerative colitis

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Abstract

BACKGROUND

It has been suggested that serum leucine-rich α-2 glycoprotein (LRG) could be a novel monitoring biomarker for the assessment of disease activity in inflammatory bowel disease. In particular, the relationship between LRG levels and the endoscopically assessed activity of ulcerative colitis (UC) has become a matter of interest.

AIM

To clarify appropriate LRG cut-off values for the prediction of endoscopic and histologic remission in Japanese patients with UC.

METHODS

This was a cross-sectional, single-center, observational study of Japanese patients with UC. Among 213 patients with UC, in whom LRG was measured from September 2020 to February 2022, we recruited 30 patients for whom a total colonoscopy and measurements of LRG and C-reactive protein (CRP) were performed on the same day. We retrospectively analyzed correlations between the LRG and CRP levels and endoscopic indices, including the Mayo endoscopic subscore and UC endoscopic index of severity.

RESULTS

Correlations between the LRG values and the Mayo endoscopic subscore or UC endoscopic index of severity were significant ($r = 0.754$, $P < 0.0001$; $r = 0.778$, $P < 0.0001$, respectively). There were also significant correlations between CRP levels and Mayo endoscopic subscore or UC endoscopic index of severity ($r = 0.599$, $P =$

0.0005; r = 0.563, P = 0.0012, respectively), although the correlation coefficients were higher for LRG. The LRG cut-off value for predicting endoscopic remission was 13.4 μg/mL for a Mayo endoscopic subscore of 0 [area under the curve (AUC): 0.871; 95% confidence interval (CI): 0.744–0.998], and 13.4 μg/mL for an UC endoscopic index of severity of 0 or 1 (AUC: 0.904; 95%CI: 0.792–1.000).

CONCLUSION

LRG may be a surrogate marker for endoscopic activity in UC, with a cut-off value of around 13.4 μg/mL for endoscopically inactive disease.

Key Words: Ulcerative colitis; Leucine-rich alpha-2 glycoprotein; C-reactive protein; Japanese patients

Core Tip: Leucine-rich α-2 glycoprotein (LRG) has recently been proposed as a reliable surrogate marker for clinical, endoscopic and histologic activity in ulcerative colitis (UC). Our aim was to determine appropriate LRG cut-off values for predicting clinical and endoscopic remission in Japanese patients with UC. LRG was found to be correlated with endoscopic indices, and the LRG cut-off value for predicting endoscopic remission was determined to be 13.4 μg/mL. LRG < 13.4 μg/mL may be predictive of endoscopically inactive disease in UC.

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INTRODUCTION

Mucosal healing (MH) has recently become an important treatment goal in ulcerative colitis (UC). The achievement of MH has been reported to decrease the recurrence, malignant transformation, hospitalization rates, and surgical requirements of various gastrointestinal disorders[1-5]. In addition, histological remission is superior to endoscopic healing in predicting long-term remission and cancer prevention[6-10]. The Selecting Therapeutic Targets in Inflammatory Bowel Diseases (IBD) IBD (STRIDE)-II initiative encompasses recommendations for treat-to-target strategies for adults and children with IBD[11]. STRIDE-II has recommended the use of clinical remission, C-reactive protein (CRP) normalization, and decreased fecal calprotectin levels as intermediate targets, with endoscopic remission and histological healing as long-term targets.

Serum leucine-rich α-2 glycoprotein (LRG) is a novel monitoring biomarker for the assessment of disease activity in IBD. LRG levels have been shown to reflect gastrointestinal inflammation[12-18]. However, appropriate LRG cut-off values have not been established in patients with UC. We thus aimed to investigate reasonable LRG cut-off values for predicting endoscopic and histologic activity in Japanese patients with UC.

MATERIALS AND METHODS

Patients

This was a cross-sectional, single-center, observational study of Japanese patients with UC. All patients were recruited at the Division of Gastroenterology and Hepatology, Iwate Medical University Hospital, Iwate, Japan. The diagnosis of UC was based on established clinical, endoscopic, radiological, and histological criteria. UC was classified into the following types: total colitis, left-sided colitis, proctitis, and segmental colitis. Exclusion criteria were as follows: presence of infectious enterocolitis, colorectal cancer, Crohn's disease (CD), or indeterminate colitis; inability to collect fecal samples; pregnancy; history of colorectal resection; or regular intake of aspirin/nonsteroidal anti-inflammatory drugs, defined as ≥ 2 tablets/wk. Blood samples were collected for the measurement of white blood cell counts, platelet counts, hemoglobin levels, and serum levels of albumin, LRG, and CRP.

We recruited 213 patients with UC for the measurement of LRG during the period from September 2020 to February 2022. Among those patients, 30 underwent total colonoscopy, and LRG and CRP measurements were made on the same day. These 30 patients were the subjects of the present study. The study protocol was approved by the Ethics Committee at Iwate Medical University Hospital (MH2020-193), and the study was conducted in accordance with the Declaration of Helsinki.

Clinical, endoscopic and histological assessment

The association between clinical activity and biomarkers was examined in all patients. The clinical activity of UC was

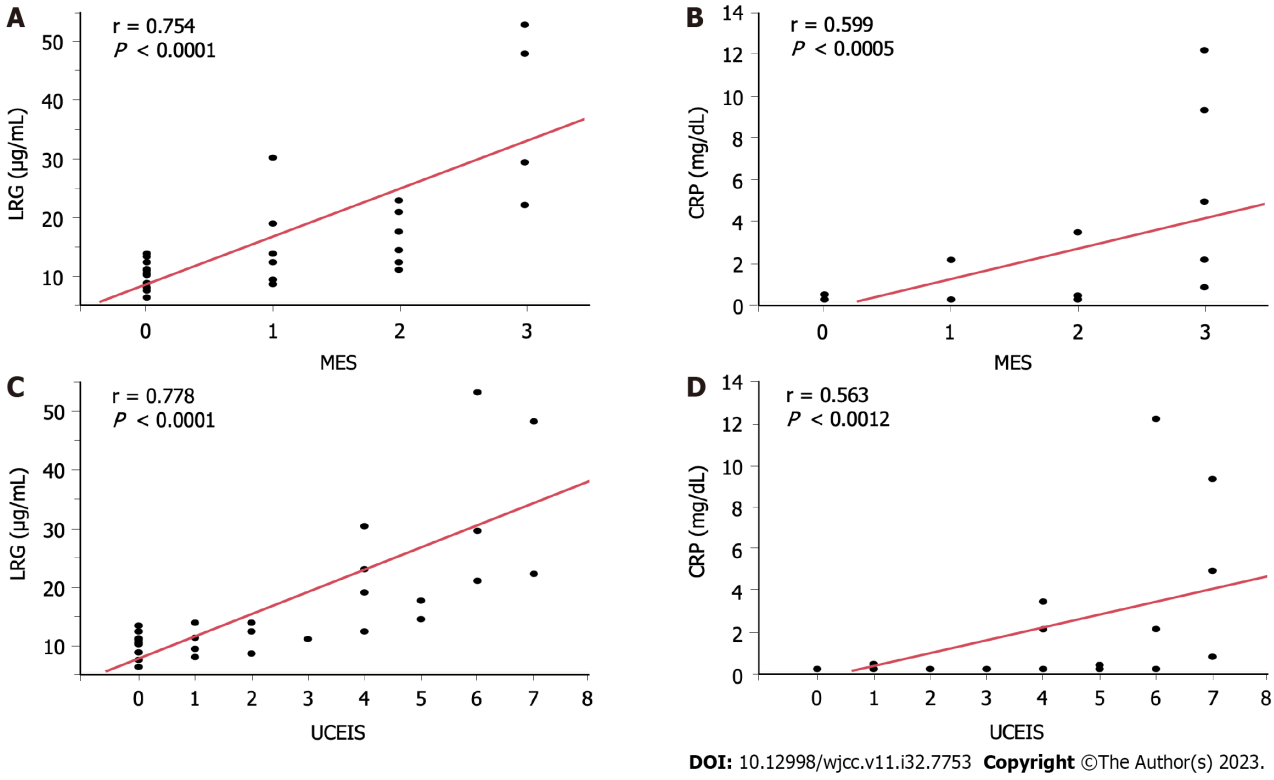

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Figure 1 Relationship between endoscopic findings and biomarkers (*n* = 30). A and B: Mayo Endoscopic Subscore; C and D: Ulcerative Colitis Endoscopic Index of Severity. CRP: C-reactive protein; LRG: Leucine-rich -glycoprotein; MES: Mayo Endoscopic Subscore; UCEIS: Ulcerative Colitis Endoscopic Index of Severity.

assessed according to the partial Mayo score (PMS)[19]; clinical remission was defined as a PMS of 0 without rectal bleeding and no requirement for steroid therapy during the previous 3 mo.

Endoscopic activity was assessed according to the Mayo Endoscopic Subscore (MES) and the UC Endoscopic Index of Severity (UCEIS)[20]. The MES is a 4-point scale (0-3). The three items included in the UCEIS were vascular pattern, bleeding, and erosion/ulceration. The sum of the scores for each endoscopic item ranged from 0 to 8. The UCEIS and MES were scored retrospectively by experienced endoscopists (MY and SY), who were blinded to patient LRG and CRP levels. The histological grade of inflammation was assessed on biopsy specimens obtained endoscopically from the most severely inflamed sites according to the Matts score[21], Riley score[22], and Geboes histopathology score (GHS)[23] by a pathologist (TS) who was blinded to endoscopic findings and LRG and CRP levels. Histologic remission for each biopsy specimen was defined as Matts grade 1, Riley's score 0 or 1, and GHS 0 or 1.

Statistical analysis

Statistical analysis was performed with JMP 13 (SAS Institute Inc., Cary, NC, United States) and SPSS version 22 software for MAC OS (SPSS Inc., Chicago, IL, United States). Numerical variables are presented as medians and interquartile ranges (IQRs), while categorical variables are presented as frequencies. Associations between LRG levels and blood test results, clinical disease activity, endoscopically assessed activity, or histological activity were evaluated with Spearman's rank sum correlation test. Receiver operating characteristic (ROC) curves were drawn to estimate the area under the curve (AUC) and the best cut-off levels of LRG that predicted clinical, endoscopically assessed, and histologic remission. Based on the cut-off levels, test characteristics, including sensitivity, specificity, positive predictive value, and positive likelihood ratio were calculated. Patient age and laboratory data were compared with the Wilcoxon test. Gender and frequency of medical treatment were compared with the χ^2 test. Relapse rates were compared between any two groups with the Cox proportional hazards model. For each analysis, $P < 0.05$ was considered statistically significant.

RESULTS

Associations between clinical or endoscopic activity and biomarkers

Table 1 summarizes the baseline characteristics of the 30 patients in whom endoscopic and histological activity were examined and LRG and CRP were measured on the same day. There were significant correlations between LRG level and MES ($r = 0.754$, $P < 0.0001$) and between LRG level and UCEIS ($r = 0.778$, $P < 0.0001$). There were also significant correlations between CRP level and MES ($r = 0.599$, $P = 0.0005$) and between CRP level and UCEIS ($r = 0.563$, $P = 0.0012$). The correlation coefficients were higher for LRG level (Figure 1).

Table 1 Baseline characteristics of the 30 patients

Parameter	Patients (*n* = 30)
Age, year, median (IQR)	37 (28-47)
Male/Females, *n*/*n*	21/9
Disease duration, year, median (IQR)	1 (0-1)
Actual disease extent, *n* (%)	
Proctitis	3 (10)
Left-sided colitis	7 (23.3)
Total colitis	20 (66.7)
Segmental colitis	0
Laboratory data	
LRG, μg/mL, median (IQR)	11.9 (9.8-20.1)
CRP, mg/dL, median (IQR)	0.10 (0.10-0.33)
Medication, *n* (%)	
5-aminosalicylic acid	30 (100)
Immunomodulators	3 (10)
Anti-TNF	2 (6.7)
Ustekinumab	1 (3.3)
Tofacitinib	3 (10)

IQR: Interquartile range; LRG: Leucine-rich α-2 glycoprotein; CRP: C-reactive protein; TNF: Tumor necrosis factor.

The LRG cut-off value for predicting clinical remission was 12.9 μg/mL for PMS = 0 [AUC: 0.951, 95% confidence interval (CI): 0.873–1.000], with sensitivity of 89% and specificity of 91%. The LRG cut-off value for predicting endoscopically assessed remission was 13.4 μg/mL for MES = 0 (AUC: 0.871, 95%CI: 0.744–0.998), with sensitivity of 100% and specificity of 64%; and 13.4 μg/mL for UCEIS = 0 or 1 (AUC: 0.904; 95%CI: 0.792–1.000), with sensitivity of 100% and specificity of 69% (Table 2).

Associations between histological activity and biomarkers

There were significant correlations between LRG level and Matts grade (r = 0.432, P = 0.017) and between LRG level and Riley's score (r = 0.380, P = 0.038). In contrast, no significant correlations were found between LRG level and GHS (r = 0.285, P = 0.126), CRP level and Matts grade (r = 0.306, P = 0.099), CRP level and Riley score (r = 0.198, P = 0.293), or CRP level and GHS (r = 0.115, P = 0.544) (Figure 2).

As to histological remission, the appropriate LRG cut-off value was 9.7 μg/mL for Matts grade (AUC: 0.889, 95%CI: 0.755–1.000), with sensitivity of 100% and specificity of 81%; 13.4 μg/mL for Riley score (AUC: 0.739, 95%CI: 0.550–0.929), with sensitivity of 100% and specificity of 46%; and 13.4 μg/mL for GHS (AUC: 0.679, 95%CI: 0.477–0.880), with sensitivity of 92% and specificity of 59% (Table 2).

DISCUSSION

LRG is a 50-kDa glycoprotein containing eight leucine-rich repeat domains. It has been reported to be a novel serum biomarker for the detection of rheumatoid arthritis and IBD[24]. The primary sites of LRG production are thought to be intestinal epithelial cells, neutrophils, and hepatocytes that are stimulated by interleukin (IL)-6, tumor necrosis factor-, and IL-22, among other cytokines[25,26]. CRP is a protein that is representative of acute phase reactants. The liver, under the stimulation of circulating IL-6, is the primary organ for CRP production[27]. Thus, it has been presumed that LRG is more sensitive than CRP for assessing the severity of inflammation in systemic diseases.

Several papers have reported that serum levels of LRG are correlated with endoscopic activity in patients with UC[12-18]. Shinzaki *et al*[14] recently published results of a prospective, observational study that evaluated serum LRG as a biomarker for disease activity in IBD (PLANET study). Their study found that serum LRG was a useful biomarker of endoscopic activity in patients with UC receiving adalimumab treatment[14]. A subanalysis of the PLANET study revealed that LRG, rather than CRP, may be a more accurate marker for predicting the trough level of adalimumab in patients with CD or UC[28].

Table 2 Associations of variables with leucine-rich α-2 glycoprotein to predict remission

Variable	Cut-off value (μg/mL)	AUC	95%CI	SENS (%)	SPEC (%)	PPV (%)	PLR
PMS 0	12.9	0.951	0.873-1.000	89	91	94	10.6
MES 0	13.4	0.871	0.744-0.998	100	64	68	2.8
UCEIS 0,1	13.4	0.904	0.792-1.000	100	69	73	3.2
Matts grade 1	9.7	0.889	0.755-1.000	100	81	37	5.4
Riley's score 0,1	13.4	0.739	0.550-0.929	100	46	32	1.8
GHS 0,1	13.4	0.679	0.477-0.880	92	59	63	2.2

LRG: Leucine-rich α-2 glycoprotein; AUC: Area under the curve; CI: Confidence interval; SENS: Sensitivity; SPEC: Specificity; PPV: Positive predictive value; PLR: Positive likelihood ratio; MS: Mayo Score; MES: Mayo Endoscopic Subscore; UCEIS: Ulcerative Colitis Endoscopic Index of Severity; GHS: Geboes Histopathology Score.

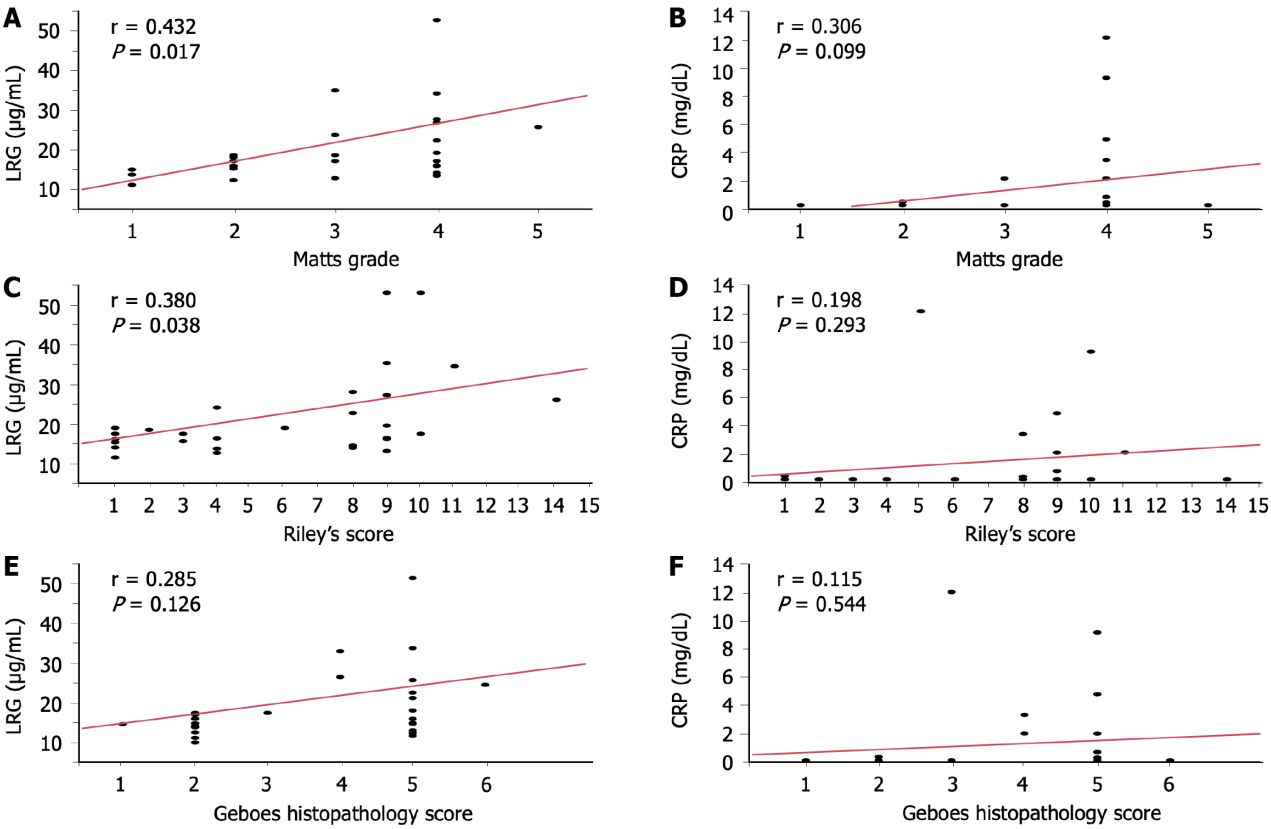

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Figure 2 Relationship between histological findings and biomarkers (*n* = 30). A and B: Matts Grade; C and D: Riley's Score; E and F: Geboes Histopathology Score. CRP: C-reactive protein; LRG: Leucine-rich -glycoprotein.

Our study included 30 patients for whom total colonoscopy and measurements of LRG and CRP were performed on the same day. There were significant correlations between LRG levels and MES and LRG levels and UCEIS. There were also significant correlations between CRP levels and MES, and CRP levels and UCEIS, although the correlation coefficients were higher for LRG level. Thus, it seems possible that LRG is a candidate that is equal or, possibly, superior to CRP for the assessment of disease activity in UC.

The recommended cut-off value of LRG for the detection of active disease in patients with UC is regarded as 16 μg/mL. Subsequently, the cut-off value of the serum level of LRG for the detection of active disease in patients with UC was reported by other investigators. Horiuchi *et al*[15] reported that a serum LRG cut-off value of 10.8 g/mL could be a novel biomarker for identifying patients with active total or left-sided colitis[15]. Shimoyama *et al*[16] reported that the optimal LRG cut-off value for the detection of endoscopically active disease defined as MES ≥ 1 was 12.7 μg/mL[16]. Yoshida *et al*[17] reported that the cut-off value of LRG for MH with the identical definition was 16.3 μg/mL[17]. Another study by Yasutomi *et al*[18] showed that the LRG cut-off for complete MH defined as an MES of 0 was 13 μg/mL[18]. The cut-off

value varies according to the definition of MH and to the study population, whereas our study revealed that the LRG cut-off value for the prediction of MH defined as an MES of 0 was 13.4 μg/mL and it was 12.9 μg/mL for the prediction of UCEIS of 0 or 1. These observations suggest that a cut-off value of LRG at around 13 μg/mL is appropriate for the prediction of MH in patients with UC.

We also showed that there were significant correlations between LRG level and two of the three widely accepted histological activity systems for UC, namely, the Matts grade and Riley score. This observation seems reasonable, because neutrophil infiltration is the main item for the assessment of activity. In contrast, we could not find a significant correlation between GHS and LRG. This may be explained by the fact that mucosal damage, rather than inflammatory infiltration, is the key histological finding. Thus, LRG may be representative of grade of inflammation in patients with UC. Also, it should be noted that the practical cut-off values of LRG for endoscopic remission and histological remission were similar, indicating the significance of LRG in clinical practice.

This study had several limitations. First, it was performed at a single center and involved a limited number of patients. Second, since it was a retrospective study, there were some variations in patient comorbidities, such as infectious colitis and rheumatoid arthritis, and in applied medications. Third, we could not compare LRG with fecal calprotectin, a reliable fecal biomarker for UC. The comparison of LRG with fecal calprotectin remains to be examined in future prospective studies.

CONCLUSION

Our analysis revealed that LRG is a biomarker for patients with UC with respect to clinical, endoscopic and histological prediction of remission, and that the cut-off value of LRG for each may be around 13 μg/mL. With the use of the appropriate cut-off value, LRG seems to be a biomarker that is more specific and more sensitive than CRP.

ARTICLE HIGHLIGHTS

Research background

Serum leucine-rich α-2 glycoprotein (LRG) can be used for the assessment of disease activity in ulcerative colitis (UC). However, practical cut-off values of LRG for remission have not been established in patients with UC.

Research motivation

LRG cut-off value for remission will lessen the need for colonoscopy.

Research objectives

To establish cut-off values of LRG for endoscopic and histological remission in UC.

Research methods

We retrospectively analyzed the relationship between LRG and clinical, endoscopic and histologic activities in patients with UC.

Research results

In 30 patients, the correlations between LRG value and Mayo Endoscopic Subscore (MES) or UC Endoscopic Index of Severity (UCEIS) were significant (r = 0.754, P < 0.0001; r = 0.778, P < 0.0001, respectively). Significant correlations were also found between CRP level and MES or UCEIS (r = 0.599, P = 0.0005; r = 0.563, P = 0.0012, respectively); however, the correlation coefficients were higher for LRG value. The LRG cut-off value for predicting endoscopic remission was 13.4 μg/mL for an MES of 0 [area under the curve (AUC): 0.871, 95% confidence interval (CI): 0.744–0.998], and 13.4 μg/mL for a UCEIS of 0 or 1 (AUC: 0.904; 95%CI: 0.792–1.000).

Research conclusions

LRG can be applied to the prediction of endoscopic and histological remission in UC.

Research perspectives

Further prospective studies are deemed to validate our findings.

FOOTNOTES

Author contributions: Yamazato M, and Yanai S performed the conception and design; Yamazato M, Yanai S, Oizumi T, Eizuka M, Yamada S, Toya Y, Uesugi N, and Sugai T performed the data collection; Yamazato M, and Yanai S contributed to the data analysis and statistical analysis; The first draft of manuscript was written by Yamazato M, and Yanai S; Matsumoto T critically reviewed and revised the manuscript; All authors read and approved the final manuscript for submission.

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ORIGINAL ARTICLE

Retrospective Study

Association between depressive mood and body image and menopausal symptoms and sexual function in perimenopausal women

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Abstract

BACKGROUND

Perimenopausal is the period when women's ovarian function begins to decline before and after menopause. During this period, women experience a series of mental state changes, such as decreased hormone levels, decreased libido, and even female sexual dysfunction (FSD) in severe cases, which reduces their quality of life. Factors affecting the occurrence of FSD include physiological and non-physiological factors, among which physiological factors are uncontrollable. Therefore, it is particularly important to ascertain the related non-physiological factors that affect the occurrence of FSD for improving the quality of sexual life of perimenopausal women.

AIM

To investigate the mediating effect of depressive mood and body image on menopausal symptoms and sexual function in perimenopausal women.

METHODS

A total of 186 perimenopausal women were enrolled between January 2019 and January 2021 and divided into the FSD (134 cases) and control (52 cases) groups based on the presence and absence of FSD. Clinical data were compared between the two groups. FSD-related factors were analyzed using logistic regression analysis. Hamilton Depression Scale (HAMD), Body Image Scale (BIS), and Menopause Rating Scale (MRS) scores were compared among women with different FSD scores. The correlation of the MRS score with the BIS and HAMD scores and the mediating effect of the BIS and HAMD scores on the MRS score and female sexual function index (FSFI) were analyzed.

RESULTS

The HAMD and BIS scores were higher in the FSD group than in the control group, and the difference in monthly income between the two groups was statistically significant (all $P < 0.05$). Monthly income of < 2000 yuan [odds ratio (OR) = 26.586, $P = 0.000$], BIS score (OR = 1.590, $P = 0.000$), and HAMD score (OR = 1.884, $P = 0.000$) were independent risk factors for FSD. MRS scores were positively correlated with BIS and HAMD scores ($r = 0.358$ and 0.244, $P = 0.000$ and 0.001, respectively) and negatively correlated with FSFI scores ($r = -0.433$, $P = 0.000$). Body image and depressive mood had partial mediating effects, accounting for 39.90% of the total effect.

CONCLUSION

Depression and body image play mediating roles between menopausal symptoms and sexual function in perimenopausal women.

Key Words: Perimenopause; Depressive mood; Body image; Sexual dysfunction; Mediating effect

Core Tip: Depressive mood and body image partially mediate the relationship between menopausal symptoms and sexual function in perimenopausal women, accounting for 39.90% of the total effect. Understanding these mediating factors can help inform interventions targeting sexual dysfunction in this population.

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INTRODUCTION

Perimenopause is the period before and after menopause, when a woman's ovarian function begins to decline. During this period, women experience alterations in their mental state, hot flashes, sweating, excitement, and irritability[1,2], which is not conducive to physical and mental health. In addition to physical discomfort, a decrease in the hormone levels, genital tissue structure, and texture, as well as vaginal mucosal atrophy, may cause low sexual desire and difficulty in sexual arousal[3], and even worse, female sexual dysfunction (FSD), which is not good for the physical and mental health of women and is also detrimental to family harmony and quality of life[4].

Relevant studies have shown that women with severe menopausal symptoms are at higher risk of developing FSD. Besides physiological factors, the occurrence of FSD is associated with multiple non-physiological factors such as sexual health concepts, income levels, negative emotions, and body image[5,6]. Xiong *et al*[7] reported that 90% of FSD is caused by psychological factors and that body image is strongly associated with female sexual behavior[5], both of which play a non-negligible role in the mechanism of FSD. Nevertheless, there are few studies on the correlation among menopausal symptoms, depressive state, body image, and sexual function in perimenopausal women. Therefore, the present study investigated whether depressive state and body image play a mediating role between menopausal symptoms and sexual function to provide theoretical guidance for the improvement of sexual quality of life in perimenopausal women.

MATERIALS AND METHODS

Participants

A total of 186 perimenopausal women were recruited between January 2019 and January 2021. The inclusion criteria were as follows: (1) Diagnosed perimenopausal women[8]; (2) signed informed consent; (3) married, spouse alive; (4) barrier-free communication and understanding of scale content; and (5) no history of mental illness before perimenopause. The exclusion criteria were as follows: (1) Mental disease; (2) estrogen replacement therapy; (3) heart, liver, kidney, and other vital organ disorders and severe chronic diseases; and (4) abnormal sexual function of the sexual partner, without sexual life for nearly four weeks. Women with a female sexual function index (FSFI) score < 26.55 were included in the FSD group (134 cases), and the rest were included in the control group (52 cases). Participants with a Menopause Rating Scale (MRS) score < 9 were included in the mild group, those with a score of 9-16 were included in the moderate group, and those with a score > 16 were included in the severe group. This study was approved by the Affiliated Hospital of Hunan Academy of Chinese Medicine.

Methods

Research methods: Baseline data such as age, spouse age, education level, and monthly income were collected and compared between the FSD and control groups to analyze FSD-related factors in perimenopausal women. Body image

status and degree of depression [assessed using the Body Image Scale (BIS) and Hamilton Depression Scale (HAMD) scores, respectively] were compared among the mild, moderate, and severe groups. The correlation between the MRS score and BIS and HAMD scores were assessed. Additionally, the mediating effects of body image status and degree of depression on menopausal symptoms and sexual function were analyzed.

Assessment of sexual function and definition of FSD: FSFI[4] was used to measure sexual function and the scale was filled out independently by the patients. The scale contains 6 dimensions and 20 items, with 0-5 points for each dimension and 1-5 points for each item, and a total score of 36 points. The lower the score, the more severe the sexual dysfunction. FSD was defined by a total score of < 26.55.

Body image assessment: BIS[9] compiled by Hopwood *et al* was used to measure the body image of patients. The BIS scale was completed independently by patients. The scale contains 10 items with 0-3 points for each item. Zero, 1, 2, and 3 points represent "not at all," "a little," "quite a lot," and "much", respectively. The total score is 30 points, and the higher the score, the worse the body image.

Depression assessment: The HAMD[6] was used for depression assessment. The scale contains 21 items, with 0-4 scores for each item. A total score of 7-17, 17-24, and > 24 represents mild, moderate, and severe depression, respectively.

Assessment of the severity of menopausal symptoms: MRS was applied for the assessment of the severity of menopausal symptoms. The scale includes 11 items with physical, psychological, and genitourinary dimensions. Each item is scored as 0, 1, 2, 3, or 4 points for "asymptomatic," "mild," "moderate," "severe," and "very severe" symptoms, respectively. The total score is 44, with a score of < 4 for asymptomatic, 4-8 for mild, 9-16 for moderate, and 16-44 for severe symptoms.

Quality control

Before the study, two medical staff members who guided participants in filling out the questionnaire were given uniform guidance language training, and the same guidance language was applied to all participants. The questionnaire was completed independently by patients in the outpatient department and issued and collected immediately.

Statistical analysis

Data were analyzed using SPSS 25.0 (IBM Corp., Armonk, NY, United States). Measurement data were expressed as mean ± SD. Differences between the groups were compared using the two-independent samples *t*-test. Count data were expressed as percentages [*n* (%)] and analyzed using the χ^2 test. Analysis of variance (ANOVA) was used to compare differences among three or more groups. The Bonferroni method was used for the pairwise comparisons. The corrected *P*-value ($P < 0.017$) was used for the pairwise comparisons. Ranked data were analyzed using the rank-sum test to compare differences among groups. Multivariate logistic regression was used to analyze FSD-related factors in perimenopausal women. Pearson's correlation analysis was used to analyze the correlation between the MRS score and the BIS and HAMD scores. A structural equation model of the correlation between menopausal symptoms, sexual function, body image, and depression was established to test the mediating effect of BIS and HAMD scores on the MRS score and FSFI. A mediating effect existed if the confidence interval was not 0. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of clinical data between the control and FSD groups

The HAMD and BIS scores were higher in the FSD group than in the control group ($P < 0.05$). The difference in the monthly income between the two groups was significant ($P < 0.05$). There were no significant differences in the other data between the two groups ($P > 0.05$; Table 1).

Logistic regression analysis of FSD-related factors in perimenopausal women

Monthly income of < 2000 yuan [odds ratio (OR) = 26.586, $P = 0.000$], BIS score (OR = 1.590, $P = 0.000$), and HAMD score (OR = 1.884, $P = 0.000$) were all independent risk factors for FSD (Table 2).

Comparison of MRS, BIS, HAMD, and FSFI scores in women with different degrees of menopausal symptoms

A comparison of the clinical data in women with different degrees of menopausal symptoms is shown in Table 3. The BIS and HAMD scores were lower in the mild and moderate groups than in the severe group. The FSFI scores were higher in the mild and moderate groups than in the severe group (all $P < 0.017$). The MRS scores were positively correlated with the BIS and HAMD scores ($r = 0.358$ and 0.244, $P = 0.000$ and 0.001, respectively) and negatively correlated with the FSFI scores ($r = -0.433$, $P = 0.000$; Table 4).

Analysis of the mediating effect of body image and depressive mood

Body image and depressive mood were part of the mediating effect. The mediating effect accounted for 39.90% of the total effect (-0.166/-0.416), among which the HAMD and BIS score accounted for 20.91% and 18.99%, respectively (Figure 1 and Table 5).

Table 1 Comparison of clinical data between the control and female sexual dysfunction groups [*n* (%), mean ± SD]

Factor	Control group (*n* = 52)	FSD group (*n* = 134)	$t/\chi^2/Z$	*P* value
Age (yr)	47.78 ± 4.03	48.49 ± 3.65	-1.156	0.249
Spouse age (yr)	51.14 ± 5.26	50.57 ± 4.80	0.707	0.480
BMI (kg/m^2)	22.34 ± 2.75	22.86 ± 2.31	-1.304	0.194
Delivery times (time)	2.64 ± 0.79	2.75 ± 0.92	-0.760	0.448
BIS score (point)	9.33 ± 2.87	14.63 ± 4.52	-7.856	0.000
Education level, *n* (%)				
Junior high school and below	34 (65.38)	102 (76.12)	-1.542	0.123
Senior middle school	14 (26.92)	27 (20.15)		
College and above	4 (7.69)	5 (3.73)		
Monthly income (yuan), *n* (%)				
< 2000	21 (40.38)	100 (74.63)	-4.652	0.000
2000-5000	15 (28.85)	23 (17.16)		
> 5000	16 (30.77)	11 (8.21)		
HAMD score (point)	7.83 ± 2.32	13.44 ± 3.65	-10.296	0.000
Retirement, *n* (%)	24 (46.15)	66 (49.25)	0.144	0.704

BMI: Body mass index; HAMD: Hamilton Depression Scale; BIS: Body Image Scale; FSD: Female sexual dysfunction.

Table 2 Logistic regression analysis results of female sexual dysfunction-related factors in perimenopausal women

Factor		*β* value	Standard error	Wald	*P* value	Odds ratio	95% confidence interval
Monthly income	> 5000 yuan			12.820	0.002	1.000	
	< 2000 yuan	3.280	0.942	12.117	0.000	26.586	4.193-168.579
	2000-5000 yuan	1.854	0.977	3.603	0.058	6.387	0.941-43.341
BIS score		0.464	0.107	18.941	0.000	1.590	1.290-1.959
HAMD score		0.633	0.124	25.981	0.000	1.884	1.477-2.403

HAMD: Hamilton Depression Scale; BIS: Body Image Scale.

DISCUSSION

FSD problems in perimenopausal women

Perimenopause is a process involving ovarian dysfunction and sex hormone fluctuations. This stage is accompanied by symptoms of menopause, increased risk of various chronic diseases, and decline in reproductive function[10,11], causing varying degrees of negative changes to women's physiological, psychological, and social relations. In addition to physical discomfort, another often-overlooked effect of perimenopause in women is FSD. A previous study showed that the incidence of FSD in perimenopausal women was as high as over 60%[3], which not only impacts mental health but also interferes with family harmony and stability. The occurrence of FSD cannot be separated from numerous independent risk factors. Besides physiological factors such as ovarian function decline, psychological factors also have a significant influence on the development of FSD[12]. Thus, our study investigated whether depression and body image play mediating roles.

Correlation between income and FSD

Female sexual behavior is strongly associated with several social factors. In this study, there was a significant difference in the monthly income between the FSD and control groups. A monthly income < 2000 yuan was an independent risk factor for FSD. Jin *et al*[13] reported that age, menstruation, financial status, and hormone supplementation were related to female sexual function, which is consistent with previous results[14]. This may be because perimenopausal women with higher monthly income may have better living conditions and enthusiasm to seek medical treatment for menopausal symptoms[15], leading to a relatively lower incidence of FSD.

Table 3 Comparison of clinical data in women with different degrees of menopausal symptoms [*n* (%), mean ± SD]

Factor	Mild group (*n* = 20)	Moderate group (*n* = 83)	Severe group (*n* = 83)	*F*/*Z*	*P* value
Age (yr)	48.01 ± 1.54	48.62 ± 2.56	48.92 ± 2.09	1.336	0.265
Spouse age (yr)	49.30 ± 2.26	50.25 ± 3.80	50.17 ± 3.14	0.659	0.519
Delivery times (time)	2.24 ± 0.57	2.50 ± 0.96	2.58 ± 0.78	1.301	0.275
Education level, *n* (%)					
Junior high school and below	11 (55.00)	65 (78.31)	60 (71.29)	4.484	0.106
Senior middle school	7 (35.00)	14 (16.87)	20 (24.10)		
College and above	2 (10.00)	4 (4.82)	3 (3.61)		
Monthly income (yuan), *n* (%)					
< 2000	13 (65.00)	51 (61.45)	57 (68.67)	1.468	0.480
2000-5000	5 (25.00)	16 (19.28)	17 (20.48)		
> 5000	2 (10.00)	16 (19.28)	9 (10.84)		
Retirement, *n* (%)	9 (45.00)	42 (50.60)	48 (57.83)	0.200	0.654
BMI (kg/m^2)	22.06 ± 1.45	22.52 ± 2.23	22.73 ± 2.30	0.781	0.459

BMI: Body mass index.

Table 4 Comparison of Menopause Rating Scale, Body Image Scale, Hamilton Depression Scale, and female sexual function index scores in women with different degrees of menopausal symptoms (mean ± SD, point)

Group	BIS score	HAMD score	FSFI score
Mild (*n* = 20)	10.25 ± 3.18[b]	10.49 ± 3.13[b]	26.21 ± 3.97[b]
Moderate (*n* = 83)	12.13 ± 4.02[b]	11.08 ± 3.06[b]	24.38 ± 5.55[b]
Severe (*n* = 83)	15.39 ± 4.82[a]	13.23 ± 4.02[a]	20.83 ± 3.65[a]
F	17.671	9.688	17.633
P value	0.000	0.000	0.000

[a]*P* < 0.05 *vs* the moderate group.
[b]*P* < 0.05 *vs* the severe group.
HAMD: Hamilton Depression Scale; BIS: Body Image Scale; FSFI: Female sexual function index.

Table 5 Mediating effect test of body image and depressive mood

Effect		Effect	Standard error	*t*	*P* value	LLCI	ULCI
Total effect		-0.416	0.064	-6.524	0.000	-0.542	-0.290
Direct effect		-0.250	0.060	-4.159	0.000	-0.369	-0.132
Mediating effect	HAMD score	-0.087	0.028	-6.155	0.000	-0.150	-0.039
	BIS score	-0.079	0.025	-3.623	0.000	-0.138	-0.036

HAMD: Hamilton Depression Scale; BIS: Body Image Scale; LLCI: Lower limit of 95% confidence interval; ULCI: Upper limit of 95% confidence interval.

Psychological factors play an important role in the development of FSD

With increasing awareness of physical and mental diseases, the role of psychological factors in FSD has received considerable attention. The current study showed that the HAMD and BIS scores were higher in the FSD group than in the control group. Moreover, BIS and HAMD scores were independent risk factors for FSD. Body image and degree of depression are vital components of individual psychological factors. Body image is a complex experience mixed with the physical self, social self, and psychological self[16], while the degree of depression is a common negative emotion of

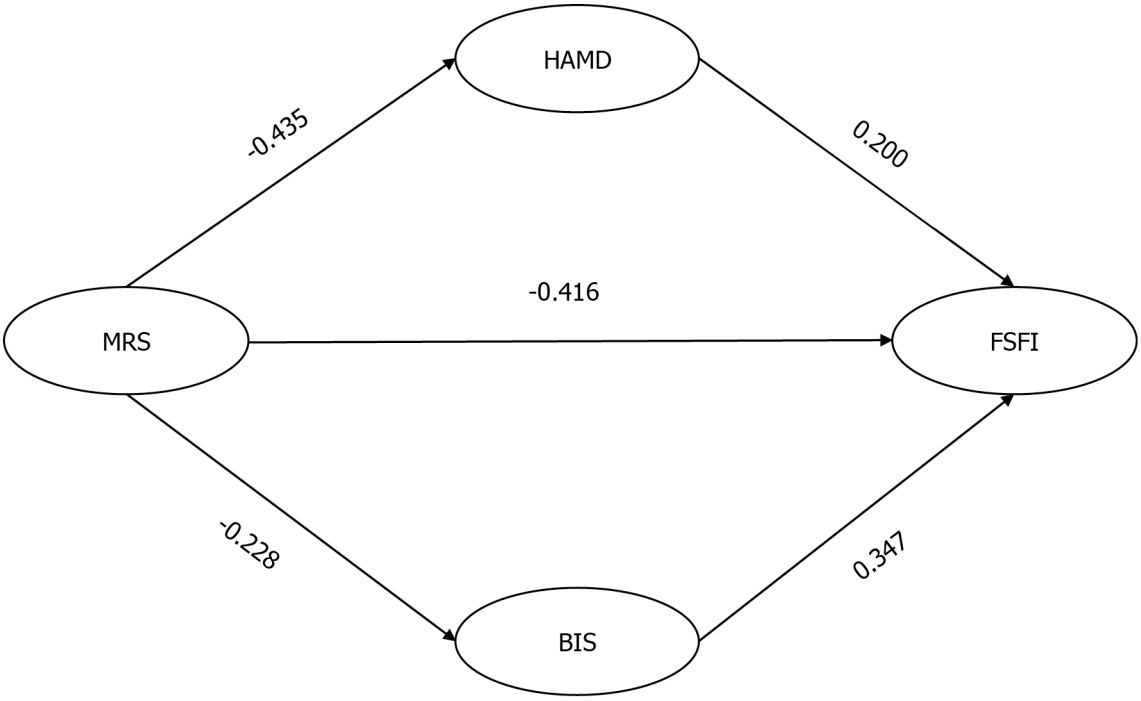

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Figure 1 Mediating effect of Hamilton Depression Scale and Body Image Scale on Menopause Rating Scale and female sexual function index. FSFI: Female sexual function index; HAMD: Hamilton Depression Scale; BIS: Body Image Scale; MRS: Menopause Rating Scale.

perimenopausal women, and both affects women's sexual behavior at a non-physiological level. Perimenopausal women are often accompanied by depression, irritability, and fatigue due to the fluctuation of sex hormones[17]. An Iranian study[18] demonstrated that depressed emotions were associated with a loss of interest, energy, and self-esteem among patients. Women in depressed states find it difficult to express their emotions and desires, which hinders their willingness to engage in sexual behaviors[18]. Simultaneously, depressive mood was an independent risk factor for FSD in perimenopausal women[19,20]. These findings are consistent with our results. Physical and psychological changes during perimenopause can diminish self-confidence and worsen body image in women. Negative self-body image contributes to resistance to sexual behavior and thus reduces sexual desire and response[21], thereby resulting in the occurrence of FSD.

Effect of the severity of menopausal symptoms on body image and depression

Health management of menopausal women should not only address their physical condition but also their psychological needs. Our study showed that the MRS, BIS, and HAMD scores were lower in the mild and moderate groups than in the severe group. The MRS scores were positively correlated with the BIS and HAMD scores. Menopausal symptoms can affect psychological factors in perimenopausal women, and such women are often troubled by several physiological changes, such as hot flashes and sweating, insomnia, paresthesia, body shape change, and headache[10]. The discomfort induced by these menopausal symptoms can affect women's mental states and attitudes toward menopause, ultimately aggravating negative evaluations of body image and depression. Hong *et al*[22] reported that menopausal symptoms are associated with body image, depression, and sexual communication, which mediates the correlation between menopausal symptoms and sexual function. It is also indicated that the effect of menopausal symptoms on sexual function in perimenopausal women includes both physiological and psychological factors.

Correlation between menopausal symptoms, depression, body image, and sexual function

Our data showed that the MRS score was negatively correlated with the FSFI, and body image and depressive mood had a partial mediating effect on menopausal symptoms and sexual function, accounting for 39.90% of the total effect, of which the HAMD and BIS scores accounted for 20.91% and 18.99%, respectively. Specifically, the MRS score negatively predicted the HAMD and BIS scores, whereas the HAMD and BIS scores positively predicted the FSFI score. These results reveal that menopausal symptoms affect sexual function, in part, through depressive mood and body image. This suggested that the improvement in sexual function of perimenopausal women could be achieved by improving body image and mood as well as self-cognition and negative emotions. Therefore, the sexual function of perimenopausal women can be improved from a multi-dimensional perspective. In addition to sex hormone replacement therapy and pelvic floor muscle training, the following is recommended to improve the sexual function of perimenopausal women: (1) Providing sexual health education to both spouses and strengthen sexual communication; (2) psychological intervention and antidepressant medication if necessary; (3) instructing women to exercise with body image as the target; and (4) advising family members and friends to support and tolerate perimenopausal women and encourage mutual

communication. Furthermore, HAMD and BIS scores played a partial mediating role, suggesting that there may be other variables affecting sexual function, which will be the focus of future studies.

Nonetheless, this study has some limitations. The scales used are all filled out subjectively by the patients, and the samples needed to be expanded to reduce bias in the results. Moreover, there are only a handful of studies on this topic, which warrants further studies with larger sample sizes to validate our conclusions.

CONCLUSION

In summary, body image and the degree of depression in perimenopausal women have a partial mediating effect on menopausal symptoms and sexual function. In addition to the treatment of menopausal symptoms, close attention should also be paid to negative emotions and body image, to improve the sexual function in perimenopausal women.

ARTICLE HIGHLIGHTS

Research background

Perimenopause is the period when women's ovarian function begins to decline before and after menopause. During this period, women experience a series of mental state changes, such as decreased hormone levels, decreased libido, and even female sexual dysfunction (FSD) in severe cases, which reduces their quality of life. Factors affecting the occurrence of FSD include physiological and non-physiological factors, among which physiological factors are uncontrollable. Therefore, it is particularly important to ascertain the related non-physiological factors that affect the occurrence of FSD for improving the quality of sexual life of perimenopausal women.

Research motivation

To observe the related non physiological factors that affect the occurrence of perimenopausal FSD, and to improve the quality of sexual life of perimenopausal women.

Research objectives

To investigate the mediating effect of depressive mood and body image on menopausal symptoms and sexual function in perimenopausal women.

Research methods

Analysis of variance (ANOVA), Bonferroni method, rank-sum test, multivariate logistic regression, and Pearson correlation analysis.

Research results

The Hamilton Depression Scale (HAMD) and Body Image Scale (BIS) scores were higher in the FSD group than in the control group. Monthly income of < 2000 yuan, BIS score, and HAMD score were independent risk factors for FSD. The MRS scores were positively correlated with the BIS and HAMD scores and negatively correlated with the female sexual function index scores. Body image and depressive mood had partial mediating effects, accounting for 39.90% of the total effect.

Research conclusions

Depression and body image play mediating roles between menopausal symptoms and sexual function in perimenopausal women.

Research perspectives

This study shows that depression and body image play mediating roles between menopausal symptoms and sexual function in perimenopausal women, and reasonable countermeasures can be considered in clinic.

FOOTNOTES

Author contributions: Ling J and Wang YH contributed equally to this work; Ling J and Wang YH designed the study; Ling J contributed to the analysis of the manuscript; Ling J and Wang YH were involved in the data and writing of this article; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Clinical study of NFNC in the treatment of acute exacerbation chronic obstructive pulmonary disease patients with respiratory failure

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Abstract

BACKGROUND

Most patients with acute exacerbation chronic obstructive pulmonary disease (AECOPD) have respiratory failure that necessitates active correction and the improvement of oxygenation is particularly important during treatment. High flow nasal cannula (HFNC) oxygen therapy is a non-invasive respiratory aid that is widely used in the clinic that improves oxygenation state, reduces dead space ventilation and breathing effort, protects the loss of cilia in the airways, and improves patient comfort.

AIM

To compare HFNC and non-invasive positive pressure ventilation in the treatment of patients with AECOPD.

METHODS

Eighty AECOPD patients were included in the study. The patients were in the intensive care department of our hospital from October 2019 to October 2021. The patients were divided into the control and treatment groups according to the different treatment methods with 40 patients in each group. Differences in patient comfort, blood gas analysis and infection indices were analyzed between the two groups.

RESULTS

After treatment, symptoms including nasal, throat and chest discomfort were significantly lower in the treatment group compared to the control group on the 3rd and 5th days ($P < 0.05$). Before treatment, the PaO_2, PaO_2/FiO_2, $PaCO_2$, and SaO_2 in the two groups of patients were not significantly different ($P > 0.05$). After treatment, the same indicators were significantly improved in both patient groups but had improved more in the treatment group compared to the control group ($P < 0.05$). After treatment, the white blood cell count, and the levels of C-reactive protein and calcitonin in patients in the treatment group were significantly higher compared to patients in the control group ($P < 0.05$).

CONCLUSION

HFNC treatment can improve the ventilation of AECOPD patients whilst also improving patient comfort, and reducing complications. HFNC is a clinically valuable technique for the treatment of AECOPD.

Key Words: Acute exacerbation chronic obstructive pulmonary disease; HFNC; Noninvasive positive pressure ventilation; Application value

Core Tip: Patients with acute exacerbation of obstructive pulmonary disease have respiratory failure, so improving oxygenation is the most important thing. The purpose of this study is to compare the efficacy of HFNC and noninvasive positive pressure ventilation in treating acute exacerbation chronic obstructive pulmonary disease (AECOPD) patients. By analyzing and comparing the differences of patients' comfort, blood gas analysis and infection index under different treatment methods. The results show that HFNC treatment can improve the ventilation function of patients with AECOPD, improve their comfort and reduce complications. This study shows that HFNC is a clinically valuable technique for the treatment of AECOPD.

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INTRODUCTION

Acute exacerbation chronic obstructive pulmonary disease (AECOPD) is a common disease characterized by persistent airflow limitation[1]. The progressive development of airflow limitation along with acute exacerbations and complications affects the severity of the disease and the prognosis of the individual. Oxygen therapy or mechanical ventilation is routinely used in the treatment of AECOPD that improves hypoxemia caused by respiratory failure and reduces hypoxia in the body extent[2,3]. The most common clinical oxygen delivery method is continuous low-flow oxygen delivery with a dual-cavity nasal catheter. This oxygen delivery method requires a low level of oxygen and can easily cause the airway mucosa to lose moisture that is not conducive to correcting the hypoxic state and patient discomfort[4]. High flow nasal cannula (HFNC) is a method that warms and humidifies oxygen to provide patients with oxygen at a constant concentration, temperature and humidity[5]. For patients with AECOPD, non-invasive positive pressure ventilation (NIPPV) is conventionally used, however, NPPV masks can cause facial compression that can affect patient communication, eating, sleeping and patient comfort[6].

HHFNC is a new type of non-invasive breathing assistance method that is used to provide oxygen at a precise concentration that is heated and humidified and meets the flow rate requirements of patients. HHFNC is advantageous as it improves ventilation and oxygenation levels and high comfortable. It is widely used in breathing patients who fail but do not meet the criteria for mechanical ventilation with tracheal intubation. In this study, we aimed to explore the clinical value of HFNC in the treatment of AECOPD.

MATERIALS AND METHODS

General information

80 AECOPD patients who were treated in our hospital from October, 2019 to October, 2021 were selected as the subjects of this study. The patients were divided into the control and treatment group with 40 cases in each group. The indications for invasive mechanical ventilation as follow: (1) Conditions that had significantly worsened with aggravated dyspnea and blood gas indicators that had not significantly improved; (2) new symptoms or complications such as pneumothorax,

aspiration, severe sputum retention and the elimination of obstacles; (3) severely ill patients; (4) hemodynamic instability; and (5) deterioration of consciousness. The patients were recruited under written informed consent. This study was approved by the Medical Ethics Committee of our hospital.

Inclusion and exclusion criteria

Inclusion criteria: (1) All patients in this study met the diagnostic criteria for AECOPD in the "AECOPD Diagnosis and Treatment Chinese Expert Consensus (Draft)"[7]. After 15 minutes, the state was stabilized and the arterial blood gas was measured; (2) the oxygenation index was ≤ 300 mmHg (oxygenation index = PaO_2/FiO_2, 1 mmHg = 0.133 kPa), and the bedside lung function test showed FEV1 ≥ 50% Pred; and (3) combined with hypercapnia ($PaCO_2$) ≥ 50 mmHg), respiratory rate ≥ 25 times/min.

Exclusion criteria: (1) Unconsciousness [Glasgow Coma Score (GCS) ≤ 12 points] who needed emergency tracheal intubation, and had previous chronic obstructive pulmonary disease, severe cardiac insufficiency, and sleep apnea; (2) patients with unstable hemodynamics and those who require vasoactive drugs; and (3) patients with > 1 severe organ dysfunction, severe non-cooperation, neuromuscular diseases, and severe mental illness.

Treatment methods

Both groups of patients were given conventional treatment including bronchodilators, low-dose glucocorticoids and antibacterial drugs. The vital signs, inflammatory response indicators, fluid balance and nutrition of the patients were monitored. The body positions were changed every two hours and chest physical therapy was performed. Patients in the control group were treated with NIPPV in which the ventilation mode was pressure support ventilation + positive end expiratory pressure. The initial inspiratory pressure was 5-8 cm H_2O. The positive end-expiratory pressure was set to 2-4 cm H_2O, and the oxygen concentration was 30%-35%. The parameters were adjusted according to the blood gas analysis results to final levels of $PaCO_2$ < 45 mmHg and PaO_2 > 60 mmHg.

Patients in the treatment group received HFNC. The initial temperature setting of the HFNC device (New Zealand) was 37 °C, the flow rate was 40L/min, and the oxygen concentration was 0.5%. The inspired oxygen concentration was adjusted to maintain a fingertip blood oxygen saturation > 92%. If the breathing cycle is stable, the flow rate was gradually lowered to 20 L/min and the oxygen concentration was lowered to 0.3. A nasal cannula was used to inhale oxygen. When the fingertip blood oxygen saturation was maintained at 92-96% for > 12 h the HFNC treatment was stopped.

In patients treated with HFNC, the clinician may decide to switch to NIPPV or establish an artificial airway for invasive mechanical ventilation. This may occur in cases of respiratory or cardiac arrest, when consciousness or anxiety is disturbed, in patients with pH ≤ 7.30 or rising $PaCO_2$ during treatment, when hypoxemia persists and cannot be corrected, when hemodynamics are unstable and require the use of vasoactive drugs, with increased airway secretions and during respiratory muscle fatigue or failure. During the treatment process, nurses assisted in expectoration and strengthened facial skin care to ensure patients could communicate.

Observational indicators

Comfort evaluation: A comfort questionnaire was used to evaluate patient comfort on the 3rd and 5th days after treatment [8]. The evaluation included headache and nasal, throat and chest discomfort. The severity of each symptom was scored using the Wong-Baker facial expression scale assessment (0 = no discomfort, 5 = severe discomfort). Both groups of patients had blood gas analysis before and after treatment and the results were compared to the partial pressure of oxygen (PaO_2), oxygenation index (PaO_2/FiO_2), partial pressure of carbon dioxide ($PaCO_2$), oxygen saturation (SaO_2), white blood cell count and levels of C-reactive protein and Calcitonin. The ventilator weaning standards were in line with the clinical application guidelines for comfort, that is, imaging examinations indicated that pneumonia was significantly or completely absorbed and routine bloods showed normal white cell count is normal and the body temperature was normal[8].

When the ventilator FiO_2 ≤ 0.4 and PEEP ≤ 5 cm H_2O, arterial blood gas analysis showed that PaO_2 ≥ 60 mmHg, PH > 7.3, and hemodynamics were stable. Before weaning, the ventilation mode adopted SIMV+PSV, and the support pressure was gradually reduced from the original parameter to 10 cm H_2O. Weaning was considered in patients who were stable for 30 min.

Statistical analysis

All data were recorded using Epidata and statistical analysis was performed using SPSS 25.0. The data were entered into a computer database by a second person to ensure completeness and accuracy. The count data was expressed as a *n* (%), using the χ^2 test. The measurement data was expressed as mean ± standard deviation (SD), using the *t*-test. A *P* value threshold of <0.05 was considered statistically significant.

RESULTS

General information comparison

80 patients with AECOPD participated in this study. The basic characteristics of patients are summarized in Table 1. The mean age of patients in the treatment and control groups were 54.78 ± 3.09 years and 54.62 ± 3.10 years, respectively. The mean body mass index (BMI) of patients in the treatment and control groups were 25.01 ± 3.67 kg/m^2 and 25.33 ± 3.65

Table 1 Comparison of the general information patients in the two groups

Group	Gender (Male/Female)	Age (yr)	BMI (kg/m^2)	Type of lung infection (*n*)			
				Germ	Fungus	Mix	Others
Therapy group (40)	26/14	54.78 ± 3.09	25.01 ± 3.67	18	13	7	2
Control group (40)	27/13	54.62 ± 3.10	25.33 ± 3.65	20	14	3	3
χ^2/t	0.056	0.231	0.391	0.201	0.056	1.829	0.213
P value	0.813	0.818	0.697	0.654	0.813	0.176	0.644

BMI: Body mass index.

kg/m^2, respectively. There were 26 males and 14 females in the treatment group and 27 males and 13 females in the control group. No significant differences were found between the two groups with regards to age, gender, and BMI (P = 0.818, P = 0.813, P = 0.697, respectively). With regard the type of lung infection, the treatment group had 18 germ, 13 fungus, seven mix, and two others, which the control group had 20 germ, 14 fungus, three mix, and three others.

Comfort situation

After treatment, the symptoms of nasal, throat and chest discomfort on the 3rd and 5th days in the treatment group were significantly lower when compared with patients in the control group (P < 0.05) (Table 2).

Blood gas analysis

Before treatment, PaO_2 (P = 0.980), PaO_2/FiO_2 (P = 0.991), $PaCO_2$ (P = 0.995), and SaO_2 (P = 0.989) were not significantly differences between the two groups. After treatment, PaO_2, PaO_2/FiO_2, $PaCO_2$, and SaO_2 were improved in both groups. Meanwhile, PaO_2 (P = 0.007), PaO_2/FiO_2 (P < 0.001), $PaCO_2$ (P = 0.012), and SaO_2 (P = 0.035) were significantly improved in the treatment group compared to the control group (Table 3).

Comparison of infection indicators

Before treatment, the levels of white blood cell count (P = 0.935), C-reactive protein (P = 0.965), and calcitonin (P = 0.799) were not significantly differences between the two groups. After treatment, the levels of white blood cell count (P = 0.017), C-reactive protein (P < 0.001), and calcitonin (P = 0.003) in the treatment group were significantly better compared to the control group (Table 4).

DISCUSSION

Chronic obstructive pulmonary disease (COPD) is a common disease of the respiratory system. AECOPD refers to the rapid deterioration of respiratory symptoms and requires additional treatment[9]. The main clinical manifestations of AECOPD are often dyspnea, increased sputum volume and purulent sputum, which is an important factor in the death of COPD patients. Acute respiratory failure caused by AECOPD often requires respiratory support treatment[10]. NIPPV is the preferred treatment for AECOPD with mild-to-moderate respiratory failure (pH 7.25-7.35). NIPPV can improve symptoms, increase oxygenation, alleviate carbon dioxide retention, and effectively reduce intubation rate and mortality [11].

HFNC is a new type of oxygen therapy that has recently become more popular in the clinic. HFNC can provide accurate inhaled oxygen concentration, good airway humidification and can provide a high flow rate of 8-80 L/min[12]. HFNC involves oxygen therapy through nasal delivery that is comfortable and well tolerated. HFNC has been used in the treatment of pure hypoxic respiratory failure and can improve the 90-d survival rate of patients[13]. HHFNC uses high-velocity gas to flush the anatomical dead space in the nasopharynx, increase alveolar ventilation, and improve lung ventilation efficiency[14]. It also reduces upper airway resistance and the effort of breathing. The warming and humidification of gas can increase lung compliance, improve airway conductivity and defense function. Also, it reduces airflow resistance, promotes sputum discharge, and generates positive airway pressure to prevent atelectasis and promote lung recruitment[15]. The HHFNC system is advantageous as it required simple equipment and uses only three indicators (flow rate, oxygen concentration, temperature) that need to be adjusted. It can provide a stable concentration of oxygen close to body temperature, reduce the stimulation of the airways, and avoid airway spasm. It is also conformable for patients with less abdominal distension and does not affect communication, sputum and eating[16].

Analysis of comfort during the two treatment methods showed that the comfort score of HHFNC 3 and 5 d after treatment was significantly lower than that of the traditional oxygen therapy method. These data suggest that this method can reduce discomfort during the treatment[17,18]. After treatment, the main blood gas indices (PaO_2, PaO_2/FiO_2, $PaCO_2$, and SaO_2) of patients in the two groups of patients were significantly improved. Patients in the treatment group improved more compared to the control group indicating that HFNC treatment can improve ventilation in AECOPD patients. A number of studies have shown that NIPPV can reduce $PaCO_2$ in patients with AECOPD and relieve respiratory distress[19,20]. The results of blood gas analysis showed that HFNC has a similar effect to NTV in improving

Table 2 Summary of the levels of comfort in the two patient groups

Group		Nose discomfort	Pain	Chest discomfort	Throat discomfort
Control group (40)	Treatment 3 d difference	1.37 ± 0.38	0.56 ± 0.20	0.49 ± 0.15	1.24 ± 0.32
	Treatment 5 d difference	1.22 ± 0.34	0.41 ± 0.18	0.45 ± 0.12	1.01 ± 0.33
Therapy group (40)	Treatment 3 d difference	1.01 ± 0.22[a]	0.55 ± 0.19	0.30 ± 0.14[a]	0.68 ± 0.35[a]
	Treatment 5 d difference	0.89 ± 0.28[a]	0.37 ± 0.20	0.28 ± 0.15[a]	0.47 ± 0.25[a]

[a]$P < 0.05$.
Compared with control group.

Table 3 Comparison of blood gas analysis between the two groups of patients before and after treatment

Group	PaO_2 (mmHg)		PaO_2/FiO_2 (mmHg)		$PaCO_2$ (mmHg)		SaO_2 (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (40)	67.44 ± 7.23	93.27 ± 8.14	172.34 ± 11.25	291.81 ± 7.82	52.23 ± 6.57	39.67 ± 2.24	94.76 ± 3.15	96.45 ± 0.15
Therapy group (40)	67.40 ± 7.22	98.37 ± 8.20	172.31 ± 11.64	322.27 ± 7.81	52.24 ± 6.53	37.23 ± 2.26	94.75 ± 3.26	97.57 ± 0.16
t	0.025	2.792	0.012	17.431	0.007	4.850	0.014	32.298
P value	0.980	0.007	0.991	< 0.001	0.995	0.012	0.989	0.035

Table 4 Analysis of infection indicators in the two groups of patients

Group	White blood cell count (10^9/L)		C-reactive protein (g/L)		Calcitonin (g/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (40)	11.38 ± 1.10	10.41 ± 1.16	23.41 ± 2.27	8.71 ± 1.56	1.57 ± 0.33	3.41 ± 0.32
Therapy group (40)	11.40 ± 1.08	8.44 ± 1.65	23.43 ± 2.25	6.50 ± 1.82	1.55 ± 0.37	5.64 ± 1.15
t	0.082	6.177	0.040	5.831	0.255	11.815
P value	0.935	0.017	0.965	< 0.001	0.799	0.003

oxygenation and alleviating CO_2 retention[21]. The mechanism of HFNC in the treatment of AECOPD is mainly considered to be due to the scouring effect of the physiological dead space. The high-flow inhalation with adjustable flow rate provided by HFNC can wash out the anatomical ineffective cavities remaining in the nose, mouth and pharynx at the end of expiration. The retained CO_2 and repeated inhalation of CO_2 is significantly reduced[22,23]. HFNC adopts nasal congestion ventilation. The maximum positive airway pressure produced is 6-7 cm H_2O and so it does not cause abdominal distension due to excessive airway pressure. The patient can eat, expectorate, talk and communicate with others at any time.

Studies have confirmed that HFNC can improve the hypoxic state of patients with AECOPD and reduce the respiratory rate[24]. In theory, HFNC can produce the gas flushing effect on the physiological dead space of the nasopharyngeal area. In COPD patients, the scouring effect of HFNC is therapeutically significant[25]. For critically ill AECOPD patients treated with mechanical ventilation after extubation, HFNC and conventional mask oxygen therapy were used to monitor the diaphragm muscle potential of the two groups of patients to evaluate the respiratory muscle work intensity of the patients[21]. Our data showed that the respiratory muscle work of the HFNC group was significantly higher than that of the conventional oxygen therapy group indicating that HFNC is beneficial to the successful weaning of severe patients with AECOPD. The use of electrical impedance tomography technology confirmed that compared with nasal cannula oxygen inhalation, HFNC can reduce the respiratory frequency of long-term oxygen therapy in patients with AECOPD in the chronic phase. It can also increase the patient's tidal volume, and reduce the work of breathing[26]. Our results provide a reference for the use of HFNC in the treatment of AECOPD.

However, the current research also has some limitations. In this study, only the symptoms of nose, throat and chest discomfort were counted on the third and fifth days, but there was no measurement of discomfort symptoms under the long-term time measurement index. In addition, the index of measuring ventilation function under different treatments in this study is relatively simple. Therefore, this study should also increase the incidence of adverse reaction symptoms under long-term measurement, and increase the measurement index to measure the oxygenation state after treatment.

CONCLUSION

In summary, the application of HFNC treatment can improve the ventilation of AECOPD patients, improve patient comfort, and reduce the occurrence of complications. It has good clinical application value and is worthy of reference for clinical treatment of AECOPD.

ARTICLE HIGHLIGHTS

Research background

Improving oxygenation is very important in the clinical treatment of patients with chronic obstructive pulmonary disease. High-flow nasal intubation (HFNC) oxygen therapy is an effective clinical treatment method to improve oxygenation.

Research motivation

The treatment of acute exacerbation chronic obstructive pulmonary disease (AECOPD) is the key point in clinic at present. The purpose of this study is to explore the clinical effect of HFNC in improving oxygen and prognosis of AECOPD.

Research objectives

To compare the efficacy of HFNC with non-invasive positive pressure ventilation in patients with AECOPD.

Research methods

The oxygenation status and clinical efficacy of AECOPD patients treated with HFNC and noninvasive positive pressure ventilation were analyzed retrospectively.

Research results

The oxygenation state, white blood cell count, C-reactive protein and calcitonin levels in HFNC treatment group were significantly increased, and the complications were significantly reduced.

Research conclusions

HFNC treatment can improve the ventilation function of patients with AECOPD, improve the nursing comfort of patients, improve the prognosis of patients, and reduce the occurrence of complications.

Research perspectives

HFNC is an effective clinical nursing method to treat patients with AECOPD, which is of great significance to improve the quality and level of clinical nursing.

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FOOTNOTES

Co-first authors: Xiang Chen and Ling Dai.

Author contributions: Chen X, Dai L, Ma JZ, and Chu XX designed the research; Dai L, Liu JM, and Guo SW performed the research; Ru XW and Zhuang XS contributed new reagents/analytic tools; Zhuang XS analyzed the data; Chen X and Dai L wrote the paper; Chen X and Dai L contributed equally to this work as co-first authors equally to this work. The reasons for designating Chen X and Dai L as co-first authors are three-fold. 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-first 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, Chen X and Dai L contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Chen X and Dai L as co-first authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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ORIGINAL ARTICLE

Retrospective Study

Mortal condition in an unusual localization, analysis of isolated tongue and tongue base abscesses

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Abstract

BACKGROUND

Tongue abscess (TA) is a very rare clinical condition and its treatment is very important. Surgical drainage is at the forefront in the treatment. Our study includes patients with tongue and tongue base abscesses.

AIM

To discuss the clinical and laboratory findings of these patients emphasizing the underlying causes and treatment options with the largest patient series in the English literature.

METHODS

We included patients with isolated TA who applied to our clinic between January 1, 2020 and January 1, 2023. Those who lack the recorded data, those who are not between the ages of 18-66, those who have not undergone surgery-interventional procedure, and those who have infection and/or abscess in another place were excluded from the study.

RESULTS

There were two female (18%) and nine male (82%) patients in our series consisting of 11 patients. Their ages ranged from 18 to 66, and the mean ± SD was 48.63 ± 16.3. Considering the localization of the abscess, three anterior abscesses (27%), two lateral abscesses (18%), and six abscesses at the base of the tongue (54%) were detected.

CONCLUSION

Tongue abscesses can cause acute upper airway obstruction and respiratory collapse. It may be necessary to act quickly for the tracheotomy procedure and this procedure can usually be performed under local anesthesia as intubation

cannot be achieved. When we encounter an abscess in an unexpected organ, difficulties may be encountered in the management of the patient.

Key Words: Tongue; Abscess; Neutrophils; Blood platelets; Lymphocytes

Core Tip: Tongue abscess is a very rare disease due to the anatomical and physiological structure of the tongue. The rarity of the disease can make it difficult to diagnose. Particular attention should be paid to airway obstruction, sepsis, and mediastinitis. Surgical drainage should be performed in abscesses larger than one centimeter.

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INTRODUCTION

Tongue abscess (TA) is a very rare disease, potentially dangerous due to possible airway obstruction. The anatomical, vascular and muscular structure of the tongue and the unique antibacterial properties of saliva promote prevention of infection. Foreign bodies and immunosuppression may predispose to infection. TA may show symptoms such as dysphagia, dyspnea, pain, referred pain, fever. Especially tongue base abscesses should be taken into consideration as they can cause sudden respiratory collapse. Drainage should be applied in the treatment of tongue abscesses[1]. Most tongue abscesses are unifocal and located in the anterior two-thirds of the tongue. Abscesses in the posterior part of the tongue (including the tongue base) mostly occur as diseases involving the lingual tonsil, infected thyroglossal duct cysts extending to the base of the tongue, ectopic thyroid gland, or dissemination of apical infections of the first or second molar teeth[2]. Most of the articles on the subject remained as case reports, and the patient series found in the literature are limited in number. A maximum of six patient series have been reported[3].

There are authors in the literature reporting that the ratios of neutrophil (NEU) and lymphocyte (LYMPH) values to each other are useful in predicting cardiac diseases, cancer, infective diseases and length of hospital stay[4-6]. There are also studies on infectious diseases involving the ratio of platelets (PLTs) and LYMPHs to each other, diseases with ischemic neuropathy hypothesis, allergic rhinitis and asthma, neonatal sepsis, congenital branchial cysts[7-10]. We aimed to discuss this article with up-to-date information, which includes the largest patient series and allows to look at the disease with different laboratory parameters.

MATERIALS AND METHODS

We included patients with isolated TA who applied to our clinic between January 1, 2020 and January 1, 2023. The patients were divided into two groups. Anterior and lateral tongue abscesses were named as group 1 (anterolateral) and tongue base abscesses were named as group 2. Patients' age, gender, location of the abscess, contrast-enhanced computed tomography (CT) results (Figures 1A and B), white blood cell (WBC, μL) count, NEU (μL) count, LYMPH (μL) count, PLT (μL) number, NEU/LYMPH ratio (NLR), PLT/LYMPH ratio (PLR), C-reactive protein (CRP, m/L) value, erythrocyte sedimentation rate (ESR, m/h) value, abscess culture results, surgeries and interventional procedures (Figures 2A and B), underlying causes, additional systemic diseases, smoking history, length of hospital stay, antibiotics used, antibiotics used before admission, pathology results were recorded. A retrospective archive search was conducted for the study. Those who lack the recorded data, those who are not between the ages of 18-66, those who have not undergone surgery-interventional procedure, and those who have infection and/or abscess in another place were excluded from the study. Pediatric patients were excluded from the study. None of the patients had a history of foreign body or piercing. TA drainage and tracheotomy surgical procedures were performed under local anesthesia, and penrose drains were placed in all patients who underwent surgical drainage. In patients with tongue base abscess, the operation was started with tracheotomy under local anesthesia, followed by external drainage of the abscess with a transhyoidal approach under general anesthesia. Transoral tongue base abscess drainage; it has not been tried because the abscesses are closer to the hyoid bone and in deeper localizations, the external method is preferred (Table 1). All of our patients were decannulated (postoperative 10th d) after treatment. All of our patients were given intravenous treatment for 14 d as standard, and 600 m of oral cefdinir was given daily for 14 d at discharge. Ethics committee approval was obtained for our study (09/286). Written and verbal consent was obtained from all patients participating in the study.

Table 1 Clinical information of patients with tongue abscess

Patient	Surgery/puncture	Incision-drainage/incision-drainage and tracheotomy	Hospitalization time (d)
1	Surgery	Incision-drainage	6
2 (HIV positive)	Surgery	Incision-drainage	4
3	Surgery	Incision-drainage	9
4	Surgery	Incision-drainage	8
5	Surgery	Incision-drainage and tracheotomy	11
6	Surgery	Incision-drainage and tracheotomy	9
7	Surgery	Incision-drainage and tracheotomy	8
8 (diabetes mellitus)	Puncture		6
9 (hypothyroidism)	Surgery	Incision-drainage	7
10	Surgery	Incision-drainage and tracheotomy	10
11 (intravenous heroin addict)	Surgery	Incision-drainage	4

HIV: Human immunodeficiency virus.

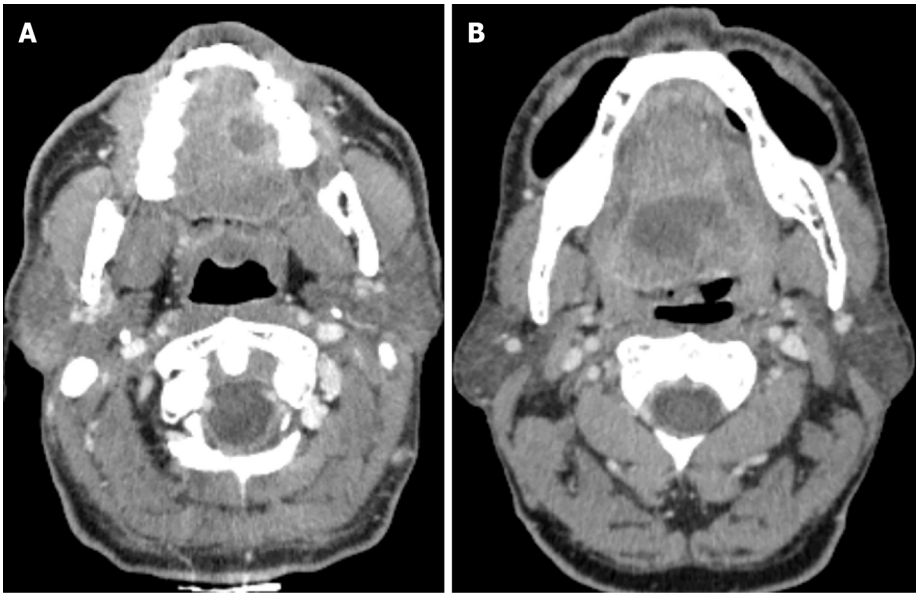

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Figure 1 Contrast-enhanced computed tomography results. A: Contrast-enhanced tomography image of lateral tongue abscess; B: Massive tongue base abscess.

RESULTS

There were 2 female (18%) and 9 male (82%) patients in our series consisting of 11 patients. Their ages ranged from 18 to 66, and the mean ± SD was 48.63 ± 16.3. Considering the localization of the abscess, three anterior abscesses (27%), two lateral abscesses (18%) in group 1, six abscesses at the base of the tongue (54%) in group 2 were detected. Contrast-enhanced CT was performed in all abscess patients, and abscess sizes ranged from 10 to 45 mm, the mean ± SD was 22.9 ± 10.79 mm. Four of the patients (36%) had additional disease; acquired immune deficiency syndrome was found in one patient, diabetes mellitus (DM) in one patient, hypothyroidism in one patient, and intravenous heroin addiction in one patient. WBC ranged from 4240 to 20470, the mean ± SD was 11330 ± 4079. NEU ranged from 220 to 17870 and the mean ± SD was 8282 ± 3839. LYMPH ranged from 1020 to 3740, the mean ± SD was 2018 ± 872. PLT ranged from 172000 to 457000, the mean ± SD was 274818 ± 94437. The NLR ranged from 1.65 to 17.51, and the mean ± SD was 5.05 ± 4.43. The PLR ranged from 60.9 to 304.41, and the mean ± SD was 159.67 ± 81.27. CRP ranged from 4.9 to 178.6 and the mean ± SD was 43.59 ± 54.34. ESR ranged from 11 to 62, the mean ± SD was 35.81 ± 16.88. Bacterial growth was observed as a result of abscess culture in 82% of patients (9 patients). *Streptococcus viridans* was detected in two patients, *Streptococcus pneumoniae* in two patients, *Streptococcus spp.* in two patients, Methicillin-sensitive coagulase negative staphylococci in one patient,

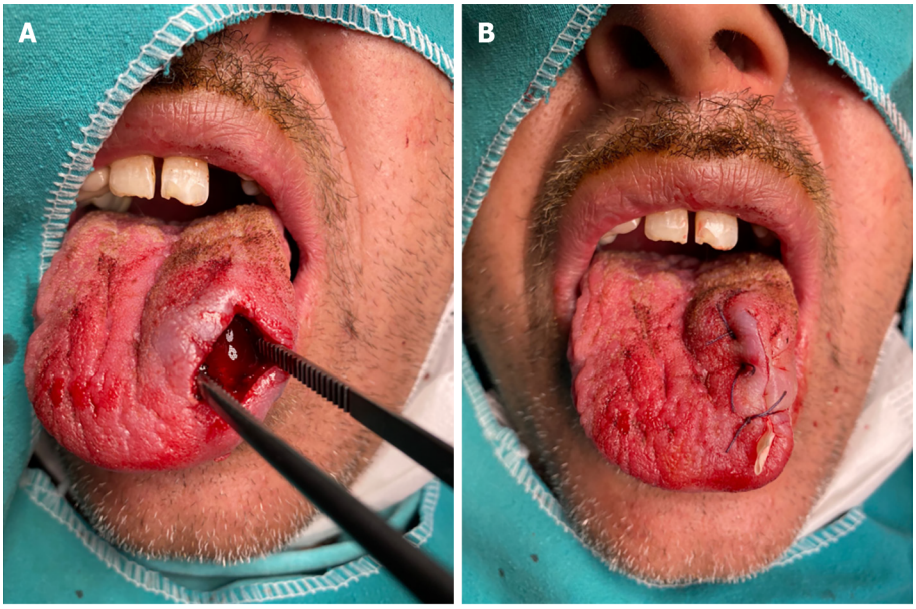

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Figure 2 Surgeries and interventional procedures. A: Intraoperative view of surgically drained tongue abscess; B: Postoperative view of tongue abscess with penrose drain placed.

Candida krusei in one patient, *Bacteroides spp*. in one patient. Abscesses of all patients were drained, incision-drainage was preferred in 10 patients, and needle aspiration was preferred in one patient. Tracheotomy was preferred in four (36%) patients to secure the airway. Five of the patients are smokers and have poor oral hygiene (45%). Etiology could be detected in four (36%) of the patients. Extension of the infected thyroglossal duct cyst to the base of the tongue in two of the patients, abscess formation 24 h after the coronavirus disease 2019 mRNA vaccine in one patient, and intravenous heroin addiction in one patient were detected. Hospitalization time ranged from 4 to 11 d, and the mean ± SD was 7.45 ± 2.29. Ampicillin-Sulbactam was given to 10 of our patients and Piperacillin-Tazobactam was given to 1 of our patients. No antibiotic revision was required in any of our patients. Antifungal treatment was also given to our patient who overgrown Candida krusei. Six of our patients (54%) used Amoxicillin-clavulanate before applying to the hospital. Pathology was sent to 10 of our patients, and cytology (a patient with needle aspiration) was sent in one of our patients. In all of the pathology results, an appearance compatible with chronic active inflammation and abscess was detected. In addition, dense actinomyces colonies were detected in one patient.

Three patients in group 1 had a history of additional diseases, one patient in group 2. There is no statistically significant difference between groups regarding the frequency of additional diseases (P = 0.545). There was no statistically significant difference between the groups in terms of WBC, NEU, LYMPH, PLT, NLR, PLR, CRP, ESR, and hospitalization time (P > 0.05 for all, respectively 0.361, 0.465, 0.584, 0.361, 0.855, 0.584, 0.273, 0.201, 0.08).

DISCUSSION

TA is a disease that is usually seen in immunocompromised people and is very rare in healthy individuals. TA is a rare clinical condition that is seen much less frequently than deep neck infections (DNIs), which are common diseases in otorhinolaryngology clinics.

Therefore, we believe that it is not correct to state the incidence for the disease. The tongue is resistant to infection with additional antimicrobial effect of the saliva. The differential diagnosis of tongue abscesses includes tumor, cyst, hematoma, hyperpituitarism, hypothyroidism, lingual thyroid, and ectopic lymphoid tissues. Generally, abscesses are unilateral and located in the anterior 2/3 of the tongue. Painful swelling, dysphagia, odynophagia, speech disorder, tongue pain - headache, high fever, dyspnea are among the symptoms[1,11]. There are 2 types of abscesses, superficial and deep. Deep abscesses of the tongue are observed in cases that go down to the muscle tissue planes. Patients present with more severe symptoms and a toxic appearance. Tracheotomy may be considered for patients with dyspnea CT, magnetic resonance imaging can be used in the diagnosis of patients. After the correct diagnosis, the safety of the airway, incision-drainage is important. Antibiotics treatments should cover streptococci, staphylococci and anaerobes. Since aspiration alone is an inadequate treatment method, it should not be preferred over drainage[2]. We preferred it in one of our patients because the abscess was located anteriorly and was small in size. To prevent complications, it is important for the clinician to take a decisive stance and act quickly if drainage and elective local tracheotomy are indicated.

In the literature, comorbidity was not observed in most patients, and the most common symptoms are painful tongue, odynophagia, and tongue swelling. Tracheotomy is performed in approximately one third of the patients[3]. Antoniades *et al*[12] reported two immunocompromised patients presenting with severe respiratory distress. And in two patients

with severe immune problems, the predisposing factors were dental intervention and odontogenic infection. Palpation can be a valuable diagnostic tool in posterior lingual abscesses. Isolated medical treatment may be sufficient for abscesses < 1 cm. Only medical treatment works for subcentimetric abscess. Posterior lingual abscesses may result in sepsis, mediastinitis, and fatal airway obstruction[13]. Although rates for airway obstruction, sepsis, and mediastinitis are given for DNIs in the literature[11], unfortunately these cannot be stated clearly for TA. We think that airway obstruction and sepsis may be a bigger problem for TA. Because the tongue is a muscular organ, it does not have potential spaces and fascias like the neck, and therefore the increased abscess size will directly cause collapse in the upper airway. Another important situation is that the tongue base is one of the most important anatomical formations of swallowing and upper airway breathing. The size of the abscess between the vallecula and tongue base may cause direct passage collapse and make possible elective or semi-elective intubations impossible. It should not be forgotten that there is always the possibility of emergency tracheotomy in this patient group, and if the indication occurs, this situation can be dramatic for the patient and the doctor. We think that due to the high blood supply and arterial network of the tongue, it is more susceptible to septic microemboli and the rate and probability of leading to sepsis may be higher than DNIs. Our study, which included 11 consecutive patients, is the largest series in the literature. Contrary to the literature, posterior lingual abscess (54%) was observed more frequently in our study and appeared as swelling at the base of the tongue. It should not be forgotten that there may be tumoral lesions that occupy space in the differential diagnosis of the disease and contrast-enhanced imaging methods can always be preferred. Contrast-enhanced CT was performed in all of our abscess patients. Abscess sizes were found to be 22.9 mm on average. All patients had odynophagia and dysphagia. Additional disease was detected in four of our patients (36%). Incision-drainage was applied to all of our patients except one. In one of our patients, only puncture was performed. Tracheotomy was performed in 36% of our patients. Five of our patients were smokers and had poor oral hygiene. Human immunodeficiency virus (HIV) infection was present in one of our patients, DM in one, and intravenous heroin use in one caused immunosuppression. Although we cannot provide sufficient data on isolated medical treatment since we do not have an abscess < 1 cm, we think that incision-drainage would be appropriate because the tongue contains dense muscle tissue and may obstruct the airway. It is necessary not to be very conservative about tracheotomy in patients with tongue base localization, because sudden collapse will result in death. Poor oral hygiene and smoking were observed as a remarkable factor in tongue abscesses. Since it is an atypical disease, an infectious disease specialist should be asked about empirical antibiotics within the framework of a multidisciplinary approach and revised antibiotics based on the bacteriological result of the abscess content.

NLR was found useful in comparing two conditions that regressed with medical treatment, such as abscess requiring incision-drainage and microabscess-cellulitis[4]. NLR has been identified as a variable predicting hospitalization time in odontogenic head and neck infections[5]. CRP is elevated in case of infection and the half-life is between 5 and 7 h. WBC determines total WBC count, values > 10000 suggest infection. In inflammatory conditions, neutrophils usually increase while LYMPHs decrease. Therefore, NLR is a more reliable marker than the total leukocyte count in the evaluation of inflammation. NLR is a good marker especially in odontogenic infections[6]. PLR is a new inflammatory marker. In a study conducted with patients with DNI, NEU and PLR values differed between patient groups requiring and not requiring airway management. NEU and PLR were found to be statistically significantly higher in patients requiring airway management[7]. It has been stated that PLR is a parameter that can also be used in neonatal sepsis[8]. NLR, PLR are important biochemical markers shown to be increased in bacterial inflammation. NLR and PLR averages of group 1 were higher than group 2. The remarkable point in our study is that patients with intravenous heroin addiction (highest) and hypothyroidism had the highest values in terms of PLR. These two patients were ranked 2nd (hypothyroidism) and 3rd (intravenous heroin addict) in terms of NLR. In patients with TA, we may encounter low immune system and/or additional disease status with high PLR, NLR values. NLR and PLR are among the recent trending fields of study in otorhinolaryngology and are thought to be useful in predicting hospitalization time and bacterial inflammation status, especially in DNIs patients. In particular, the fact that NLR is a significant marker in odontogenic DNIs may be the subject of a new and original study with a large case series in the group of patients with TA who have predisposing factors of poor oral hygiene. Systemic additional diseases that cause immunosuppression and diseases that create an insidious clinical course, such as HIV, can cause serious problems in cases of TA. We routinely monitor hemogram, biochemical parameters and CRP in all our patients to whom we perform drainage and puncture, and request a preoperative serological marker for viral diseases such as hepatitis B, C and HIV, which are transmitted through blood and contact. Depending on the status of additional diseases, we take the advice of the relevant branch and treat this serious illness with a multidisciplinary approach.

CONCLUSION

TA is a very rare disease due to the anatomical and physiological structure of the tongue. The rarity of the disease can make it difficult to diagnose. Particular attention should be paid to airway obstruction, sepsis, and mediastinitis. Surgical drainage should be performed in abscesses larger than one centimeter.

ARTICLE HIGHLIGHTS

Research background

Discussing the treatment methods and complications of this rare disease will contribute to science. Its rarity may make

the disease difficult to diagnose and cause increased mortality.

Research motivation
The fact that our patient series has the highest number of patients in the English literature makes our study very valuable.

Research objectives
We aimed to discuss this very rare disease, which can be fatal, within the literature information. Because there is no algorithm or general information about its treatment.

Research methods
We have eleven patients in our approximately three-year study, where patient data is complete.

Research results
Three anterior abscesses (27%), two lateral abscesses (18%) in group 1, six abscesses at the base of the tongue (54%) in group 2 were detected.

Research conclusions
Surgical drainage of abscesses larger than one centimeter is inevitable and the clinician should be hurried as soon as the need for a tracheotomy occurs.

Research perspectives
Poor oral hygiene and prevention of odontogenic diseases can prevent this fatal disease.

FOOTNOTES

Author contributions: Bal KK, Gür H, Demir I, Ismi O, Vayisoglu Y, Gorur K, Ozcan C, and Unal M contributed to the conception and design, data collection and analysis of this study, and manuscript drafting.

Institutional review board statement: Ethics committee approval was received for our study.

Informed consent statement: Written and verbal consent was obtained from all patients participating in the study.

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

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ORIGINAL ARTICLE

Retrospective Study

Adult-onset hypophosphatemic osteomalacia as a cause of widespread musculoskeletal pain: A retrospective case series of single center experience

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Abstract

BACKGROUND

Osteomalacia (OM) is frequently confused with various musculoskeletal or other rheumatic diseases, especially in patients with adult-onset widespread musculoskeletal pain because of its low prevalence and non-specific manifestations.

AIM

To facilitate the early diagnosis and etiology-specific treatment of adult-onset hypophosphatemic OM.

METHODS

A retrospective review of medical records was performed to screen adult patients who visited a physiatry locomotive medicine clinic (spine and musculoskeletal pain clinic) primarily presenting with widespread musculoskeletal pain at a single tertiary hospital between January 2011 and December 2019. We enrolled patients with hypophosphatemia, high serum bone-specific alkaline phosphatase levels, and at least one imaging finding suggestive of OM.

RESULTS

Eight patients with adult-onset hypophosphatemic OM were included. The back was the most common site of pain. Proximal dominant symmetric muscle weakness was observed in more than half of the patients. Bone scintigraphy was the most useful imaging modality for diagnosing OM because radiotracer uptake in OM showed characteristic patterns. Six patients were diagnosed with adefovir (ADV)-induced Fanconi syndrome, and the other two patients were diagnosed with tumor-induced OM and light-chain nephropathy, respectively. After phosphorus and vitamin D supplementation and treatment for the underlying etiologies, improvements in pain, muscle strength, and gait were observed in all patients.

CONCLUSION

Mechanical pain characteristics, hypophosphatemia, and distinctive bone scintigraphy patterns are the initial diagnostic indicators of adult-onset hypophosphatemic OM. ADV-induced Fanconi syndrome is the most common etiology of hypophosphatemic OM in hepatitis B virus-endemic countries.

Key Words: Hypophosphatemia; Osteomalacia; Widespread musculoskeletal pain; Bone scintigraphy; Hepatitis B virus; Phosphaturic mesenchymal tumor

Core Tip: This retrospective study assessed the clinical manifestations as well as laboratory, and imaging findings of patients with adult-onset hypophosphatemic osteomalacia (OM) to highlight the importance of early diagnosis and etiology-specific treatment. Physicians should consider OM as a possible cause of widespread musculoskeletal pain in adult patients. Mechanical pain characteristics, insufficiency fracture sites, distribution of muscle weakness, hypophosphatemia, and distinctive patterns on bone scintigraphy can be the initial diagnostic indicators. Adefovir-induced Fanconi syndrome, phosphaturic mesenchymal tumors, and light-chain nephropathy can cause hypophosphatemic OM.

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INTRODUCTION

Osteomalacia (OM) is characterized by bone matrix hypomineralization, and its histological hallmarks include hyperosteoidosis and delayed mineralization[1]. The symptoms of OM include widespread musculoskeletal pain due to multiple bone fractures, arthralgia, skeletal deformities, height loss, and muscle weakness[2-4]. Most patients complain of generalized or localized bone pain, which usually occurs in the axial skeleton, rib cage, shoulder/pelvic girdle, and weight-bearing bones, particularly patients with adult-onset disease. Hence, patients with adult-onset OM commonly visit physiatric or musculoskeletal pain clinics rather than endocrinology or rheumatology clinics. Owing to variable clinical manifestations, non-specific radiological findings, and non-characteristic routine biochemical changes, adult-onset OM is often confused with various musculoskeletal diseases or other rheumatic diseases, and a high clinical index of suspicion is essential for diagnosing OM[4-7].

The etiologies of OM include vitamin D deficiency or resistance, calcium deficiency, hypophosphatemic disorders, and mineralization inhibitors. Although the most common cause of OM is vitamin D deficiency due to lack of exposure to the sun and inadequate intake, which results in secondary hyperparathyroidism, hypophosphatemic OM of various etiologies other than vitamin D deficiency is yet another important cause of OM[2,3,8-11].

This study assessed the clinical manifestations and laboratory and imaging findings of patients with adult-onset hypophosphatemic OM and summarized the points differentiating this disease from other musculoskeletal or rheumatic diseases. We focused on the imaging findings of the skeletal system and etiologies of hypophosphatemia to facilitate the early diagnosis of this rare, but treatable and, even curable cause of widespread musculoskeletal pain.

MATERIALS AND METHODS

Participants

We retrospectively analyzed the databases of a physiatry locomotive medicine clinic (spine and musculoskeletal pain clinics) at a single tertiary hospital between January 2011 and December 2019. Patients with clinical, laboratory, and radiological findings consistent with adult-onset hypophosphatemic OM were included. As the diagnosis was not confirmed by bone biopsy, we set the inclusion criteria based on those reported in previous studies[8,12]. We included

adult patients presenting with widespread musculoskeletal pain, hypophosphatemia, high serum bone-specific alkaline phosphatase, and at least one of the following imaging findings suggestive of OM: Looser's zone/pseudo-fracture or codfish vertebrae on radiography, and costochondral junction beadings ("rachitic rosary" appearance) on bone scintigraphy[13].

Data collection

The data on patient demographics, clinical histories, physical examination findings of the skeletal system, and results of laboratory tests, electromyographic studies, and imaging studies [plain radiographs, bone scintigraphy using technetium 99m-methyl diphosphonate, dual-energy X-ray absorptiometry (DEXA), computed tomography (CT), magnetic resonance imaging, and ^{68}Ga-DOTATOC positron-emission tomography/CT (PET/CT)] were extracted. In particular, we evaluated the presence of typical bone scintigraphy findings of OM, such as the "adult rachitic rosary" appearance, pseudo-reactivation of the growth plate, and the "tie sign" of the sternum[13-15].

Differential diagnosis of hypophosphatemia

The diagnostic approach for patients with hypophosphatemia in our clinic was based on previous reports on the differential diagnosis of various causes of hypophosphatemia[3,8,10]. Initially, we determined whether the hypophosphatemia was renal or extrarenal based on the renal tubular reabsorption rate of phosphate in the patient. Within these categories, a specific diagnosis was made based on the family history, medical history, dietary history, nutritional status, medication history, and serum parathyroid hormone, and vitamin D {25-hydroxyvitamin D [25(OH)D]} levels. The serum fibroblast growth factor (FGF)-23 levels were measured only when the etiology was not found in the above two steps and FGF23-related causes were suspected. Finally, serum/urine protein electrophoresis with light chain analysis or ^{68}Ga-DOTATOC PET/CT was performed when light-chain nephropathy or tumor-induced OM (TIO) was suspected.

RESULTS

Eight patients with adult-onset hypophosphatemic OM, comprising three men and five women, were identified. Of the eight patients, one and seven patients were classified as having possible and definite OM, respectively, according to the Japanese diagnostic criteria[8]. The average age at diagnosis was 62 years (range, 52-76 years), and the average interval between symptom onset and diagnosis of OM was 23.8 mo (range, 6-61 mo). Two cases (patients #2 and #7) had been described in our previous case report, and these cases provided insights on the suspicion and diagnosis of OM in adult patients presenting with widespread musculoskeletal pain[15].

Clinical features

The most common site of pain was the back, followed by the shoulders, chest wall, and lower extremities. The pain characteristics corresponded to the mechanical pain patterns (aggravation with movement and relief with rest). Five patients were misdiagnosed and treated for other diseases before the OM diagnosis. Seven patients had a history of fractures; however, the majority of fractures were atraumatic. Height loss after the development of widespread pain was observed in seven patients. Physical examination revealed focal tenderness over the bony regions in six patients. Significant deformities of the skeleton, such as bowing or varus/valgus deformities of the long bones, were not observed, and hypertrophy of the costochondral junctions was not detected upon palpation. Signs of joint inflammation were absent in all the patients (Table 1).

Neuromuscular examination showed symmetric muscular weakness of the proximal limb girdle in five patients, including two with shoulder and pelvic girdle muscle weakness and three with only pelvic girdle muscle weakness. Bilateral compensated Trendelenburg gait (waddling gait) was observed in all five patients, four of whom showed a positive Gower sign. The muscle strength of the hip abductors was grade 0-4 (Medical Research Council scale) and that of the hip flexors or knee extensors was grade 4. However, knee jerk was preserved in all patients (Table 1).

Laboratory tests and electromyographic test

All patients showed low tubular reabsorption of phosphate and a low ratio of tubular maximum reabsorption of phosphate to the glomerular filtration rate, indicating renal tubular phosphate wasting. Two patients had decreased serum calcium levels; however, normal ionized calcium levels were observed. None of the patients had severe vitamin D deficiency [serum 25(OH)D concentration < 30 nmol/12 ng/mL]. FGF23 levels, assessed in two patients without a history of antiviral treatment for hepatitis B virus (HBV) infection, were within the normal range. Despite evidence of proximal girdle muscle weakness, denervation, myopathic evidence on needle electromyography, and elevated serum creatine kinase (CK) levels, were not found in any patient (Supplementary Table 1).

Imaging studies of the skeletal system

On bone scintigraphy, multiple hot uptakes were observed in all patients (Table 2). The most common sites of involvement were the thoracic vertebrae, costochondral junctions, costovertebral/costotransverse process joints, and arc of the ribs. The uptakes were not necessarily symmetric. Multiple hot uptakes at the bilateral costochondral junctions revealed a characteristic "adult rachitic rosary" appearance in five patients (Figure 1A). Pseudoreactivation of the growth plate was observed in the distal femur (two patients) and proximal tibia (three patients) (Figure 1B). None of the patients showed the "tie sign" of the sternum. Chest CT in patient #2 confirmed the fractures of the neck and tubercle of the ribs,

Table 1 Clinical features of patients with adult-onset hypophosphatemic osteomalacia

	Sex/age	Location of pain	Previous misdiagnosis before OM diagnosis	Weakness (MRC grade)	Gait	Gower sign	Height loss (cm)
1	F/52	Low back, left scapula and chest wall, bilateral mid-thigh	N/A	Hip flexor - 4 Hip abductor - 3	Bilateral compensated Trendelenburg gait	(-)	(-)
2	M/62	Thoracic back, bilateral chest wall and knee	N/A	Negative	Normal	(-)	170 to 166
3	F/55	Thoracic and low back, bilateral flank, left shoulder	Osteoporotic compression fracture	Negative	Normal	(-)	159 to 153
4	F/76	Low back, right shoulder, left knee	Pathological scapular fracture	Negative	Normal	(-)	145 to 143
5	M/62	Low back, bilateral chest wall buttock, and flank, left heel	Polymyalgia rheumatica. Osteoporosis	NT	Bilateral compensated Trendelenburg gait	(+)	164 to 161
6	F/74	Neck, low back, bilateral shoulder, ASIS, knee, and ankle	Polymyalgia rheumatica. Somatization syndrome	U/E proximal - 4 L/E proximal - 4	Bilateral compensated Trendelenburg gait	(+)	150 to 144
7	M/54	Low back, bilateral chest wall, right hip, thigh, and knee	Stress fracture of tibia. Osteoporotic compression fracture	L/E proximal - 4	Bilateral compensated Trendelenburg gait	(+)	171 to 165
8	M/61	Low back, bilateral thigh and calf	N/A	U/E proximal - 3 L/E proximal - (hip abductor - 0, hip flexor, knee extensor, knee flexor - 4) L/E distal - 4	Bilateral compensated Trendelenburg gait	(+)	158 to 151

F: Female; M: Male; OM: Osteomalacia; MRC: Medical Research Council; N/A: Not applicable; NT: Not tested; ASIS: Anterior superior iliac spine; U/E: Upper extremity; L/E: Lower extremity.

where multiple hot radiotracer uptakes of the costovertebral/costotransverse process joints were observed on bone scintigraphy (Figure 1C). CT in patient #8 confirmed an insufficiency fracture at the sites of pseudo-reactivation of the growth plate on bone scintigraphy and the calcaneus (Figures 1D and E). Looser's zones (pseudo-fractures) or overt fractures on plain radiographs or CT scans were observed in all patients, which correlated with the hot-uptake sites on bone scintigraphy (Figures 1F and G). Typical "codfish vertebrae" findings due to multiple compression fractures of the vertebrae were observed in only one patient. According to the DEXA scans of the lumbar spine and femoral neck, four patients were in the osteoporotic range, whereas the other four were in the osteopenic range.

Etiology of hypophosphatemia

Six patients were diagnosed with adefovir (ADV)-induced Fanconi syndrome because they had a history of long-term ADV use and improved after ADV discontinuation or switching to other antiviral agents. Five of the six patients were taking regular doses (10 mg/d); however, the dose was unknown in the other patient because the antiviral medications were prescribed at other hospitals. The duration of ADV use before OM diagnosis was 4-11 years (Table 3).

The other two patients (patients #1 and #6) had no history of surgery or medications that could cause OM, and their dietary history was not remarkable. In patient #1, ^{68}Ga-DOTATOC PET/CT was conducted to identify the culprit lesion of the phosphaturic mesenchymal tumor (PMT) and revealed hot uptake of the radiotracer in the right temporal bone of the calvarium (Figure 1H). Histological examination of the surgically excised tumor showed spindle- to ovoid-shaped tumor cell infiltration with a well-developed, rich capillary network and prominent osteoid deposition. Two days after tumor removal, the serum phosphate levels normalized. The patient was diagnosed with TIO secondary to a PMT. In patient #6, protein electrophoresis revealed monoclonal protein in the serum and the free light chain ratio (Kappa/Lambda) increased to 11.7. A subsequent bone marrow biopsy revealed an increased proportion of monoclonal plasma cells (15%). Therefore, the patient was diagnosed with multiple myeloma (MM), and Fanconi syndrome due to light-chain nephropathy was the cause of the hypophosphatemic OM. There was no family history to suspect the hereditary origin of OM in all patients (Table 3).

Treatment and prognosis

All patients received phosphorus supplements (500-1240 mg/d), and calcitriol was administered in six patients (0.25-0.5 μg/d). Three of the six patients with ADV-induced Fanconi syndrome changed the drug to entecavir, one patient was changed to tenofovir alafenamide fumarate, and one patient discontinued the medication altogether. Patient #2 had a history of jaundice after ADV discontinuation; therefore, ADV treatment was continued with simultaneous phosphate

Table 2 Sites of increased radiotracer uptake on bone scintigraphy

	Spine				Girdles		Long bone (focal)				Long bone (pseudo-reactivation of the growth plate)		Hand and Foot				Rib cage				Others	
	C	T	L	S	Scapula	Pelvis	Humerus	Femur	Tibia	Patella	Femur	Tibia	Carpals	Calcaneus	Mid tarsals	Meta tarsals	CV/CT JT	CC jnc	Rosary	Arc	Mandible	Sternum
1		•	•		•		•	•	•	•				•			•	•	•	•	•	
2	•	•		•								•	•	•		•	•	•	•	•	•	•
3		•		•														•				
4		•	•		•			•	•		•	•		•	•		•	•		•		
5	•	•	•	•		•	•							•	•	•	•	•	•	•		
6	•	•	•		•		•	•	•	•				•			•	•	•	•	•	
7		•	•	•	•	•		•	•						•		•	•		•		•
8		•	•		•	•		•	•		•	•	•	•	•		•	•	•	•		

C: Cervical; T: Thoracic; L: Lumbar; S: Sacral; CV/CT JT: Costovertebral/costotransverse joint; CC jnc: Costochondral junction.

and calcitriol supplementation. After supplementation and treatment for causes (when possible), improvements in pain, muscle strength, and gait were observed in all patients within 1 wk to 3 mo. In six patients, the serum phosphate levels normalized within 2 d to 9 mo. Although patient #2 was continuously taking ADV, there was a significant improvement in the symptoms after phosphorus supplementation, and the phosphate level remained low for 3 years. In patient #6 with light-chain nephropathy, the serum phosphate level did not normalize because the smoldering MM was not treated with chemotherapeutic agents. However, after a month of phosphorus supplementation, the pain and muscle strength improved.

DISCUSSION

We summarized the characteristics of eight patients with adult-onset hypophosphatemic OM of various etiologies. The most common cause was ADV-induced Fanconi syndrome, whereas the other two rare causes of renal tubular phosphate wasting were PMT and light-chain nephropathy. The most important indicators of OM suspected as a cause of widespread musculoskeletal pain are low serum phosphate levels and characteristic findings on bone scintigraphy.

Since the most common symptom of OM is widespread skeletal pain, it can mimic various musculoskeletal or rheumatic diseases, such as osteoporosis, myofascial pain syndrome, degenerative spondylosis, fibromyalgia, polymyalgia rheumatica (PMR), spondyloarthritis (SpA), and inflammatory myositis; hence, it may be easily misdiagnosed or underdiagnosed[3,5-7,16]. Adult-onset OM should be differentiated from inflammatory rheumatic diseases, such as PMR or SpA. Two of our patients were initially suspected of having PMR before visiting our clinic. As the

Table 3 Etiology, treatment, and outcome of adult-onset hypophosphatemic osteomalacia

	Etiology	Onset to diagnosis (mo)	ADV dose (mg/d)	ADV duration (yr)	Medication change	Time to symptom improvement (mo)	Time to normalization of phosphate (mo)
1	Tumor-induced osteomalacia	25	N/A	N/A	N/A	7 d	2 d
2	ADV-induced nephropathy	25	10	6	Keep ADV	3	Never
3	ADV-induced nephropathy	24	10	11	Change to ETV	0.5	3.5
4	ADV-induced nephropathy	6	10	10	Discontinuation of ADV	3	3
5	ADV-induced nephropathy	9	Unknown	11	Change to ETV	2	8
6	Light-chain nephropathy due to multiple myeloma	14	N/A	N/A	N/A	1	Never
7	ADV-induced nephropathy	27	10	4	Change to ETV	2	9
8	ADV-induced nephropathy	61	10	7	Change to TAF	1	1

N/A: Not applicable; ADV: Adefovir; ETV: Entecavir; TAF: Tenofovir alafenamide fumarate.

prominent features of PMR and SpA are periarticular and articular inflammation, their pain presented with inflammatory pain characteristics[17]. In contrast, pain in OM presents with mechanical pain characteristics because fractures due to weak bone strength are the source of pain. Thus, pain characteristics in a patient's history are vital for differentiating between OM and inflammatory rheumatic diseases. OM may also be misdiagnosed as osteoporosis owing to the accompanying multiple fractures. Unlike osteoporotic fractures, which usually involve the neck of the femur, vertebral bodies, and wrists, OM fractures mainly involve the ribs, shoulder/pelvic girdle, spine, and long bones[3,4]. In our case series, insufficiency fractures occurred mainly in the neck/tubercle of the ribs, long bones of the lower extremities, sacral ala, calcaneus, and vertebral bodies. The accompanying muscle weakness and biochemical abnormalities in OM, especially hypophosphatemia and alkaline phosphatase elevation, could also be crucial for differential diagnoses.

More than half of the patients in this study showed evidence of proximal muscle weakness in the lower extremities. Osteomalacic myopathy usually involves the proximal muscles around the shoulder and pelvic girdles, causing gait disturbance, difficulty in sit-to-stand, and difficulty in climbing up and down stairs; when properly treated, it has a good prognosis and is rapidly reversible[1,3,4,18-20]. Although proximal muscle weakness in OM may lead to misdiagnosis as a primary muscle disease, such as inflammatory myositis, normal CK levels and characteristic findings on bone scintigraphy can easily differentiate OM from inflammatory myositis. The pathophysiological mechanism of proximal weakness in OM is assumed to be multifactorial; however, no clear mechanism for muscle weakness has been identified in OM[20]. In our patient, electromyography did not reveal evidence of denervation or myopathic motor unit action potential, and serum CK levels were within the normal range. These findings suggest that muscle weakness in OM is not caused by denervation or muscle cell death but by disturbed energy metabolism of muscle cell contraction, probably due to phosphorus deficiency. In an animal study, significant muscle force reduction occurred only when vitamin D deficiency was accompanied by hypophosphatemia[21]. Thus, muscle weakness in OM can be reversed with appropriate treatments. The early improvement (within 3 mo after treatment) in muscle strength and disappearance of the waddling gait in our cases support this hypothesis.

Bone scintigraphy is the most useful imaging modality for diagnosing OM, or at least one type of metabolic bone disease. This is because it permits the examination of the whole skeleton at a glance, and the patterns of uptake in OM are distinct from those of other skeletal diseases, such as metastatic bone disease and osteoporosis. In our cases, "adult rachitic rosary" appearance at the chest cage or pseudo-reactivation of the growth plate at the distal femur/proximal tibia was noted in all patients, except two. Thus, these two characteristics are highly suggestive of, but not specific to OM. A characteristic finding of OM on plain radiographs is a pseudofracture or Looser's zone, which is a radiolucent line through one cortical plate, often with sclerosis at the margins. This insufficiency fracture is usually observed prior to the occurrence of other radiologic changes in OM[22]. In the present case series, it was commonly observed in the long bones, pelvic rami, scapula, and posterior arcs of the ribs. However, standard plain radiography did not reveal definite cortical disruption at any site.

Previously, vitamin D deficiency was considered the most common cause of OM. However, with improvements in the nutritional status, hypophosphatemic OM due to other causes has become more common. There have been several reports of adult-onset hypophosphatemic OM and renal Fanconi syndrome induced by regular doses (10 mg/d) of ADV after long-term use (mostly for 2-7 years) since 2000, especially in HBV-endemic areas[15,16,23]. In the present case series, ADV-induced Fanconi syndrome was the most common cause of hypophosphatemic OM. Therefore, when hypophos-

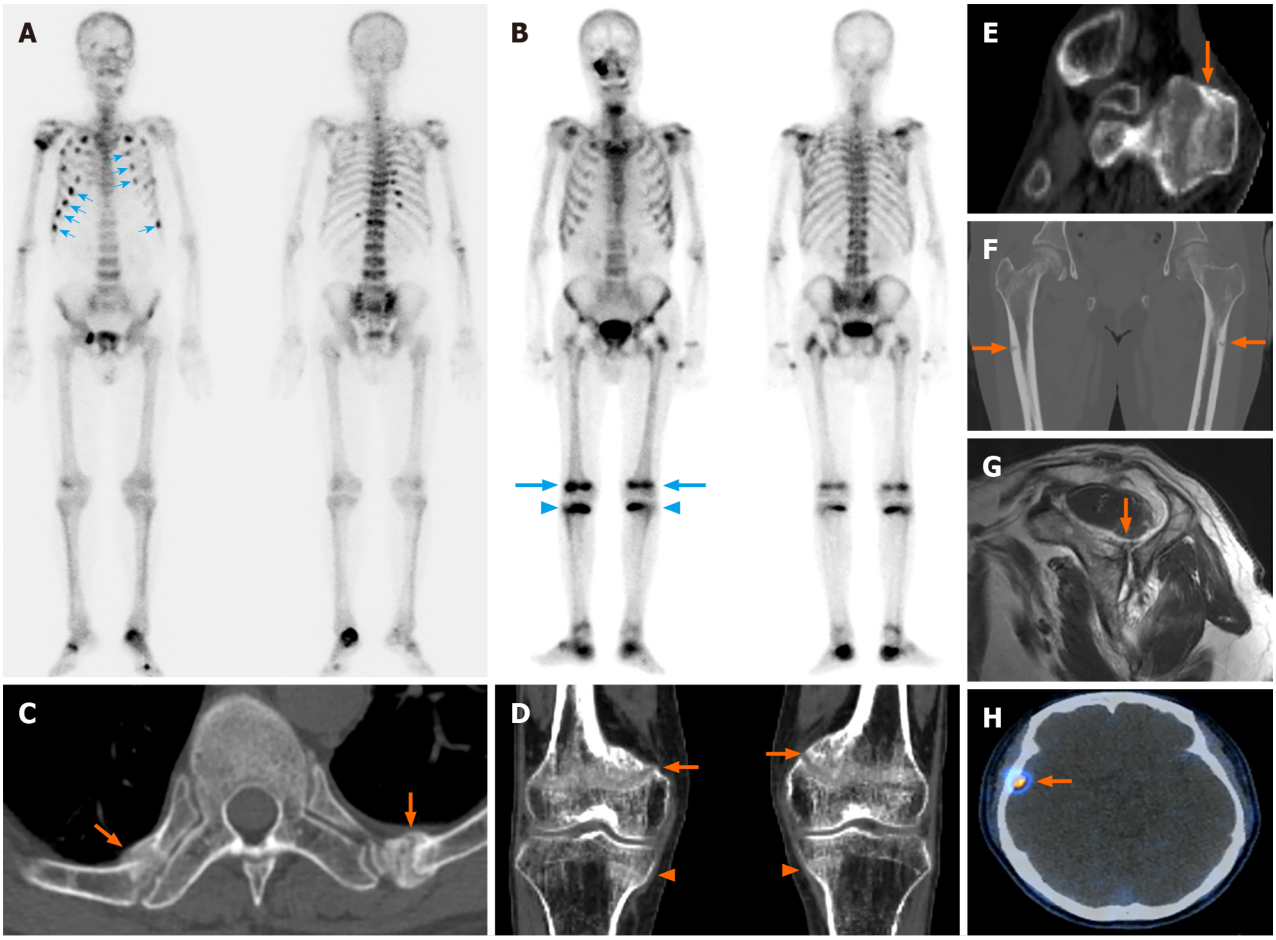

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Figure 1 Bone scintigraphic and radiologic findings of adult-onset hypophosphatemic osteomalacia. A: Bone scintigraphy of patient #5 shows multiple foci of increased radiotracer uptake in multiple costovertebral/costotransverse joints, bilateral costochondral junctions (blue thin arrows: Costochondral beading or "adult rachitic rosary" appearance), arc of the ribs, cervicothoracolumbar vertebral bodies, sacrum, right humerus, left calcaneus, and right midtarsal bone; B: Bone scintigraphy of patient #8 shows multiple foci of increased radiotracer uptake in the thoracolumbar vertebral bodies, costovertebral junctions, costochondral junctions, posterior arc of the ribs, bilateral scapula, sacrum, pelvic bone, bilateral distal femur and proximal tibia (blue arrows and arrowheads: Pseudo-reactivation of the growth plate), bilateral calcaneus, right distal tibia, and right midtarsal bone; C: Axial computed tomography (CT) image of patient #2 shows insufficiency fracture of the neck and tubercle of the ribs (thick orange arrows); D and E: Coronal and sagittal CT images of patient #8 reveals insufficiency fracture of bilateral distal femur (thick orange arrows in D, proximal tibia (orange arrowheads in D), and left calcaneus (thick orange arrow in E); F: CT of patient #1 shows transverse linear radiolucency on the lateral aspects of the subtrochanteric area of both femurs (Looser's zone or pseudo-fracture) (thick orange arrows); G: Magnetic resonance imaging of the shoulder of patient #4 shows overt fracture of the right scapula (thick orange arrow); H: Axial image of ^{68}Ga-DOTATOC positron emission tomography/CT of patient #1 shows small, focal increased radiotracer uptake on the inner surface of the right temporal bone (thick orange arrow).

phatemic OM is suspected to be the cause of widespread musculoskeletal pain, careful history taking for the use of anti-HBV medications is imperative. Regular monitoring of serum phosphate levels is also recommended for the early detection of hypophosphatemia in patients taking ADV for hepatitis B.

Although rare, light-chain nephropathy or PMT can cause adult-onset hypophosphatemic OM when there is no history of causative medications that induce OM. Light-chain nephropathy causes hypophosphatemic OM due to proximal tubular dysfunction caused by crystal deposition in the proximal tubule cells[24,25]. Therefore, latent MM should be considered in patients with acquired hypophosphatemic OM. In TIO, the tumor secretes a factor called phosphatonin, which causes phosphaturia and hypophosphatemia. The tumors were morphologically distinct and classified as a single histopathological entity named PMT[26]. As PMTs are often small and exist within the bone, they are difficult to locate. The recent development of somatostatin-receptor functional scintigraphy and PET/CT using ^{68}Ga-radiolabeled DOTA-conjugated peptides has helped in diagnosis[6,10,13]. Although serum FGF23 levels in blood samples from the antecubital vein of one patient with TIO in this case series were within the normal range, ^{68}Ga-DOTATOC PET/CT detected the culprit lesion for PMT. Although autosomal dominant hypophosphatemic rickets (ADHR) is one of the causes of adult-onset hypophosphatemic OM because it is characterized by variability in the age of the clinically evident disease, genetic studies for ADHR were not performed because other causes of hypophosphatemia were clearly identified in our cases.

The treatment of OM requires the management of the underlying disease or drugs that cause it, along with simultaneous phosphate and vitamin D supplementation. In our cases, the bone pain improved within a short period when appropriate treatment was administered. In some of our patients, the symptoms tended to improve even if the

phosphorus level was not completely normalized. This can be explained by the inaccuracy of serum phosphate levels in predicting total phosphorus levels in the body[27]. The favorable prognosis in our cases emphasizes the importance of the early diagnosis of hypophosphatemic OM in adult-onset patients presenting with multiple musculoskeletal pain.

Our study had some limitations. The most crucial limitation was the lack of a pathological diagnosis of OM. However, a bone biopsy is rarely performed at our institute for the diagnosis of OM because of its invasiveness. We attempted to include highly compatible patients using the criteria set by a thorough review of the literature. All patients presented with a clear etiology of OM. Another limitation was the inherent bias due to the retrospective nature of the study and the relatively small number of patients recruited in a single center. Larger prospective multi-centered cohort studies are needed to establish a more precise clinical picture of the disease entity. Additionally, ADV has been used as a drug of choice for treating HBV infection for years. However, after the introduction of other anti-HBV medications with better efficacy including entecavir and tenofovir, ADV is not recommended for the treatment of chronic HBV infection in European and Korean clinical guidelines[28,29]. Thus, our conclusion that ADV-induced Fanconi syndrome is the most common etiology of adult-onset hypophosphatemic OM in HBV-endemic countries may have little clinical significance in the future. However, as a considerable number of patients continue to receive ADV for their long-term maintenance therapy, physicians in HBV-endemic countries should be aware of this clinical entity.

CONCLUSION

Therefore, physicians should consider the possibility of adult-onset hypophosphatemic OM as a cause of widespread musculoskeletal pain. Although it is not a common disease, the quality of life of affected patients can be severely compromised if the diagnosis is delayed. Once the correct diagnosis is made, there is dramatic improvement with proper treatment. The mechanical pain characteristics, hypophosphatemia, and distinctive patterns on bone scintigraphy may be initial diagnostic indicators. When hypophosphatemic OM is confirmed, a diagnostic work-up based on the proposed diagnostic algorithm is necessary. Drugs, such as antiviral agents for hepatitis B, may be the most common etiology of adult-onset hypophosphatemic OM in HBV-endemic countries.

ARTICLE HIGHLIGHTS

Research background

Adult-onset hypophosphatemic osteomalacia (OM) is a rare disorder primarily presenting with widespread musculoskeletal pain.

Research motivation

As the most common symptom of OM is widespread skeletal pain, it can be easily misdiagnosed as other musculoskeletal or rheumatic diseases.

Research objectives

This study aimed to facilitate the early diagnosis and etiology-specific treatment of adult-onset hypophosphatemic OM.

Research methods

This retrospective study included patients diagnosed with adult-onset hypophosphatemic OM at a single tertiary hospital between January 2011 and December 2019. Clinical features, diagnostic test results, treatments and prognosis of the patients were reviewed.

Research results

Eight patients with adult-onset hypophosphatemic OM were included, and five patients were misdiagnosed and treated for other diseases. Six patients were diagnosed with adefovir-induced Fanconi syndrome, and the other two patients were diagnosed with tumor-induced OM and light-chain nephropathy, respectively.

Research conclusions

Mechanical pain characteristics, hypophosphatemia, and distinctive bone scintigraphy patterns are the initial diagnostic indicators of adult-onset hypophosphatemic OM.

Research perspectives

Physicians should consider the possibility of adult-onset hypophosphatemic OM as a cause of widespread musculoskeletal pain because it is rare, but treatable disorder.

FOOTNOTES

Author contributions: Kim SW, Kim DH and Sung DH contributed to the conceptualization of this study; Kim S, Lee BC, and Kim SW involved in the investigation and data curation of this manuscript; Kim S and Kim SW wrote the original draft; Lee BC, Kim DH, and Sung DH participated to the writing - review & editing; and all authors have read and agreed to the published version of the manuscript.

Institutional review board statement: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional review board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its subsequent amendments. This study was approved by the Institutional Review Board of Samsung Medical Center (approval number: 2020-09-027-001).

Informed consent statement: Informed consent was waived by the Institutional Review Board because of the retrospective nature of the study and the analysis used anonymous clinical data.

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

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Efficacy and safety of laparoscopic *vs* open gastrectomy after neoadjuvant therapy for locally advanced gastric cancer

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Abstract

BACKGROUND

Laparoscopic gastrectomy (LG) is widely accepted as a minimally invasive approach for the treatment of early gastric cancer. However, its role in locally advanced gastric cancer (LAGC) after neoadjuvant therapy (NAT) remains controversial. This study aimed to compare the efficacy and safety of LG *vs* open gastrectomy (OG) after NAT for the treatment of LAGC.

AIM

To compare the efficacy and safety of LG *vs* OG after NAT for LAGC.

METHODS

We conducted a prospective study of 76 patients with LAGC who underwent NAT followed by LG (n = 38) or OG (n = 38) between 2021 and 2023. The primary endpoint was overall survival (OS), and the secondary endpoints were disease-free survival (DFS), surgical complications, and quality of life (QOL).

RESULTS

The two groups had comparable baseline characteristics, with a median follow-up period of 24 mo. The 3-year OS rates in the LG and OG groups were 68.4% and 60.5%, respectively (P = 0.42). The 3-year DFS rates in the LG and OG groups were 57.9% and 50.0%, respectively (P = 0.51). The LG group had significantly less blood loss (P < 0.001), a shorter hospital stay (P < 0.001), and a lower incidence of surgical site infection (P = 0.04) than the OG group. There were no significant differences in other surgical complications between the groups, including anastomotic leakage, intra-abdominal abscess, or wound dehiscence. The LG group had significantly better QOL scores than the OG group regarding physical functioning, role functioning, global health status, fatigue, pain, appetite loss, and body image at 6 months postoperatively (P < 0.05).

CONCLUSION

LG after NAT is a viable and safe alternative to OG for the treatment of LAGC, with similar survival outcomes and superior short-term recovery and QOL. LG patients had less blood loss, shorter hospitalizations, and a lower incidence of surgical site infections than OG patients. Moreover, the LG group had better QOL scores in multiple domains 6 mo postoperatively. Therefore, LG should be considered a valid option for patients with LAGC who undergo NAT, particularly for those who prioritize postoperative recovery and QOL.

Key Words: Laparoscopic gastrectomy; Open gastrectomy; Neoadjuvant therapy; Locally advanced gastric cancer; Efficacy; Safety

Core Tip: Laparoscopic gastrectomy (LG) is a viable and safe approach to treating locally advanced gastric cancer (LAGC) following neoadjuvant therapy (NAT). This study aimed to compare the efficacy and safety of LG *vs* open gastrectomy (OG) after NAT in patients with LAGC. The results demonstrated comparable overall survival and disease-free survival rates between the two groups. Additionally, LG exhibits advantages such as reduced blood loss, a shorter hospital stay, and a lower incidence of surgical site infection than OG. The two groups had similar rates of other surgical complications. Furthermore, LG yielded better quality of life (QOL) scores in terms of physical functioning, role functioning, global health status, fatigue, pain, appetite loss, and body image at 6 months postoperatively. These findings suggest that LG after NAT is a feasible and safe option for LAGC, providing comparable survival outcomes along with improved short-term recovery and QOL compared to OG.

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INTRODUCTION

Gastric cancer stands as one of the predominant malignancies globally, securing its position as the third leading cause of cancer-related mortalities worldwide[1]. Despite advancements in early detection and therapeutic strategies, a substantial proportion of patients, exceeding half, are diagnosed with locally advanced gastric cancer (LAGC)[2]. The prognosis of LAGC remains poor, with a 5-year overall survival (OS) rate of < 30%[3].

Neoadjuvant therapy (NAT), consisting of chemotherapy, radiotherapy, or chemoradiotherapy, has been increasingly used to treat LAGC in recent years[4,5]. The potential benefits of NAT include tumor downstaging, increasing the R0 resection rate, eradicating micrometastases, improving compliance with adjuvant therapy, and providing an early assessment of tumor response. Several randomized controlled trials and meta-analyses have shown that NAT can improve survival outcomes compared with surgery alone or surgery followed by adjuvant therapy for LAGC[6-8].

Laparoscopic gastrectomy (LG) is widely accepted as a minimally invasive approach for early gastric cancer, with advantages such as less blood loss, less pain, faster recovery, a shorter hospital stay, and better cosmetic results than open gastrectomy (OG)[9-11]. However, its role in LAGC after NAT remains controversial. Some studies have suggested that LG after NAT is feasible and safe for selected patients with LAGC[12-14], whereas others have raised concerns about technical difficulties, oncological adequacy, and long-term outcomes[15-17]. Therefore, more evidence is needed to evaluate the efficacy and safety of LG *vs* OG after NAT for LAGC.

We conducted a prospective study of 76 patients with LAGC who underwent NAT followed by LG or OG between 2021 and 2023. We compared survival outcomes, surgical complications, and quality of life (QOL) between the two groups.

MATERIALS AND METHODS

Study design and population

This prospective, single-center, non-randomized study was conducted at the Department of Gastrointestinal Surgery of our hospital between January 2021 and December 2023. The study protocol was approved by the institutional review board. All patients provided written informed consent prior to enrollment.

The inclusion criteria were as follows: (1) Histologically confirmed adenocarcinoma of the stomach; (2) linical stages II–III according to the 8th edition of the American Joint Committee on Cancer staging system[18]; (3) no distant metastasis or peritoneal dissemination; (4) age 18-75 years; (5) eastern Cooperative Oncology Group (ECOG) performance status 0-1; (6) adequate organ function; and (7) completion of NAT.

The exclusion criteria were: (1) Previous history of gastric surgery or other malignancies; (2) contraindications to laparoscopic surgery or NAT; (3) pregnancy or lactation; and (4) refusal to participate in the study.

NAT

All patients underwent preoperative NAT. The NAT regimen consisted of three cycles of capecitabine plus oxaliplatin (XELOX), administered every 3 wk. Each cycle consisted of oral capecitabine 1000 mg/m^2 twice daily on days 1-14 and intravenous oxaliplatin 130 mg/m^2 on day 1. The response to NAT was evaluated using computed tomography according to the Response Evaluation Criteria in Solid Tumors version 1.1[19]. Patients who achieved complete response, partial response, or stable disease were considered eligible for surgery, whereas those with progressive disease or intolerable toxicity were excluded from the study.

Surgical procedures

All the patients underwent LG or OG according to the surgeon's preference and provided informed consent. Surgical procedures were performed by experienced surgeons who had performed more than 100 LG or OG procedures for gastric cancer. The type of gastrectomy (total or subtotal), reconstruction method (Billroth I, Billroth II, or Roux-en-Y), and extent of lymphadenectomy (D1+, D2, or D3) were determined based on tumor location, size, and stage. The surgical principles and techniques followed the Japanese Gastric Cancer Treatment Guidelines. The LG procedures were performed using five trocars and a pneumoperitoneum pressure of 12 mmHg. OG was performed *via* an upper midline incision. The resected specimens were retrieved through a small incision in the LG group and through the original incision in the OG group.

Postoperative management and follow-up

All patients received standardized postoperative care according to our institutional protocol. Postoperative complications were recorded and graded according to the Clavien-Dindo classification. QOL was assessed using the European Organization for Research and Treatment of Cancer QOL Questionnaire-Core 30 at baseline, before surgery, and 6 months after surgery. QOL scores ranged from 0 to 100, with higher scores indicating better functioning, better global health status, or worse symptoms.

All patients received postoperative adjuvant chemotherapy consisting of four cycles of XELOX administered every 3 wk. Follow-up visits were scheduled every three months for the first two years, every six months for the next three years, and annually thereafter. Follow-up examinations included a physical examination, blood tests, tumor marker testing, chest radiography, abdominal ultrasonography, and endoscopy. Survival outcomes were calculated from the date of surgery to the date of death from any cause or last follow-up.

Statistical analysis

The primary endpoint was OS, and the secondary endpoints were disease-free survival (DFS), surgical complications, and QOL. OS was defined as the time from surgery to death from any cause or the last follow-up. DFS was defined as the time from surgery to recurrence, death from any cause, or last follow-up.

The sample size calculation was based on the assumption that LG would have a non-inferior OS rate compared to OG after NAT for LAGC. Based on previous studies[20-22], we estimated that the 3-year OS rate was 60% in both groups with a non-inferiority margin of 10%. With a power of 80% and a one-sided alpha level of 0.025, we calculated that 35 patients would be required in each group. Considering a dropout rate of 10%, we planned to enroll 38 patients in each group.

The baseline characteristics, perioperative outcomes, and QOL scores of the two groups were compared using the chi-square test or Fisher's exact test for categorical variables and the t-test or Mann-Whitney U test for continuous variables. The survival outcomes of the two groups were compared using the Kaplan-Meier method and log-rank test. The Cox proportional hazards model was used to perform a multivariate analysis of factors associated with survival outcomes. All statistical analyses were performed using SPSS version 26.0 software (IBM Corp., Armonk, NY, United States). Statistical significance was set at $P < 0.05$.

RESULTS

Baseline characteristics

This study enrolled 76 patients with LAGC who underwent NAT, followed by LG ($n = 38$) or OG ($n = 38$). The baseline characteristics of the two groups are shown in Table 1. There were no significant differences in age, sex, body mass index, ECOG performance status, comorbidities, tumor location, tumor size, clinical stage, pathological response, or gastrectomy type between the two groups.

Perioperative outcomes

The perioperative outcomes of the two groups are shown in Table 2. The LG group had significantly less blood loss ($P < 0.001$), a shorter hospital stay ($P < 0.001$), and a lower incidence of surgical site infection ($P = 0.04$) than the OG group. There were no significant differences in operation time, R0 resection rate, number of harvested lymph nodes, proximal margin, distal margin, or other surgical complications such as anastomotic leakage, intra-abdominal abscess, or wound dehiscence between the two groups.

Table 1 Baseline characteristics of the two groups, *n* (%)

Variable	LG group (*n* = 38)	OG group (*n* = 38)	*P* value
Age (yr)	59.3 ± 9.8	60.5 ± 10.2	0.59
Sex-male	24 (63.2)	26 (68.4)	0.71
Sex-female	14 (36.8)	12 (31.6)	
BMI (kg/m)[2]	23.4 ± 3.2	22.9 ± 2.9	0.48
ECOG PS-0	28 (73.7)	29 (76.3)	0.86
ECOG PS-1	10 (26.3)	9 (23.7)	
Comorbidities-yes	14 (36.8)	16 (42.1)	0.67
Comorbidities-no	24 (63.2)	22 (57.9)	
Tumor location-upper third	10 (26.3)	12 (31.6)	0.75
Tumor location-middle third	14 (36.8)	13 (34.2)	
Tumor location-lower third	14 (36.8)	13 (34.2)	
Tumor size (cm)	5.2 ± 1.8	5.4 ± 2.1	0.66
Clinical stage[1]-II	14 (36.8)	15 (39.5)	0.82
Clinical stage[1]-III	24 (63.2)		
Pathological response-complete[2]	4 (10.5)	3 (7.9)	0.69
Pathological response-partial[2]	18 (47.4)	19 (50.0)	
Pathological response-stable[2]	12 (31.6)	11 (28.9)	
Pathological response-progressive[2]	4 (10.5)	5 (13.2)	
Type of gastrectomy-total[2]	20 (52.6)	21 (55.3)	0.88
Type of gastrectomy-subtotal[2]	18 (47.4)	17 (44.7)	

[1]According to the 8th edition of the American Joint Committee on Cancer staging system.
[2]According to the RECIST version 1.1.
LG: Laparoscopic gastrectomy; OG: Open gastrectomy; BMI: Body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status.

Survival outcomes

Table 3 presents the survival outcomes of the two groups. The median follow-up duration was 24 mo. The 3-year OS rates in the LG and OG groups were 68.4% and 60.5%, respectively (P = 0.42). The 3-year DFS rates in the LG and OG groups were 57.9% and 50.0%, respectively (P = 0.51). There were no significant differences in OS or DFS between the two groups.

QOL

Table 4 shows the QOL scores of the two groups. The LG group had significantly better QOL scores than the OG group regarding physical functioning, role functioning, global health status, fatigue, pain, appetite loss, and body image six months after surgery (P < 0.05). The two groups showed no significant differences in other QOL domains such as emotional functioning, cognitive functioning, social functioning, nausea and vomiting, dyspnea, insomnia, constipation, diarrhea, and financial difficulties.

DISCUSSION

We compared the efficacy and safety of LG and OG after NAT for the treatment of LAGC in a prospective cohort of 76 patients. The main findings of this study were as follows: (1) LG after NAT was feasible and safe for LAGC, with comparable survival outcomes and better short-term recovery and QOL than OG; (2) LG after NAT had significantly less blood loss, shorter hospital stay, and lower incidence of surgical site infection than OG; (3) LG after NAT had comparable operation time, R0 resection rate, number of harvested lymph nodes, proximal margin, distal margin, and other surgical complications, such as anastomotic leakage, intra-abdominal abscess, and wound dehiscence, to OG; and (4) LG after NAT had significantly better QOL scores than OG regarding physical functioning, role functioning, global health status, fatigue, pain, appetite loss, and body image at 6 mo postoperatively.

Table 2 Perioperative outcomes of the two groups

Variable	LG group (*n* = 38)	OG group (*n* = 38)	*P* value
Operation time (min)	210 ± 45	220 ± 50	0.28
Blood loss (mL)	100 ± 50	300 ± 100	< 0.001
R0 resection rate (%)	36 (94.7)	35 (92.1)	0.64
Number of harvested lymph nodes[1]	22 ± 8	23 ± 9	0.57
Proximal margin (cm)[2]	3.5 ± 1.2	3.6 ± 1.3	0.72
Distal margin (cm)[3]	4.2 ± 1.4	4.3 ± 1.5	0.79
Hospital stay (days)[4]	10 ± 3	15 ± 4	< 0.001
Anastomotic leakage-Grade I-IIA[5] (%)	2 (5.3)	3 (7.9)	0.67
Anastomotic leakage-Grade IIB-IVB[5] (%)	0	1 (2.6)	
Intra-abdominal abscess-Grade I-IIA[5] (%)	1 (2.6)	2 (5.3)	0.54
Intra-abdominal abscess-Grade IIB-IVB[5] (%)	0	1 (2.6)	
Wound dehiscence-Grade I-IIA[5] (%)	1 (2.6)	2 (5.3)	0.73
Wound dehiscence-Grade IIB-IVB[5]	0	0	
Surgical site infection-Grade I-IIA[5] (%)	2 (5.3)	8 (21.1)	0.04
Surgical site infection-Grade IIB-IVB[5]	0	0	
Other complications-Grade I-IIA[5] (%)	4 (10.5)	5 (13.2)	0.47
Other complications-Grade IIB-IVB[5]	0	1 (2.6)	

[1]Only for patients who underwent D2 lymphadenectomy.
[2]Only for patients who underwent total gastrectomy.
[3]Only for patients who underwent subtotal gastrectomy.
[4]From the day of surgery to the day of discharge.
[5]According to the Clavien-dindo classification.
LG: Laparoscopic gastrectomy; OG: Open gastrectomy.

NAT has emerged as a progressively utilized intervention for LAGC in recent years because of its potential to enhance survival outcomes in comparison with surgical approaches alone or surgery followed by adjuvant therapy[6-8]. Nevertheless, NAT may concurrently elevate the technical and surgical challenges associated with gastrectomy, introducing risks of fibrosis, adhesion, inflammation, bleeding, infection, and anastomotic failure[23-25]. Therefore, the choice of surgical approach after NAT is crucial for the optimal treatment of LAGC.

LG is widely accepted as a minimally invasive approach for early gastric cancer; however, its role in LAGC after NAT remains controversial. Some studies have suggested that LG after NAT is feasible and safe for selected patients with LAGC[12-14], whereas others have raised concerns about technical difficulties, oncological adequacy, and long-term outcomes[15-17]. Therefore, more evidence is needed to evaluate the efficacy and safety of LG *vs* OG after NAT for LAGC.

To the best of our knowledge, this is the first prospective study to compare the efficacy and safety of LG and OG after NAT for LAGC. Previous studies on this topic have been mostly retrospective or observational, with small sample sizes and short follow-up periods[26,27]. Moreover, most of these studies did not assess the QOL of patients after surgery, an important outcome measure for evaluating the benefits of minimally invasive surgery with comparable survival outcomes, better short-term recovery, and QOL than OG. The LG group had significantly less blood loss, a shorter hospital stay, and a lower incidence of surgical site infections than the OG group. These results are consistent with those of previous studies that reported the advantages of LG over OG in terms of perioperative outcomes[28,29]. The reduced blood loss and surgical trauma associated with LG may contribute to faster recovery and lower infection rates. A shorter hospital stay at LG may also reduce medical costs and improve patient satisfaction.

The LG group had a comparable operation time, R0 resection rate, number of harvested lymph nodes, proximal margin, distal margin, and other surgical complications such as anastomotic leakage, intra-abdominal abscess, and wound dehiscence to the OG group. These results indicated that LG after NAT can achieve adequate oncological outcomes and is safe for patients with LAGC. The operation time of LG was not significantly longer than that of OG, which may reflect the experience and skills of the surgeons who performed LG. The R0 resection rate and number of harvested lymph nodes in the LG were similar to those in the OG, suggesting that the LG can achieve sufficient tumor resection and lymphadenectomy for LAGC after NAT. The proximal and distal margins of LG were also comparable to those of OG, which may imply that LG can ensure adequate surgical margins for LAGC after NAT. Other surgical complications of LG were not significantly higher than those of OG, which may demonstrate that LG avoids the potential

Table 3 Univariate and multivariate analyses of survival outcomes

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Overall survival				
Group				
LG	1 (reference)		1 (reference)	
OG	1.28 (0.67-2.45)	0.46	1.24 (0.64-2.40)	0.52
Age				
≤ 60	1 (reference)		1 (reference)	
> 60	1.35 (0.72-2.54)	0.35	1.32 (0.69-2.51)	0.40
Sex				
Male	1 (reference)		1 (reference)	
Female	0.86 (0.45-1.64)	0.65	0.84 (0.43-1.61)	0.59
BMI				
≤ 25	1 (reference)		1 (reference)	
> 25	1.12 (0.58-2.16)	0.74	1.09 (0.56-2.13)	0.79
Tumor location				
Upper third	1 (reference)		1 (reference)	
Middle third	0.97 (0.47-2.01)	0.94	0.95 (0.45-1.98)	0.89
Lower third	0.92 (0.44-1.91)	0.82	0.89 (0.42-1.86)	0.75
Tumor size				
≤ 5 cm	1 (reference)		1 (reference)	
> 5 cm	1.41 (0.75-2.65)	0.28	1.38 (0.72-2.62)	0.32
Pathological stage[1]				
II	1 (reference)		1 (reference)	
III	2.15 (1.12-4.13)	0.02	2.12 (1.09-4.10)	0.03
Pathological response[2]				
Complete	1 (reference)		1 (reference)	
Partial	1.22 (0.38-3.94)	0.74	1.18 (0.36-3.86)	0.79
Stable	1.45 (0.45-4.66)	0.54	1.41 (0.43-4.59)	0.57
Progressive	2.67 (0.81-8.80)	0.11	2.61 (0.78-8.68)	0.12
Disease-free survival				
Group				
LG	1 (reference)		1 (reference)	
OG	1.19 (0.64-2.21)	0.58	1.16 (0.62-2.17)	0.64
Age				
≤ 60	1 (reference)		1 (reference)	
> 60	1.25 (0.68-2.30)	0.47	1.23 (0.66-2.27)	0.51
Sex				
Male	1 (reference)		1 (reference)	
Female	0.91 (0.49-1.70)	0.77	0.89 (0.47-1.66)	0.71
BMI				
≤ 25	1 (reference)		1 (reference)	

> 25	1.08 (0.57-2.05)	0.81	1.05 (0.54-2.01)	0.88
Tumor location				
Upper third	1 (reference)		1 (reference)	
Middle third	0.99 (0.49-2.02)	0.98	0.97 (0.47-1.99)	0.93
Lower third	0.94 (0.46-1.93)	0.87	0.91 (0.44-1.88)	0.80
Tumor size				
≤ 5 cm	1 (reference)		1 (reference)	
> 5 cm	1.32 (0.72-2.42)	0.37	1.29 (0.69-2.38)	0.42
Pathological stage				
II	1 (reference)		1 (reference)	
III	2.03 (1.08-3.81)	0.03	2.01 (1.06-3.78)	0.03
Pathological response				
Complete	1 (reference)		1 (reference)	
Partial	1.18 (0.38-3.67)	0.78	1.15 (0.36-3.59)	0.82
Stable	1.36 (0.43-4.30)	0.60	1.32 (0.41-4.23)	0.64
Progressive	2.49 (0.77-8.07	0.13	2.43 (0.74-7.97)	0.14

[1]According to the 8th edition of the AJCC staging system.
[2]According to the RECIST version 1.1.
LG: Laparoscopic gastrectomy; OG: Open gastrectomy; BMI: Body mass index; HR: Hazard ratio; CI: Confidence interval.

Table 4 Quality of life scores of the two groups

Period	Variable	LG group (*n* = 38)	OG group (*n* = 38)	*P* value
Baseline	Physical functioning[1]	83 ± 12	82 ± 13	0.79
	Role Functioning[1]	80 ± 15	79 ± 16	0.83
	Emotional functioning[1]	76 ± 14	75 ± 15	0.88
	Cognitive functioning[1]	78 ± 13	77 ± 14	0.81
	Social functioning[1]	79 ± 16	78 ± 17	0.86
Before surgery	Physical functioning[1]	71 ± 14	70 ± 15	0.79
	Role functioning[1]	68 ± 17	67 ± 18	0.83
	Emotional functioning[1]	64 ± 16	63 ± 17	0.88
	Cognitive functioning[1]	66 ± 15	65 ± 16	0.81
	Social functioning[1]	67 ± 18	66 ± 19	0.86
Six mo after surgery	Physical functioning[1]	81 ± 13	72 ± 16	0.01
	Role functioning[1]	78 ± 16	69 ± 19	0.02
	Emotional functioning[1]	74 ± 15	67 ± 18	0.07
	Cognitive functioning[1]	76 ± 14	71 ± 16	0.11
	Social functioning[1]	77 ± 17	71 ± 19	0.12

[1]Higher scores indicate better functioning or global health status.
Higher scores indicated more severe symptoms. LG: Laparoscopic gastrectomy; OG: Open gastrectomy.

risks of NAT, such as fibrosis, adhesion, inflammation, bleeding, infection, and anastomotic failure.

The OS and DFS were comparable between the LG and OG groups. The 3-year OS rates in the LG and OG groups were 68.4% and 60.5%, respectively (P = 0.42). The 3-year DFS rates in the LG and OG groups were 57.9% and 50.0%, respectively (P = 0.51). There were no significant differences in OS or DFS between the two groups. These results suggested that LG after NAT can achieve survival outcomes similar to those of OG for LAGC. The survival outcomes in this study were comparable to those reported in previous studies that evaluated the efficacy of NAT in LAGC[6-8]. Multivariate analysis showed that pathological stage was the only independent prognostic factor for both OS and DFS, which is consistent with previous studies indicating that pathological stage is the most important predictor of survival in gastric cancer[29-31].

The LG group had significantly better QOL scores than the OG group regarding physical functioning, role functioning, global health status, fatigue, pain, appetite loss, and body image at 6 months postoperatively (P < 0.05). There were no significant differences in other QOL domains such as emotional functioning, cognitive functioning, social functioning, nausea and vomiting, dyspnea, and insomnia.

This study showed that LG after NAT is feasible and safe for the treatment of LAGC, constipation, diarrhea, and financial difficulties between the two groups. These outcomes suggest that, compared to OG, LG following NAT can enhance the QOL of patients with LAGC. Improved QOL after LG may be related to reduced blood loss, surgical trauma, infection rate, and hospital stay, which may lead to less pain, fatigue, appetite loss, better physical and role functioning, and the global health status of patients. The improved body image of LG may also be attributed to the smaller incision and better cosmetic results.

Limitations

This study had some limitations. First, this was a single-center, non-randomized study with a relatively small sample size and a short follow-up period, which may limit the generalizability and reliability of the results. Second, the surgical approach was determined based on the surgeon's preference and the patient's consent, which may have introduced selection bias and confounding factors. Third, the NAT regimen was not standardized and may vary according to tumor response and toxicity. Fourth, QOL assessment was only performed 6 mo postoperatively, which may not reflect the long-term QOL of the patients.

CONCLUSION

This study demonstrated that LG after NAT is a feasible and safe strategy for managing LAGC, achieving comparable survival outcomes and superior short-term recovery and QOL relative to OG. Following NAT, LG can achieve adequate oncological outcomes and is safe for patients with LAGC. LG after NAT can improve the QOL of patients with LAGC compared with OG. Further studies with larger sample sizes, longer follow-up periods, and randomized designs are required to confirm our findings.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer is a significant global health concern, and treatment of locally advanced gastric cancer (LAGC) remains challenging. Laparoscopic gastrectomy (LG) has gained acceptance as a minimally invasive approach for early gastric cancer treatment; however, its role in LAGC after neoadjuvant therapy (NAT) is still debated. Open gastrectomy (OG) is the traditional surgical approach for LAGC; however, it is associated with significant morbidity and a longer recovery time. Therefore, there is a need to assess the efficacy and safety of LG compared to those of OG in the context of LAGC after NAT.

Research motivation

The motivation behind this study is to address the controversy surrounding the role of LG in the treatment of LAGC after NAT. Although LG is widely accepted as a minimally invasive approach for early gastric cancer, its effectiveness and safety in LAGC after NAT remain debated. By comparing LG with OG in terms of overall survival (OS), disease-free survival (DFS), surgical complications, and quality of life (QOL), this study aimed to provide evidence of the suitability of LG as an alternative to OG for patients with LAGC. Additionally, this study aimed to identify the potential benefits of LG, such as reduced blood loss, shorter hospital stays, lower incidence of surgical site infection, and improved QOL scores in multiple domains.

Research objectives

The main objectives of this study were to compare the efficacy and safety of LG with OG after NAT for LAGC and to evaluate the impact of these surgical approaches on patient outcomes and QOL.

Research methods

This prospective study compared the efficacy and safety of LG *vs* OG after NAT for LAGC. A total of 76 patients with

LAGC who underwent NAT were included in the study, with 38 patients undergoing LG and 38 patients undergoing OG between 2021 and 2023. The novelty of this study lies in the comparison of LG and OG after NAT in patients with LAGC, focusing on survival outcomes, surgical complications, and QOL. By conducting a prospective study and utilizing statistical analysis, this study provides valuable insights into the efficacy and safety of LG as an alternative to OG in the treatment of LAGC. These findings contribute to the existing knowledge and help in making evidence-based recommendations for selecting the optimal surgical approach for patients with LAGC after NAT.

Research results

The research results demonstrated that LG is a viable and safe alternative to OG for the treatment of LAGC after NAT. The study compared the efficacy and safety of LG *vs* OG in 76 LAGC patients who underwent NAT. The OS and DFS rates were similar between the LG and OG groups. LG had several advantages, including reduced blood loss, a shorter hospital stay, and a lower incidence of surgical site infection compared to OG. Both groups had comparable rates of other surgical complications. Additionally, LG resulted in better QOL scores in multiple domains at 6 mo postoperatively. These findings contribute to the field by providing evidence-based recommendations for selecting the optimal surgical approach for LAGC patients after NAT. However, further research is needed to explore long-term survival outcomes and refine patient selection criteria.

Research conclusions

We compared the efficacy and safety of LG *vs* OG after NAT for treating LAGC. This study aimed to provide evidence-based recommendations for selecting the optimal surgical approach for patients with LAGC after NAT, based on a comparison of outcomes and QOL between LG and OG.

Research perspectives

Future research should prioritize investigating long-term survival outcomes, refining patient selection criteria, conducting comparative cost analyses, and standardizing NAT protocols. These efforts aim to enhance the management of LAGC after NAT. By gaining a deeper understanding of the effectiveness and durability of treatment options such as LG *vs* OG, identifying specific patient characteristics for optimized surgical approaches, assessing economic implications, and establishing standardized protocols, future studies can contribute to improved patient outcomes and inform clinical decision-making in the treatment of LAGC.

FOOTNOTES

Author contributions: Yu CD and Zhang K contributed to the data collection; Yu CD and Zhang K contributed to the data collection; Yu CD and Zhang K contributed to the formal analysis; Yu CD and Zhang K participated in the survey; Yu CD and Zhang K contributed to these methods; Yu CD guided the research; Yu CD and Zhang K jointly validated this study; Zhang K contributed to the visualization of this study; Yu CD drafted the first draft; and Yu CD and Zhang K jointly reviewed and edited the manuscript.

Institutional review board statement: This study was reviewed and approved by the Medical Ethics Committee of Jiujiang First People's Hospital.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Effect of anesthesia induction with butorphanol on postoperative nausea and vomiting: A randomized controlled trial

Fang Xie, De-Feng Sun, Lin Yang, Zhong-Liang Sun

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Abstract

BACKGROUND

Postoperative nausea and vomiting (PONV) are common complications that affect the recovery and well-being of elderly patients undergoing gastrointestinal laparoscopic surgery.

AIM

To investigate the effect of butorphanol on PONV in this patient population.

METHODS

A total of 110 elderly patients (≥ 65 years old) who underwent gastrointestinal laparoscopic surgery were randomly assigned to receive butorphanol (40 μg/kg) or sufentanil (0.3 μg/kg) during anesthesia induction in a 1:1 ratio. The measured outcomes included the incidence of PONV at 48 h after surgery, intraoperative dose of propofol and remifentanil, Bruggrmann Comfort Scale score in the postanesthesia care unit (PACU), number of compressions for postoperative patient-controlled intravenous analgesia (PCIA), and time to first flatulence after surgery.

RESULTS

The results revealed a noteworthy reduction in the occurrence of PONV at 24 h after surgery in the butorphanol group, when compared to the sufentanil group (T1: 23.64% *vs* 5.45%, T2: 43.64% *vs* 20.00%, $P < 0.05$). However, no significant variations were observed between the two groups, in terms of the clinical characteristics, such as the PONV or motion sickness history, intraoperative and postoperative 48-h total infusion volume and hemodynamic parameters, intraoperative dose of propofol and remifentanil, number of postoperative PCIA compressions, time until the first occurrence of postoperative flatulence, and incidence of PONV at 48 h post-surgery (all, $P > 0.05$). Furthermore, patients in

the butorphanol group were more comfortable, when compared to patients in the sufentanil group in the PACU.

CONCLUSION
The present study revealed that butorphanol can be an efficacious substitute for sufentanil during anesthesia induction to diminish PONV within 24 h following gastrointestinal laparoscopic surgery in the elderly, simultaneously improving patient comfort in the PACU.

Key Words: Butorphanol; Sufentanil; Enhanced recovery after surgery; Anesthesiology; Gastrointestinal surgery; Postoperative nausea and vomiting

Core Tip: In this study, butorphanol was used for anesthesia induction, and it was found that the incidence of postoperative nausea and vomiting was significantly lower at 24 h after surgery in the butorphanol group, when compared to the sufentanil group. In addition, the Bruggrmann Comfort Scale scores in the postanesthesia care unit were significantly better in the butorphanol group, when compared to the sufentanil group.

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INTRODUCTION

Postoperative nausea and vomiting (PONV) is the second most common postoperative adverse reaction after pain, which has an estimated incidence of 30% in the general surgical population, and an incidence that can reach as high as 80% in high-risk patients[1]. Aspiration pneumonia caused by PONV is a severe risk, particularly in elderly patients with poor pharyngeal reflex recovery after general anesthesia. In addition, PONV may cause electrolyte imbalance, poor incision healing, insufficient blood volume, and delayed discharge from the hospital.

The concept of enhanced rehabilitation after surgery emphasizes the role of minimizing adverse reactions after surgery, in order to improve the quality and pace of recovery[2]. The high-risk types of surgery with PONV include laparoscopic, bariatric, and gynecological surgery. The mechanism of PONV induced by the laparoscopic surgery remains unclear. Recent clinical studies have suggested that this may be correlated to the decrease in pain threshold of patients undergoing laparoscopic surgery, the stimulation of residual postoperative carbon dioxide in the abdominal cavity, and the pulling state of the peritoneum, which can result in increased demand for postoperative analgesia, such as opioids, leading to an increased likelihood of PONV[3]. For patients undergoing gastrointestinal laparoscopic surgery, nausea and vomiting are more likely to occur after surgery. Therefore, the balance between analgesia and PONV remains as a major challenge for anesthesiologists.

Traditional opioids produce an analgesic effect by exciting the μ (μ1 and μ2) receptors. However, the excitation of μ2 receptors can enhance the sensitivity to vestibule stimulation, affect the chemoreceptor triggering area, and delay gastric emptying, thereby triggering PONV[4]. In contrast, butorphanol, which is a synthetic opioid receptor agonist-antagonist with 5-8 times the analgesic potency of morphine, exhibits low activity to δ receptors, while stimulating the κ and μ1 receptors, and antagonizing μ2 receptors[5]. Through its antagonistic effect on μ2 receptors, butorphanol significantly reduces the incidence of PONV caused by traditional opioids. Furthermore, clinical studies have revealed that butorphanol has a good analgesic effect on patients with chronic visceral pain through the activation of κ receptors[6,7]. At present, few studies have compared butorphanol and sufentanil in the incidence of PONV during general anesthesia. Therefore, the present study aimed to investigate the effect of butorphanol on PONV in elderly patients who underwent gastrointestinal laparoscopic surgery.

MATERIALS AND METHODS

General information

The present study was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2020-161 [X]), and registered in the China Clinical Trial Center (ChiCTR2100045860). Patients ≥ 65 years old, who underwent gastrointestinal laparoscopic surgery from February 2020 to February 2021, were enrolled for the present study. Using the computer statistics software, these patients were randomly allocated into two groups in a 1:1 ratio: Sufentanil and butorphanol groups.

Based on preliminary experiments and previous studies[8], the sample size was calculated according to the incidence of PONV. The preliminary experiment results indicated that the incidence of PONV was approximately 35% in the sufentanil group, and 13% in the butorphanol group. In order to ensure adequate statistical power with 85% power at 5% level of significance, at least 49 patients were required for each group. Accounting for the potential 10% dropout rate, a total of 110 patients were included for the present study.

Inclusion and exclusion criteria

Inclusion criteria: Patients ≥ 65 years old, who underwent gastrointestinal laparoscopic surgery, and provided a written informed consent. Exclusion criteria: Hypersensitivity to butorphanol and sufentanil, serious respiratory complications, severe obstructive sleep apnea-hypopnea syndrome or obesity [body mass index (BMI) ≥ 28 kg/m^2], opioid dependence, significant abnormalities in liver or kidney function, and severe visual or auditory impairment.

Anesthesia monitoring

The following basic clinical information were recorded at one day prior to surgery: Age, gender, height, weight, BMI, American Society of Anesthesiologists (ASA) classification, smoking status, and history of PONV and motion sickness. These patients were required to fast for six hours, and have water deprivation for two hours before the surgery, with no preoperative drugs administered. Upon entering the operation room, the electrocardiogram, heart rate, oxygen saturation (SpO_2), non-invasive blood pressure, bispectral index, and oral and sublingual temperature were monitored. In addition, invasive arterial blood pressure was monitored *via* radial artery catheterization and internal jugular vein catheterization, in order to detect any hemodynamic changes, and facilitate the administration of fluids and medications, when necessary.

Anesthetic method

Anesthesia induction was administered to patients in the sufentanil group at a dose of 0.3 μg/kg of sufentanil, while patients in the butorphanol group were given 40 μg/kg of butorphanol, based on the analgesic titer ratio. During the anesthesia induction, the intravenous administration of 1-2 mg/kg of propofol and 0.3 mg/kg of benzensulfonate atracurium was performed, while remifentanil was pumped at a rate of 5-10 μg/kg/h. Then, tracheal intubation was performed under visual laryngoscopy after the muscle relaxant took effect. The anesthesia maintenance during the operation consisted of the intravenous infusion of 4-6 mg/kg/h of propofol, 5-10 μg/kg/h of remifentanil, and 0.10-0.15 mg/kg/h of benzenesulfonate atracurium. When the surgery was completed, the infusion of benzenesulfonate atracurium, propofol and remifentanil were stopped, while 0.1 mg/kg of butorphanol was given for patient-controlled intravenous analgesia (PCIA). Then, these patients were transferred to the postanesthesia care unit (PACU), and vital signs monitoring was continued for 48 h. The study assistants were responsible for the preparation and administration of the studied medications. The other assistants were responsible for the monitoring and recording of the results during data collection. All assistants were blinded to the study.

Outcome measures

The primary outcome of the study was the incidence of PONV, which was evaluated using the PONV grading scale in the PACU (T1), and at 24 h (T2) and 48 h (T3) after surgery (Table 1). The other observed parameters were, as follows: Intra-operative dose of propofol and remifentanil, total infusion volume (at intraoperative and postoperative 24 and 48 h), operation time, the agitation[9] and Bruggrmann Comfort Scale (BCS)[10] scores in the PACU, the number of compressions for PCIA within 48 h after surgery, and the time to first postoperative flatulence. The cumulative dose of propofol and remifentanil administered through a micropump infusion device, both during the induction and maintenance phases of anesthesia, was calculated using the following formula: Dose = infusion rate (mg/kg/min) × patient weight (kg) × duration of surgery (min). The BCS scores were utilized to assess the level of patient comfort in the two groups: 0, indicates continuous pain; 1, represents no pain at rest, but with severe pain during deep breathing or coughing; 2, indicates no pain while lying at rest, and slight pain during deep breathing or coughing; 3, represents no pain during deep breathing; 4, represents no pain during coughing[11].

Statistical methods

For normally distributed measurement data, mean ± SD was used for the statistical description, and independent sample *t*-test was performed to determine the statistical difference. For non-normally distributed measurement data, median (M) and interquartile range were used for the statistical description, and the Mann-Whitney *U*-test was performed to determine the statistical difference. χ^2 test was used to analyze the difference between groups for the enumeration data. Frequency (rate) was used to describe the ordinal data, and this was analyzed using the Wilcoxon rank sum test. SPSS 26.0 was used for the statistical analysis. A P value of < 0.05 was considered statistically significant.

RESULTS

A total of 168 elderly patients, who underwent gastrointestinal laparoscopic surgery from February 2020 to February 2021, were screened in the present study. Among these patients, 35 patients did not agree to participate, and 18 patients were excluded based on the exclusion criteria. During the trial, five patients were excluded due to the following reasons: Rejection and loss to follow-up. Finally, a total of 110 patients (66 male and 44 female patients) were included for the present study (Figure 1).

Table 1 Postoperative nausea and vomiting grading scale

PONV grade	Patient response
0	Without PONV
I	Nausea without vomiting
II	Nausea with vomiting (< 3 times/d)
III	Vomiting ≥ 3 times/d

PONV: Postoperative nausea and vomiting.

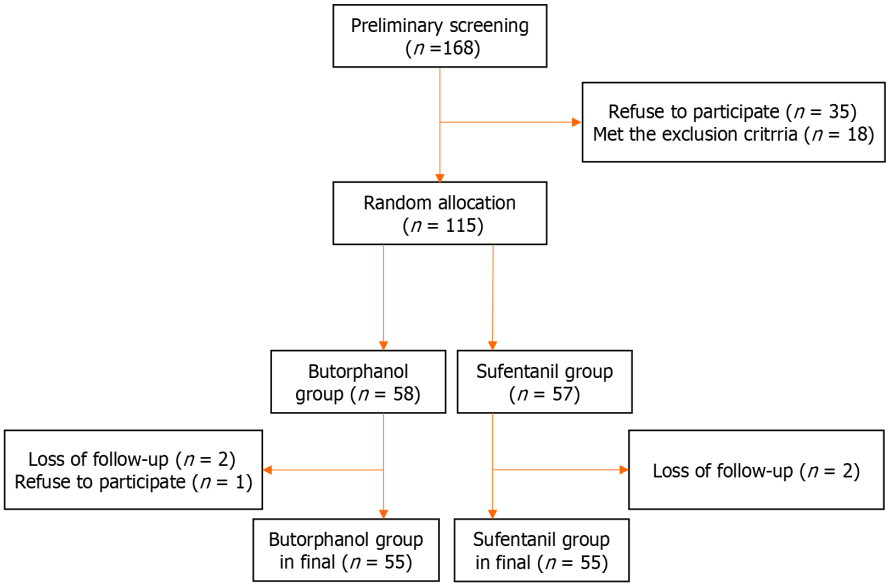

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Figure 1 The patient inclusion, randomization, and follow-up flowchart.

Comparison of baseline characteristics

No significant differences were observed between the two groups, in terms of age, BMI, gender, ASA grade, smoking history, PONV or motion sickness history, intraoperative and postoperative 48-h total infusion volume (Table 2), and hemodynamic parameters (Table 3) ($P > 0.05$).

Comparison of PONVs at postoperative 48 h

As shown in Table 4, there was a significant difference in the occurrence of PONV at T1 ($P = 0.005$) and T2 ($P = 0.001$), while there was no statistical difference at T3 ($P = 0.169$), between the sufentanil and butorphanol groups (Table 4).

Comparison of intraoperative propofol and remifentanil

There was no significant difference in the total dose of intraoperative propofol ($P = 0.893$) and remifentanil ($P = 0.438$) between the sufentanil and butorphanol groups (Table 5).

Comparison of agitation and BCS scores

The BCS scores were significantly better in the butorphanol group, when compared to the sufentanil group ($P = 0.028$), although there was no significant difference in agitation scores in the PACU between the two groups ($P = 0.439$) (Table 5).

Comparison of PCIA effective compressions and time to first postoperative flatulence

There were no statistically significant differences observed between the two groups, in terms of the number of PCIA effective compressions at postoperative 48 h ($P = 0.881$), and at the time to first postoperative flatulence ($P = 0.822$) (Table 5).

Table 2 Comparison of baseline characteristics between the sufentanil and butorphanol groups

	Sufentanil group (*n* = 55)	Butorphanol group (*n* = 55)	*P* value
Age	71.0 ± 5.7	69.6 ± 5.7	0.199
Gender (male/female)	32/23	34/21	0.698
ASA (I/II/III)	0/33/22	0/30/25	0.847
Weight (kg)	63.6 ± 10.3	68.6 ± 11.3	0.058
BMI (kg/m^2)	21.1 ± 1.8	20.81 ± 1.7	0.403
Smoking (yes/no)	25/30	26/29	0.703
PONV or motion sickness history (yes/no)	14/41	20/35	0.218
Operation time (h)	3.41 ± 1.30	3.25 ± 1.07	0.484
Intraoperative infusion volume (mL)	1290.9 ± 404.7	1243.6 ± 316.8	0.497
Postoperative 24-h infusion volume (mL)	2380.9 ± 137.6	2342.7 ± 133.8	0.143
Postoperative 48-h infusion volume (mL)	2152.7 ± 128.9	2125.5 ± 117.4	0.249

ASA: American Society of Anesthesiologists; BMI: Body mass index; PONV: Postoperative nausea and vomiting.

Table 3 Comparison of hemodynamics between the sufentanil and butorphanol groups

	HR (BPM)			SBP (mmHg)			DBP (mmHg)		
	Sufentanil	Butorphanol	*P* value	Sufentanil	Butorphanol	*P* value	Sufentanil	Butorphanol	*P* value
Pre-operation	69.2 ± 9.0	67.9 ± 7.1	0.400	145.2 ± 15.2	146.1 ± 12.0	0.748	67.8 ± 6.2	67.51 ± 5.1	0.828
One minute before induction	70.2 ± 9.5	68.8 ± 6.5	0.348	149.5 ± 17.9	149.3 ± 12.4	0.966	71.2 ± 8.8	68.4 ± 5.4	0.056
One minute after tracheal intubation	69.8 ± 9.2	68.8 ± 6.1	0.480	144.3 ± 18.4	147.8 ± 10.5	0.233	69.5 ± 8.7	67.6 ± 4.3	0.156
Intraoperative maintenance	67.3 ± 8.1	68.5 ± 6.3	0.388	145.2 ± 13.9	149.1 ± 9.8	0.098	68.3 ± 7.6	68.1 ± 4.5	0.867

HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Table 4 Comparison of postoperative nausea and vomiting within postoperative 48 h between the sufentanil and butorphanol groups

	Sufentanil group (*n* = 55)	Butorphanol group (*n* = 55)	*Z*	*P* value
T1 PONV (0/I/II/III)	42/6/6/1	52/3/0/0	-2.786	0.005[a]
T2 PONV (0/I/II/III)	21/11/11/2	44/4/7/0	-3.188	0.001[a]
T3 PONV (0/I/II/III)	50/3/2/0	54/1/0/0	-1.375	0.169

[a]There is significant statistical difference between the two groups, with $P < 0.05$.

T1: During the postanesthesia care unit period; T2: Return to the ward for 24 h; T3: Return to the ward for 24-48 h. PONV: Postoperative nausea and vomiting.

DISCUSSION

The present study compared the effects of sufentanil and butorphanol on the incidence of PONV in elderly patients who underwent gastrointestinal laparoscopic surgery. The results revealed that the incidence of PONV was lower in the PACU, and at 24 h after surgery in the butorphanol group, when compared to the sufentanil group, although there was no statistical difference observed at 48 h after surgery between the two groups.

The complex mechanism of PONV involves the following risk factors: Female gender, smoking, history of PONV or motion sickness, and opioids[12,13]. Several studies have revealed that traditional opioids that are commonly used for pain management, such as μ agonists, have been associated with nausea and vomiting, while providing analgesic efficacy [14,15]. Traditional opioids produce an analgesic effect by exciting the μ (μ1 and μ2) receptors. However, the excitation of

Table 5 Comparison of actual doses of propofol and remifentanil, agitation scores, Bruggrmann comfort scale scores, and effective compressions of patient-controlled intravenous analgesia pump

	Sufentanil group (*n* = 55)	Butorphanol group (*n* = 55)	*Z*	*P* value
Propofol (mg)	1027.2 ± 461.6	1016.4 ± 379.4	-	0.893
Remifentanil (mg)	1.3 ± 0.6	1.2 ± 0.5	-	0.438
Agitation score (0/1/2/3)	42/8/5/0	47/6/2/0	-0.774	0.439
BCS score (0/1/2/3/4)	6/5/30/14/0	1/4/24/25/1	-2.195	0.028[a]
Effective compressions of PCIA	1.00 (2.00-1.00)	1.00 (2.00-1.00)	-	0.881

[a]There is significant statistical difference between the two groups, with $P < 0.05$.
BCS: Bruggrmann comfort scale; PCIA: Patient-controlled intravenous analgesia pump.

μ2 receptors can enhance the sensitivity to vestibule stimulation, affect the chemoreceptor triggering area, and delay gastric emptying, thereby triggering PONV[4].

Butorphanol, which is a synthetic opioid receptor agonist-antagonist with 5-8 times the analgesic potency of morphine, exhibits low activity to δ receptors, while stimulating the κ and μ1 receptors, and antagonizing μ2 receptors[5]. Sufentanil has a long clearance half-life in elderly patients, and its effect on opioid receptors can persist for several hours after surgery, increasing the incidence and duration of PONV. Since sufentanil undergoes metabolism and clearance over time, its effect on opioid receptors decreases, which may explain the different effects of sufentanil and butorphanol on PONV at different time points.

Recent studies have revealed that butorphanol can effectively inhibit the hemodynamic fluctuations caused by tracheal intubation during anesthesia induction, which is consistent with the results of the hemodynamic parameter analysis in a previous study[16]. In the present study, there was no significant difference in hemodynamic fluctuations before and after endotracheal intubation between the sufentanil and butorphanol groups, and both drugs effectively inhibited the circulation fluctuations caused by the endotracheal intubation. Furthermore, there was no significant difference in intraoperative remifentanil dose, PACU agitation score, or the number of effective compressions for postoperative PCIA between the sufentanil and butorphanol groups. Thus, it was considered that the induction of anesthesia with butorphanol can produce similar and relatively complete analgesic effects as sufentanil. More importantly, butorphanol can activate the κ receptors, and exert sedative effects. Although there was no statistical difference in intraoperative propofol dose between the two groups in the present study, the BCS scores were higher in the butorphanol group, indicating that the postoperative comfort level of patients induced by butorphanol was higher.

Previous studies have reported that intravenous butrophanol can promote the recovery of postoperative gastrointestinal function, and shorten the time to first postoperative flatulence in elderly patients undergoing radical laparoscopic nephrectomy[17]. However, there was no statistical difference in the time to first postoperative flatulence between the sufentanil and butorphanol groups, which was possibly due to the following factors: Postoperative ambulation time, postoperative dietary recovery, and the use of glycerine enema. Therefore, further comprehensive analyses are required to verify this conclusion.

The limitations of the present study should be acknowledged. Merely the occurrence of nausea and vomiting within 48 h after surgery were observed, and the PDNV was not followed up. Furthermore, the present study merely included elderly patients ≥ 65 years old, who underwent gastrointestinal laparoscopic surgery. Thus, patients in other age groups, especially young women, needs to be investigated. Moreover, the specific operation methods of gastrointestinal surgery were not statistically analyzed in the present study. In addition, other high-risk surgeries, such as pelvic surgery, thyroid surgery, strabismus repair, and middle ear surgery, were not included in the present study[18,19]. Therefore, the conclusions need to be supported by further evidence and more information.

CONCLUSION

In summary, the administration of butorphanol has shown potential in significantly reducing the occurrence of PONV within 24 h after gastrointestinal surgery in elderly patients, and improving the comfort of patients in the PACU. Therefore, the present study contributes valuable evidence that support strategies targeted at mitigating PONV during the perioperative period.

ARTICLE HIGHLIGHTS

Research background

Postoperative nausea and vomiting (PONV) are common complications after surgery, seriously affects the prognosis of elderly patients for laparoscopic gastrointestinal surgery.

Research motivation
This prospective, double-blind randomized controlled trial aimed to investigate the effect of butorphanol on PONV in this patient population.

Research objectives
Elderly patients (≥ 65 years old) who underwent gastrointestinal laparoscopic surgery.

Research methods
Patients were randomly assigned to receive butorphanol (40 μg/kg) or sufentanil (0.3 μg/kg) during anesthesia induction in a 1:1 ratio. The measured outcomes included the incidence of PONV at 48 h after surgery, intraoperative dose of propofol and remifentanil, Bruggrmann Comfort Scale (BCS) score in the postanesthesia care unit (PACU), number of compressions for postoperative patient-controlled intravenous analgesia (PCIA), and time to first flatulence after surgery.

Research results
The results revealed a noteworthy reduction in the occurrence of PONV at 24 h after surgery in the butorphanol group, when compared to the sufentanil group. However, no significant variations were observed between the two groups, in terms of the clinical characteristics, such as the PONV or motion sickness history, intraoperative and postoperative 48-h total infusion volume and hemodynamic parameters, intraoperative dose of propofol and remifentanil, number of postoperative PCIA compressions, time until the first occurrence of postoperative flatulence, and incidence of PONV at 48 h post-surgery. Furthermore, patients in the butorphanol group were more comfortable, when compared to patients in the sufentanil group in the PACU.

Research conclusions
The administration of butorphanol has shown potential in significantly reducing the occurrence of PONV within 24 h after gastrointestinal surgery in elderly patients, and improving the comfort of patients in the PACU.

Research perspectives
Anesthesia induction with butorphanol may reduce the incidence of PONV, especially for some patients with a high risk of PONV (young women, no-smoking, PONV or motion sickness history, high-risk surgeries, such as pelvic surgery, thyroid surgery, strabismus repair, and middle ear surgery).

FOOTNOTES

Co-first authors: Fang Xie and Lin Yang.

Author contributions: Xie F drafted the manuscript and critically revised the manuscript for important intellectual content; Sun DF approved the final version to be published; Yang L agreement to be accountable for all aspects of the work, ensuring that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; Sun ZL substantial contribution to the conception and design of the study; and all authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Randomized Clinical Trial

Efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute stroke

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Abstract

BACKGROUND

Aspirin is a widely used antiplatelet agent that reduces the risk of recurrent ischemic stroke and other vascular events. However, the optimal timing and dose of aspirin initiation after an acute stroke remain controversial.

AIM

To evaluate the efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute stroke.

METHODS

We conducted a randomized, open-label, controlled trial in 60 patients with acute ischemic or hemorrhagic stroke who were admitted to our hospital within 24 h of symptom onset. Patients were randomly assigned to receive either aspirin 300 mg daily or no aspirin within 48 h of stroke onset. The primary outcome was the occurrence of recurrent stroke, myocardial infarction, or vascular death within 90 d. The secondary outcomes were functional outcomes at 90 d measured using the modified Rankin Scale (mRS), incidence of bleeding complications, and mortality rate.

RESULTS

The mean age of the patients was 67.8 years and 55% of them were male. The median time from stroke onset to randomization was 12 h. The baseline characteristics were well balanced between the two groups. The primary outcome occurred in 6.7% of patients in the aspirin group and 16.7% of patients in the no aspirin group (relative risk = 0.40, 95% confidence interval: 0.12-1.31, P = 0.13). The mRS score at 90 d was significantly lower in the aspirin group than in the no aspirin group (median, 2 *vs* 3, respectively; P = 0.04). The incidence of bleeding complic-

ations was similar between the groups (6.7% *vs* 6.7%, P = 1.00). The mortality rates were also comparable between the two groups (10% *vs* 13.3%, P = 0.69).

CONCLUSION

Aspirin use is associated with favorable functional outcomes but does not significantly reduce the risk of recurrent vascular events. Its acceptable safety profile is comparable to that of no aspirin. Further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings.

Key Words: Aspirin; Acute stroke; Antiplatelet therapy; Recurrent stroke; Recurrent vascular events; Myocardial infarction

Core Tip: While aspirin use within 48 h of acute stroke showed improved functional outcomes, it did not significantly reduce the risk of recurrent vascular events compared to no aspirin. The safety profile of aspirin was acceptable and comparable to no aspirin. Further research with larger sample sizes and longer follow-up is required to validate these findings and determine the optimal timing and dose of aspirin initiation after an acute stroke.

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INTRODUCTION

Stroke is a major cause of death and disability worldwide, affecting more than 15 million people annually[1]. Approximately 80% of strokes are ischemic in nature, caused by the occlusion of a cerebral artery by a thrombus or embolus, and 20% are hemorrhagic, caused by the rupture of a cerebral vessel[2]. The risk of recurrent stroke is high after an initial event, particularly within the first few days or weeks[3]. Therefore, the early prevention of secondary stroke is crucial for improving the prognosis and quality of life of stroke survivors.

Aspirin is a well-established antiplatelet agent that inhibits the synthesis of thromboxane A2, a potent platelet activator and vasoconstrictor[4]. Aspirin has been shown to reduce the risk of recurrent ischemic stroke and other vascular events by approximately 25% in patients with a transient ischemic attack or minor stroke[5]. However, the optimal timing and dose of aspirin initiation after an acute stroke remain unclear. Some studies have suggested that early administration of aspirin within 48 h of stroke onset may have additional benefits over delayed treatment, such as reducing the risk of early recurrence, enhancing reperfusion, and preventing progression or extension of ischemic lesions[6-8]. However, other studies have raised concerns regarding the potential adverse effects of early aspirin use, such as an increased risk of hemorrhagic transformation, intracranial hemorrhage, and gastrointestinal bleeding[9-11]. Moreover, the optimal dose of aspirin for acute stroke prevention is unclear because higher doses may have more antiplatelet and adverse effects than lower doses[12-14].

Therefore, we conducted a randomized, open-label, controlled trial to evaluate the efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute ischemic or hemorrhagic stroke.

MATERIALS AND METHODS

Study design and participants

This single-center, randomized, open-label controlled trial was conducted at our hospital between January 2019 and December 2020. Patients were admitted to our hospital within 24 h of symptom onset with a diagnosis of acute ischemic or hemorrhagic stroke confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). The inclusion criteria were as follows: Age 18 years or older, informed consent from the patient or a legally authorized representative, and no contraindications to aspirin use. The exclusion criteria were as follows: Previous use of aspirin or other antiplatelet agents within 7 d before stroke onset, use of anticoagulants or thrombolytic agents, severe stroke with a National Institutes of Health Stroke Scale score of 25 or higher, intracranial hemorrhage with a volume of 30 mL or more, known allergy or intolerance to aspirin, active bleeding or bleeding tendency, severe liver or renal dysfunction, pregnancy or lactation, and participation in another clinical trial.

Randomization and intervention

Eligible patients were randomly assigned to receive either aspirin 300 mg daily or no aspirin within 48 h of stroke onset. Randomization was performed using a computer-generated random number sequence with a 1:1 allocation ratio and a

block size of four. The allocation was concealed in sealed opaque envelopes opened by the treating physician after informed consent was obtained. The intervention was open-label because patients and physicians were aware of the treatment assignment. However, the outcome assessors and data analysts were blinded to the treatment allocation.

Patients in the aspirin group received the first dose of aspirin as soon as possible after randomization and continued to receive aspirin 300 mg daily for 90 d. The patients in the no-aspirin group did not receive any antiplatelet agents during the study period[15]. Intravenous fluids, oxygen therapy, blood pressure control, glucose control, fever control, infection prophylaxis, dysphagia screening, nutritional support, and early mobilization could be given. The use of other medications such as statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, and antidiabetic agents was at the discretion of the treating physician.

Outcomes

The primary outcome was the occurrence of recurrent stroke (ischemic or hemorrhagic), myocardial infarction, or vascular death within 90 d of randomization. Recurrent stroke was defined as a new focal neurological deficit lasting > 24 h with evidence of a new ischemic or hemorrhagic lesion on CT or MRI. Myocardial infarction was defined as an increase and/or decrease in cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit and at least one of the following: Symptoms of ischemia, new or presumed new significant ST-segment/T-wave changes or new left bundle branch block, development of pathological Q waves in the electrocardiogram, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality. Vascular death was defined as death owing to stroke, myocardial infarction, heart failure, pulmonary embolism, aortic dissection, peripheral arterial disease, or sudden cardiac death.

The secondary outcomes were as follows: (1) The functional outcomes at 90 d measured using the modified Rankin Scale (mRS), which ranges from 0 (no symptoms) to 6 (death); (2) the incidence of bleeding complications within 90 d, including intracranial hemorrhage (any type), gastrointestinal bleeding (requiring transfusion or endoscopic intervention), and other major bleeding (requiring transfusion or surgical intervention); and (3) the mortality rate within 90 d.

All outcomes were assessed by trained neurologists who were blinded to the treatment allocation. The primary and secondary outcomes were adjudicated by an independent committee blinded to the treatment allocation.

Sample size

The sample size calculation was based on the assumption that aspirin use would reduce the primary outcome by 50% compared to no aspirin use. With an alpha level of 0.05 and a power of 80%, we estimated that we would need 54 patients in each group to detect this difference. We planned to enroll 60 patients in each group to allow for a dropout rate of 10%.

Statistical analysis

An intention-to-treat analysis was performed for all outcomes. Descriptive statistics were used to summarize the baseline characteristics, which were compared between the two groups using the *t*-test for continuous variables and chi-square test for categorical variables. The relative risk (RR) and 95% confidence interval (CI) were used to compare the incidence of the primary outcome and its components between the two groups. The Mann–Whitney *U* test was used to compare the mRS scores; the Kaplan–Meier curve and log-rank test were used to compare survival rates; and the Fisher's exact test was used to compare the incidence of bleeding complications between the two groups. Statistical significance was set at $P < 0.05$. Data analyses were conducted using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., United States).

RESULTS

Baseline characteristics

A total of 132 patients with acute stroke were screened, and 60 patients who met the inclusion and exclusion criteria were enrolled. Of these, 30 patients were randomly assigned to receive aspirin and 30 were assigned to receive no aspirin within 48 h of stroke onset. The mean age was 67.8 years, and 55% of the patients were male. The median time from stroke onset to randomization was 12 h. Baseline characteristics were well balanced between the two groups (Table 1).

Primary outcome

The primary outcomes occurred in 6.7% of patients in the aspirin group and 16.7% of patients in the no-aspirin group (RR = 0.40, 95%CI: 0.12-1.31, $P = 0.13$). Components of the primary outcomes are listed in Table 2. There was no significant difference between the aspirin and no-aspirin groups in the incidence of recurrent stroke (3.3% *vs* 10%, RR = 0.33, 95%CI: 0.04-2.76, $P = 0.31$), myocardial infarction (3.3% *vs* 3.3%, RR = 1.00, 95%CI: 0.07-14.42, $P = 1.00$), or vascular death (3.3% *vs* 6.7%, RR = 0.50, 95%CI: 0.05-4.79, $P = 0.55$).

Secondary outcomes

The mRS score at 90 d was significantly lower in the aspirin group than in the no-aspirin group (median, 2 *vs* 3; $P = 0.04$). The incidence of bleeding complications was similar between the two groups (6.7% *vs* 6.7%, $P = 1.00$). There were no cases of intracranial hemorrhage or gastrointestinal bleeding in either group; however, there were two cases of other major bleeding events in each group, as shown in Table 3. Mortality rates were also comparable between the two groups (10%

Table 1 Baseline characteristics of the patients

Characteristic	Aspirin group (*n* = 30)	No aspirin group (*n* = 30)	*P* value
Age, yr (mean ± SD)	67.5 ± 11.2	68.1 ± 10.4	0.80
Male sex, *n* (%)	17 (56.7)	16 (53.3)	0.41
Time from stroke onset to randomization, h [median (IQR)]	12 (8-16)	12 (9-15)	0.27
Stroke type, *n* (%)			
Ischemic	25 (83.3)	24 (80)	0.77
Hemorrhagic	5 (16.7)	6 (20)	0.36
Stroke location, *n* (%)			
Anterior circulation	20 (66.7)	18 (60)	0.64
Posterior circulation	5 (16.7)	6 (20)	0.43
Lacunar	5 (16.7)	6 (20)	0.43
NIHSS score at admission, points (mean ± SD)	8.3 ± 4.2	8.7 ± 4.5	0.69
Medical history, *n* (%)			
Hypertension	22 (73.3)	21 (70)	0.82
Diabetes mellitus	10 (33.3)	11 (36.7)	0.51
Dyslipidemia	12 (40)	13 (43.3)	0.38
Coronary artery disease	8 (26.7)	9 (30)	0.67
Atrial fibrillation	6 (20)	7 (23.3)	0.31
Previous stroke or TIA	4 (13.3)	5 (16.7)	0.42

IQR: Interquartile range; NIHSS: National Institutes of Health Stroke Scale; TIA: Transient ischemic attack.

Table 2 Primary outcome and its components

Outcome	Aspirin group (*n* = 30)	No aspirin group (n = 30)	Relative risk (95%CI)	*P* value
Primary outcome, *n* (%)	2 (6.7)	5 (16.7)	0.40 (0.12-1.31)	
Recurrent stroke, *n* (%)	1 (3.3)	3 (10)	0.33 (0.04-2.76)	0.31
Myocardial infarction, *n* (%)	1 (3.3)	1 (3.3)	1.00 (0.07-14.42)	1.00
Vascular death, *n* (%)	1 (3.3)	2 (6.7)	0.50 (0.05-4.79)	0.55

95%CI: 95% confidence interval.

vs 13.3%, $P = 0.69$). The causes of death were stroke (two patients in each group), myocardial infarction (one patient in the no-aspirin group), and pneumonia (one patient in the no-aspirin group).

DISCUSSION

In this randomized, open-label controlled trial, aspirin antiplatelet therapy within 48 h of acute stroke was found to be associated with favorable functional outcomes at 90 d, but did not significantly reduce the risk of recurrent vascular events compared to no aspirin. The safety profile of aspirin was acceptable and comparable to that of no aspirin.

Our findings are consistent with those of previous studies, suggesting the benefits of early aspirin use after acute stroke [16-18]. For example, the International Stroke Trial, which enrolled more than 19000 patients with acute stroke, showed that the initiation of aspirin 300 mg daily within 48 h of stroke onset reduced the risk of early recurrent ischemic stroke by 43% and improved functional outcomes at 6 mo. Similarly, the Chinese Acute Stroke Trial, which enrolled more than 21000 patients with acute stroke, showed that the initiation of aspirin 160 mg daily within 48 h of stroke onset reduced the risk of early recurrent ischemic stroke by 34% and improved functional outcomes at 4 wk. A meta-analysis of these two trials and other smaller trials confirmed that early aspirin use after acute stroke reduced the risk of early recurrent ischemic stroke by 38% and improved functional outcomes at the end of follow-up.

Table 3 Secondary outcomes

Outcome	Aspirin group (*n* = 30)	No aspirin group (*n* = 30)	*P* value
mRS score at 90 d, median (IQR)	2 (1-3)	3 (2-4)	0.04
Bleeding complications, *n* (%)	2 (6.7)	2 (6.7)	1.00
Intracranial hemorrhage, *n* (%)	0 (0)	0 (0)	-
Gastrointestinal bleeding, *n* (%)	0 (0)	0 (0)	-
Other major bleeding, *n* (%)	2 (6.7)	2 (6.7)	-
Mortality rate, *n* (%)	3 (10)	4 (13.3)	0.69

IQR: Interquartile range; mRS: Modified Rankin Scale.

However, our findings are in contrast to those of other studies that failed to demonstrate a benefit or even suggested the harm of early aspirin use after acute stroke[19-21]. For instance, the Early Treatment with Aspirin for Stroke trial, which enrolled more than 1500 patients with acute ischemic stroke, showed that the initiation of aspirin 300 mg daily within 24 h of stroke onset did not reduce the risk of recurrent ischemic stroke or improve functional outcomes at 3 mo. Moreover, the Aspirin in Acute Stroke (AAS) trial, which enrolled more than 1000 patients with acute ischemic or hemorrhagic stroke, showed that the initiation of aspirin 250 mg daily within 12 h of stroke onset increased the risk of hemorrhagic transformation and intracranial hemorrhage without reducing the risk of recurrent ischemic stroke or improving functional outcomes at 3 mo. A meta-analysis of these two trials and other smaller trials found that early aspirin use after acute stroke increased the risk of hemorrhagic transformation by 54% and intracranial hemorrhage by 67% without reducing the risk of recurrent ischemic stroke or improving functional outcomes at the end of follow-up.

The reasons for these discrepancies are unclear but may be related to differences in study design, population, intervention, and outcome assessment. For example, our study included both patients with ischemic stroke and those with hemorrhagic stroke, whereas some previous studies only included patients with ischemic stroke. Our study used a higher dose of aspirin (300 mg) than previous studies (160 or 250 mg). Our study measured functional outcomes using the mRS score, whereas previous studies used other scales, such as the Barthel Index or the Glasgow Outcome Scale. Our study had a longer follow-up period (90 d) than previous studies (4 wk or 2 mo). Therefore, it is possible that our study captured more benefits and less harm from early aspirin use after acute stroke than previous studies.

The mechanisms by which early aspirin use may improve functional outcomes after acute stroke are not fully understood but may involve several pathways. Aspirin may contribute to improved outcomes in the following ways: (1) Prevention of platelet aggregation and thrombus formation in ruptured atherosclerotic plaques or cardiac emboli, thereby reducing the risk of early recurrent ischemic stroke; (2) enhancement of cerebral blood flow and reperfusion by inhibiting thromboxane A2-mediated vasoconstriction and promotion of nitric oxide-mediated vasodilation; (3) attenuation of inflammation and oxidative stress by inhibiting cyclooxygenase-2-mediated prostaglandin E2 synthesis and nuclear factor-kappa B activation; and (4) modulation of neurogenesis and neuroplasticity by stimulating the expression of brain-derived neurotrophic factors and synaptic remodeling.

The safety profile of early aspirin use after acute stroke was acceptable and comparable to that of no aspirin use. No cases of intracranial hemorrhage or gastrointestinal bleeding were observed in either group. This may be due to the careful selection of patients with no contraindications to aspirin, such as those with severe stroke, large intracranial hemorrhage, active bleeding, or a bleeding tendency. Moreover, we used a moderate dose of aspirin (300 mg), which may have less adverse effects than higher doses (500 mg or more)[22-24]. However, other major bleeding events in both groups were observed, including hematuria, epistaxis, and hemoptysis. These bleeding complications may be related to other factors such as hypertension, infection, trauma, or coagulation disorders. Therefore, we suggest that early aspirin use after acute stroke should be carefully monitored for any signs or symptoms of bleeding and discontinued if necessary.

Our study had several limitations. First, our sample size was small and our study was underpowered to detect a significant difference in the primary outcome between the two groups. Therefore, we cannot exclude the possibility of a type II error or false-negative result. Second, our study was open-label and not placebo-controlled, which may have introduced bias and confounding factors into the intervention and outcome assessments. However, we attempted to minimize these potential sources of bias using concealed randomization, blinded outcome assessment, and independent outcome adjudication. Third, this was a single-center study conducted in a specific population, which may have limited the generalizability and external validity of our findings. Therefore, our results should be interpreted with caution and confirmed in larger, multicenter, double-blind placebo-controlled trials with different populations.

CONCLUSION

In conclusion, aspirin antiplatelet therapy within 48 h of acute stroke is associated with favorable functional outcomes at 90 d, but does not significantly reduce the risk of recurrent vascular events compared with that of no-aspirin therapy. The safety profile of aspirin is acceptable and comparable to that of aspirin. Further studies with larger sample sizes and

longer follow-up periods are required to confirm our findings.

ARTICLE HIGHLIGHTS

Research background

The optimal timing and dose of aspirin initiation after an acute stroke are still debated. This study aimed to evaluate the efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute stroke. A randomized controlled trial was conducted. The primary outcome was the occurrence of recurrent stroke, myocardial infarction, or vascular death within 90 d. Secondary outcomes comprised functional outcomes, bleeding complications, and mortality rates. Results showed favorable functional outcomes with aspirin use, but no significant reduction in recurrent vascular events. Larger studies with longer follow-up periods are needed for further confirmation.

Research motivation

The optimal timing and dose of aspirin initiation after acute stroke are still debated, highlighting the need for further investigation. This study aimed to evaluate the efficacy and safety of aspirin antiplatelet therapy within 48 h of symptom onset in patients with acute stroke. Understanding the impact of aspirin use on functional outcomes and recurrent vascular events is crucial for informing clinical decision-making and optimizing patient care. Larger studies with longer follow-up periods will provide more conclusive evidence in this field and guide future management strategies for acute stroke patients.

Research objectives

The primary aim was to assess the occurrence of recurrent stroke, myocardial infarction, or vascular death within 90 days. Secondary objectives included evaluating functional outcomes at 90 d using the modified Rankin Scale, determining the incidence of bleeding complications, and comparing mortality rates between the aspirin and no aspirin groups. By addressing these objectives, the study aimed to provide valuable insights into the use of aspirin in acute stroke management.

Research methods

A randomized, open-label, controlled trial was conducted involving 60 patients with acute ischemic or hemorrhagic stroke admitted within 24 h of symptom onset. Patients were randomly assigned to receive either a daily dose of 300 mg aspirin or no aspirin within 48 h of stroke onset. The primary outcome measured was the occurrence of recurrent stroke, myocardial infarction, or vascular death within 90 d. Secondary outcomes included functional outcomes at 90 d using the modified Rankin Scale (mRS), the incidence of bleeding complications, and mortality rate. Baseline characteristics were balanced between the two groups, and statistical analyses were performed to assess the relative risk and significance of the outcomes.

Research results

Among the 60 patients included, those in the aspirin group showed favorable functional outcomes compared to the no aspirin group, as indicated by significantly lower modified Rankin Scale (mRS) scores at 90 d. However, there was no significant reduction in the occurrence of recurrent stroke, myocardial infarction, or vascular death between the two groups. The incidence of bleeding complications and mortality rates were comparable between the aspirin and no aspirin groups. Further studies with larger sample sizes and longer follow-up periods are necessary to validate these findings.

Research conclusions

Aspirin use within 48 h of symptom onset in acute stroke patients is associated with improved functional outcomes. However, there is no significant reduction in the risk of recurrent stroke, myocardial infarction, or vascular death compared to not using aspirin. The safety profile of aspirin is similar to that of no aspirin in terms of bleeding complications and mortality rates. To validate these results, further research with larger sample sizes and longer follow-up periods is necessary.

Research perspectives

The study results highlight the need for further investigation into the optimal timing and dose of aspirin initiation after acute stroke. Future studies should consider larger sample sizes and longer follow-up periods to confirm the findings regarding functional outcomes and the risk reduction of recurrent vascular events. Additionally, exploring alternative antiplatelet therapies or combination treatments may provide valuable insights into improving outcomes in acute stroke management. Overall, ongoing research is necessary to refine the use of aspirin and optimize its benefits in the context of acute stroke.

FOOTNOTES

Author contributions: Zhang JQ proposed the concept of this study; Zhang JQ and Pan ZB contributed to data collection; Zhang JQ

contributed to formal analysis; Pan ZB participated in the survey; Zhang JQ contributed to the methods; Zhang JQ guided the research; Zhang JQ and Pan ZB validated this study; Zhang JQ and Pan ZB contributed to the visualization of this study; Zhang JQ prepared the first draft; Zhang JQ and Pan ZB jointly reviewed and edited the manuscript.

Institutional review board statement: This study obtained the ethical review and approval of the First Affiliated Hospital of Jiangxi Medical College.

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META-ANALYSIS

Analysis of the effectiveness of cognitive rehabilitation for patients with chronic mental illness: A meta-analysis

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Abstract

BACKGROUND

People suffering from chronic mental illness are sensitive to stressful stimuli, lack coping skills, and have low self-esteem due to problems such as social situations. They also experience depression, isolation, fear, and frustration. Due to cognitive dysfunction, people suffering from chronic mental illness have inadequate cognitive processes that lead to distorted thinking.

AIM

To confirm the effectiveness of cognitive rehabilitation therapy in improving cognitive function and alleviating behavioral and psychological symptoms in patients with chronic mental illness, and to identify the cognitive function that had the main effect.

METHODS

The quality of the studies was evaluated using the Assessment of Multiple Systematic Reviews criteria, and data published from 2011 to December 2022 were searched using PubMed, Cochrane, RISS, KISS, and DBpia. The keywords used in the search were "mental illness," "cognitive rehabilitation," "cognition," and "mental." A meta-analysis was conducted on the 12 selected papers.

RESULTS

The level of evidence for the 12 documents was that of a randomized experimental study. Intervention types in cognitive rehabilitation can be divided into cognitive behavior, cognitive training, cognitive rehabilitation, and computerized cognitive programs. Most of the studies were on schizophrenia, and the measurement areas were cognitive functions (*e.g.*, concentration, memory, and executive function) as well as depression, sociability, and quality of life. As a result of the meta-analysis of each variable, the effect size for cognitive rehabilitation treatment was in the following order: Sociability, memory, concentration, executive function, quality of life, and depression. Particularly, sociability and memory exhibited significant effects.

CONCLUSION

Cognitive rehabilitation aids cognitive function and sociability in patients with chronic mental illness and can be used as evidence for cognitive rehabilitation in mental health and occupational therapy.

Key Words: Cognitive function; Mental illness; Cognitive rehabilitation; Cognitive training; Cognitive therapy; Schizophrenia; Occupational therapy

Core Tip: This study demonstrates the effectiveness of cognitive rehabilitation in patients with chronic mental illness, both domestically and internationally, through a meta-analysis of 12 selected papers. Cognitive rehabilitation interventions can be divided into cognitive behavior, cognitive training, cognitive rehabilitation, and computerized cognitive programs. Based on the meta-analysis of each variable, the effect size of the cognitive rehabilitation treatment was in the following order: Sociability, memory, concentration, executive function, quality of life, and depression. Particularly, sociality and memory had significant effects. We aimed to investigate the effectiveness of cognitive rehabilitation for each mental illness and symptom, presenting applicable evidence for clinical use.

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INTRODUCTION

A person with chronic mental illness refers to one who has suffered from a mental illness for more than two years and has physical, psychological, and social impairments due to the disease[1]. People with chronic mental illness react sensitively to stressful stimuli, lack coping skills, and develop low self-esteem due to personal and social situations and problems such as social prejudice, stigma, and lack of family formation; they also experience depression, isolation, fear, and frustration[2]. This further exacerbates various symptoms closely related to social relationships and causes cognitive dysfunction, which causes errors in information processing in specific situations[3].

Due to cognitive dysfunction, people with chronic mental illness have inappropriate cognitive processes that lead them to distorted thinking[4]. Consequently, it becomes difficult to properly recognize and interpret social information, judge others' intentions, and react appropriately[5]. Due to the influence of cognition, behavior, and perception, chronic mental illness has a significant impact on individual motivation, quality of life, social role, and adaptation[3]. Therefore, appropriate management and interventions for the cognitive function of patients with chronic mental illnesses are needed.

Although drug therapy is the most commonly used treatment method for patients with chronic mental illness, there have been reports that it does not have a significant effect on cognitive symptoms, even if there is an improvement in clinical mental symptoms[6]. In order to compensate for this, non-pharmacological treatment has recently been performed in parallel with drug treatment, and cognitive rehabilitation is a representative non-pharmacological treatment implemented to improve the cognitive function of mentally ill patients[7].

Cognitive rehabilitation therapy is a structured approach that can help with social adaptability in addition to reducing the main symptoms of chronic mental illness. It is based on the theory that a patient's emotions and behavior can be determined[8]. Effective treatment plans and interventions for cognitive dysfunction can be implemented through a method of applying relearning or compensation by distinguishing what can or cannot be performed during cognitive function processing[9]. In the treatment of mental disorders, cognitive rehabilitation is mainly applied to patients with chronic mental disorders, such as depression, anxiety disorders, schizophrenia, and alcoholism, and reduces anxiety or severity in stressful situations[10]. In addition, through the correction of thinking, negative thoughts change into positive ones, providing positive effects that increase motivation and participation in the work one wants to do[11].

Previous studies of cognitive rehabilitation in patients with chronic mental illness found improvements in concentration, attention, memory, and working memory after the implementation of cognitive rehabilitation in patients with chronic schizophrenia in hospital[12]. Cognitive behavior-based art and music therapies have shown significant effects on

stress perception and coping methods in patients with chronic mental illness[13]. However, despite previous studies on cognitive rehabilitation for patients with chronic mental illness, discussions on its effectiveness continue because of different diseases, dependent variables, and the use of measurement tools; thus, there are limitations in generalizing the results[14]. Therefore, there is a need to supplement the limitations of individual studies on cognitive rehabilitation and to prove its effectiveness on a consistent and scientific basis[15].

A representative method for proving the effectiveness of research is meta-analysis[16]. Meta-analysis is a statistical method used to aggregate the effect estimates of multiple individual studies conducted on the same topic and is an objective method of deriving results that can be used to summarize a specific topic or efficiently synthesize a large amount of literature data[17]. However, previous studies on this subject have been mainly limited to systematic reviews, and although some meta-analyses have been conducted, they are difficult to generalize due to limited interventions and subjects, such as computerized cognitive rehabilitation and patients with severe mental illness[7,14].

Therefore, in this study, we attempted to prove the effectiveness of cognitive rehabilitation in patients with chronic mental illness at home and abroad through a meta-analysis. Through this, the effectiveness of cognitive rehabilitation according to each mental disease and symptom was investigated, and evidence data that can be applied in clinical practice were presented.

MATERIALS AND METHODS

Criteria for selection of research papers and data collection method

This study was a meta-analysis to analyze the effectiveness of cognitive rehabilitation treatment in patients with chronic mental illness. For literature collection, papers published in domestic and foreign journals between January 2011 and December 2022 were searched. A measurement tool, Assessment of Multiple Systematic Reviews, was used to improve the quality of research based on academic theses, including dissertations. The literature selection criteria for this study were as follows: Studies applying cognitive rehabilitation treatment to patients with chronic mental illness, studies that can confirm experimental data and expertise, and randomized controlled trials (RCTs) with experimental and control groups. Studies involving only drug interventions, single-case studies, reviews, qualitative studies, and academic conference literature were excluded.

For the literature search, online databases were used; PubMed and Cochrane were used for overseas databases, and the RISS, KISS, and DBpia databases were used for domestic databases. The keywords used in the search were selected in Korean and English as "mental illness" and "cognitive rehabilitation" or "cognition" or "mental" and "cognition" or "mental" and "cognition." Literature collection and selection were performed by the authors reviewing papers individually. If the reviewed papers did not match, the authors reviewed them together. In total, 27523 papers were retrieved in the primary search using keywords from domestic and foreign databases. A secondary review was conducted on the titles and abstracts of the literature centering on the searched papers; 26976 papers that did not meet the criteria were excluded, and a total of 547 papers were selected. Afterwards, we checked the full text of 547 papers and excluded 56 subjects without chronic mental illness, 281 case studies, systematic reviews and meta-studies, 196 academic conference literature studies, and 3 studies where comparative analysis was difficult due to no common independent variables. A total of 12 articles were ultimately selected for final analysis(Figure 1).

Meta-analysis

The five-level classification method developed by Arbesman *et al*[18] was used for the level of evidence in the literature selected for this study. Because the literature selection was based on RCTs with experimental and control groups, it was confirmed that the qualitative evidence level of all target studies selected in this study corresponded to the highest level, stage 1 (random control study).

For data coding, the number of subjects in the experimental and control groups, mean and standard deviation, and a confidence interval of 95.0% were applied, and descriptive statistics were used for general characteristics. A meta-analysis was performed by coding the characteristics of the 12 selected studies, and the statistical heterogeneity, effect size, and publication bias were analyzed. Homogeneity was confirmed using a chi-squared test[19]. According to the statistical heterogeneity test of each study, a random-effects model was applied for statistically heterogeneous cases and a fixed-effects model was applied for homogeneous cases. Based on the results derived thereafter, the effect size and publication bias were analyzed, and the effect size was calculated using a forest plot and the publication bias was calculated using a funnel plot[20]. The meta-analysis program used Review Manager (RevMan) 5.3 provided by the Cochrane Alliance, and an effect size of 0.8 or more was interpreted as a large effect, an effect size of 0.5 as a moderate effect, and an effect size of 0.2 or less as a small effect[21]. After reviewing the selected studies, the results of each measurement tool suitable for this study were derived.

RESULTS

General characteristics of meta-analysis target studies

The general characteristics of the 12 articles selected for this study are presented in Table 1. All papers were published in professional journals, and 836 participants were included in the study. As for the housing type of the study subjects, were living in hospitals and nursing facilities. Schizophrenia was the most common diagnosis among the participants; there

Table 1 Characteristics of included study

No.	Ref.	Intervention	Evaluation		Experimental group			Control group		
					Pre (mean ± SD)	Post (mean ± SD)	Subjects (W/M)	Pre (mean ± SD)	Post (mean ± SD)	Subjects (W/M)
1	Song *et al*[25]	Rehacom	CNT	Memory	31.8 ± 6.2	36.4 ± 5.8	4/6	30.3 ± 5.1	31.2 ± 5.3	4/6
				Attention	36.9 ± 7.6	50.9 ± 32.8		41.3 ± 9.8	60.5 ± 36.1	
2	Kim and Kim *et al*[24]	Visuospatial Rehabilitation	RCFT	Memory	11.5 ± 5.7	14.6 ± 6.1	8/6	12.3 ± 9.9	12.3 ± 9.9	8/7
			Stroop	Executive Function	33 ± 6.5	37.4 ± 7.1		34.7 ± 10.3	34.5 ± 12.7	
			WCST	Attention	44.1 ± 30.7	33.2 ± 23.9		9.5 ± 4.4	11.3 ± 4.3	
3	Pijnenborg *et al* [28]	REFLEX/CRT	QUID-Sr	Depression	4.1 ± 1.7	3.7 ± 1.9	59	3.8 ± 1.8	3.7 ± 1.9	62
			MANSA	Quality of life	58.179.2	58.8 ± 9.3		58.1 ± 9.9	56.9 ± 10.7	
4	Iwata *et al*[22]	CogPack	BACSJ	Memory	0.2 ± 0.8	0.6 ± 0.8	22/7	-0.2 ± 1.1	0.1 ± 1.1	23/8
				Attention	0.1 ± 1	0.5 ± 1		-0.1 ± 1	0.1 ± 1.1	
				Execution function	0.1 ± 1.1	0.3 ± 0.7		-0.1 ± 0.9	-0.1 ± 0.9	
			LASMI	Social skill	14.1 ± 5.5	9.7 ± 5.4		14.5 ± 7.4	14.3 ± 7.5	
5	Kim[26]	Group art therapy	ATQ-N	Depression	14 ± 5.3	11.7 ± 5.4	3/5	15.1 ± 4.9	15.6 ± 5.6	3/5
6	Salomonsson *et al*[29]	CBT	MADRS-S	Depression	15.6 ± 6.7	13.6 ± 8.3	58/23	14.6 ± 7.2	10.6 ± 7.3	51/29
7	Jung and Oh [23]	Group art therapy	BES	Memory	22.8 ± 2.5	24.6 ± 2.9	8/4	23.2 ± 2.9	22.4 ± 1.9	5/7
				Attention						
				Executive Function						
8	Twamley *et al* [30]	CCT	SSPA	Social Skills	4.1 ± 0.63	3.9 ± 0.11	34/43	4.2 ± 0.7	4 ± 0.1	32/44
			QOLI	Quality of life	4 ± 1.5	4.8 ± 0.2		4.1 ± 1.38	3.8 ± 0.2	
			Ham-D	Depression	12.9 ± 6.9	10.4 ± 1.2		13 ± 6.8	14.9 ± 1.3	
9	Lee *et al*[33]	Cognitive behavioral social skills Training	WHOQOL-BREF	Quality of life	6 ± 1.2	7.6 ± 1.2	5/3	6.7 ± 2.2	6 ± 2	7/5
10	Kim and Cho [27]	CBT	MHCS	Depression	3 ± 0.51	3.5 ± 0.6	6/7	3.2 ± 0.5	3.2 ± 0.7	5/8
			RCS	Social skill	2.9 ± 0.6	3.4 ± 0.6		3 ± 0.7	3.1 ± 0.7	
11	Kingston *et al* [32]	Reasoning and Rehabilitation 2	CSS-M	Social skill	36.4 ± 11.6	29.7 ± 14.1	48	35.6 ± 14.6	35.9 ± 15.2	49
12	Hyun[31]	Cognitive Behavioral Group Therapy	Social skills scale	Social skills	39.1 ± 10.2	37.5 ± 9.6	13/13	39.7 ± 9.4	39.3 ± 9	15/11

CNT: Computer assisted cognitive rehabilitation; RCFT: Rey-osterrieth complex figure test; WCST: Wisconsin card sorting test; QUID-Sr: The Quick Inventory of Depressive Symptomatology Self-Report; MANSA: The self-rating Manchester Short Assessment of Quality of Life; BACSJ: Brief assessment of cognition in schizophrenia-Japane; LASMI: Life Assessment Scale for Mentally; ATQ-N: Automatic Thoughts Questionnaire-Negative; MADRS-S: Montgomery-Asberg Depression Rating Scale; BES: Basic Empathy Scale; CCT: Compensatory cognitive training; SSPA: Social Skills Performance Assessmen; QOLI: Quality of life interview; HAM-D: Hamilton depression rating scale; WHOQOL-BREF: World Health Organization Quality of Lif-BREF; CBT: Cognitive-behavior therapy; MHCS: Mental health confidence scale; RCS: Relationship change scale; CSS-M: The criminal sentiments scale-modified.

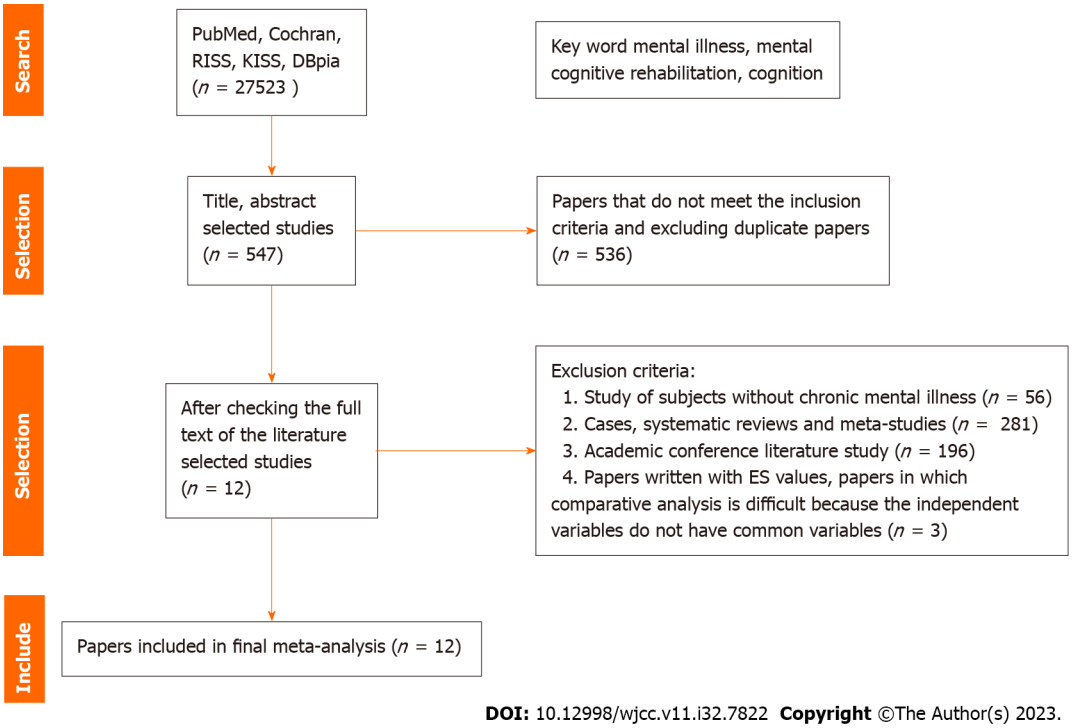

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Figure 1 Flow diagram of the literature selection process.

were more male subjects than female, and the average age was in their 40s. The cognitive rehabilitation treatments used in the study were cognitive behavior, cognitive training, cognitive rehabilitation, computerized cognitive programs, and various intervention methods. The intervention was applied twice a week for > 60 min.

Meta-analysis on the effects of cognitive rehabilitation treatment

To analyze the effects of cognitive rehabilitation treatment on patients with chronic mental illness, 12 studies were analyzed by dividing them into dependent variables. Dependent variables in the target studies were classified into 4 concentration, 4 memory, 3 executive function, 5 depression, 5 sociability, and 3 quality of life. As a result of the meta-analysis of each variable, the effect size for cognitive rehabilitation treatment was in the following order: Sociability, memory, concentration, executive function, quality of life, and depression.

Effects of cognitive rehabilitation therapy on concentration: Among the 12 studies, there were 4 papers with concentration as the dependent variable. As a result of analyzing these 4 studies, the overall effect size was 0.75 (95%CI: 0.39 to 1.39), which showed a medium effect size and was statistically significant ($P < 0.05$) (Table 2)[22-25].

The effect of cognitive rehabilitation treatment on memory: Among the 12 studies, there were 4 papers that used memory as a dependent variable. As a result of analyzing these 4 studies, the overall effect size for memory was 0.96 (95%CI: 0.59 to 1.32), which showed a large effect size and was statistically significant ($P < 0.05$) (Table 3)[22-25].

Effects of cognitive rehabilitation therapy on executive function: Among the total of 12 studies, there were 3 papers that used executive function as a dependent variable. As a result of analyzing these 3 papers, the overall effect size for executive function was 0.29 (95%CI: 0.18 to 0.40), indicating a small effect size and statistically significant ($P < 0.05$) (Table 4)[22-24].

Effects of cognitive rehabilitation therapy on depression: Among the total of 12 studies, there were 5 papers with depression as a dependent variable. As a result of analyzing these 5 studies, the overall effect size was 0.20 (95%CI: 0.17 to 0.23), which was a small effect size and was statistically significant ($P < 0.05$) (Table 5)[26-30].

The effects of cognitive rehabilitation therapy on sociality: Among the 12 studies, there were 5 papers with sociality as a dependent variable. As a result of analyzing these 5 studies, the overall effect size was 1.21 (95%CI: 0.98 to 1.43), which showed a large effect size and was statistically significant ($P < 0.05$) (Table 6)[22,27,30-32].

Effects of cognitive rehabilitation therapy on quality of life: Among the 12 studies, there were 3 papers with quality of life as the dependent variable. As a result of analyzing these three studies, the overall effect size was 0.29 (95%CI: 0.25-0.33), which was small and statistically significant ($P < 0.05$) (Table 7)[28,30,33].

Publication convenience

As a result of analyzing the publication convenience of the effects of cognitive rehabilitation treatment on concentration,

Table 2 Effect size of attention

Study	Diagnosis	Intervention	Effect size	95%CI	Weight (%)
Iwata *et al*[22]	Schizophrenia	CR using computer software	0.66	0.14-1.18	46.2
Jung and Oh[23]	Schizophrenia	CB group art therapy program	0.89	0.04-1.74	17.5
Kim and Kim[24]	Schizophrenia	Visuospatial rehabilitation	0.71	-0.04-1.47	22.0
Song *et al*[25]	Schizophrenia	CCP (RehaCom)	0.92	-0.01-1.85	14.4
Total			0.75	0.39-1.10	100

CR: Cognitive rehabilitation; CB: Cognitive behavior; CCP: Computerized cognition program.

Table 3 Effect size of memory

Study	Diagnosis	Intervention	Effect size	95%CI	Weight (%)
Iwata *et al*[22]	Schizophrenia	CR using computer software	1.26	0.70-1.82	42.6
Jung and Oh[23]	Schizophrenia	CB group art therapy program	0.68	-0.15-1.51	19.4
Kim and Kim[24]	Schizophrenia	Visuospatial rehabilitation	0.47	-0.27-1.21	24.2
Song *et al*[25]	Schizophrenia	CCP (RehaCom)	1.26	0.28-2.24	13.8
Total			0.96	0.59-1.32	100

CR: Cognitive rehabilitation; CB: Cognitive behavior; CCP: Computerized cognition program.

Table 4 Effect size of executive function

Study	Diagnosis	Intervention	Effect size	95%CI	Weight (%)
Iwata *et al*[22]	Schizophrenia	CR using computer software	0.22	0.09-0.35	71.2
Jung and Oh[23]	Schizophrenia	CB group art theraly program	0.28	-0.04-0.60	11.8
Kim and Kim[24]	Schizophrenia	Visuospatial rehabilitation	0.60	0.33-0.87	17.0
Total			0.29	0.18-0.40	100

CR: Cognitive rehabilitation; CB: Cognitive behavior.

Table 5 Effect size of depression

Study	Diagnosis	Intervention	Effect size	95%CI	Weight (%)
Kim[26]	Schizophrenia	CB group art therapy program	0.42	-0.04-0.89	0.4
Kim and Cho [27]	Schizophrenia	CB Program	0.38	0.09-0.68	1.0
Pijnenborg *et al*[28]	Psychosis	Social Cognitive Group Treatment	0.18	0.12-0.24	22.5
Salomonsson *et al*[29]	Mental Disorders	CB Therapy	0.29	0.24-0.33	40.3
Twamley *et al*[30]	Mental Illnesses	Compensatory CT	0.10	0.05-0.16	35.7
Total			0.20	0.17-0.23	100

CB: Cognitive behavior, CT: Cognitive training.

Table 6 Effect size of social skill

Study	Diagnosis	Intervention	Effect size	95%CI	Weight (%)
Hyun[31]	Schizophrenia	CB group therapy	0.41	-0.14-0.96	17.2
Iwata *et al*[22]	Schizophrenia	CR using computer coftware	3.01	2.25-3.76	9.2
Kim and Cho[27]	Schizophrenia	CB Program	1.91	0.95-2.86	5.7
Kingston *et al*[32]	Mental Illnesses	Cognitive skills program	2.48	1.95-3.02	18.2
Twamley *et al*[30]	Mental Illnesses	Compensatory CT	0.60	0.27-0.92	49.6
Total			1.21	0.98-1.43	100

CB: Cognitive behavior, CT: Cognitive training.

Table 7 Effect size of quality of life

Study	Diagnosis	Intervention	Effect size	95%CI	Weight (%)
Lee *et al*[33]	Psychosis	CBSS	0.45	0.40-0.50	60.4
Pijnenborg *et al*[28]	Psychosis	Socialcognitive group treatment	0.04	-0.03-0.10	38.7
Twamley *et al*[30]	Mental illnesses	Compensatory CT	0.96	0.53-1.38	0.9
Total			0.29	0.25-0.33	100

CBSS: Cognitive behavioral social skills, CT: Cognitive training.

memory, executive function, depression, sociability, and quality of life in the selected studies using a funnel plot, they were found to be generally symmetrical. It was determined that there was no significant bias (Figure 2).

DISCUSSION

As a result of confirming the effectiveness of cognitive rehabilitation for mentally ill patients through meta-analysis, it was identified as a very effective intervention method for concentration and memory among cognitive functions. It was also a very suitable arbitration law to improve sociality. In the future, the focus of clinical trials should be on improving concentration, memory, and social skills for mentally ill patients.

Based on the general characteristics of the 12 studies selected for analysis, the types of cognitive rehabilitation interventions were largely divided into cognitive behavior, cognitive training, cognitive rehabilitation, and computerized cognitive programs. In a previous study by Tomás *et al*[34], which analyzed cognitive rehabilitation, training programs for enhancing cognitive function, compensatory rehabilitation programs, and computer training programs were used as intervention methods. Other programs include remediation therapy and cognitive enhancement therapy, and compensatory rehabilitation programs include errorless learning and cognitive adaptation training. Additionally, Gradior, RehaCom, and the Neuropsychological Educational Approach to Rehabilitation were presented as computer training programs. The dependent variables that confirmed the intervention effect in this study were primarily cognitive functions, such as concentration, memory, and executive function, and secondarily included behavioral and psychological variables related to cognition, such as depression, sociality, and quality of life. This may be because cognitive rehabilitation therapy is a method of systematic intervention that improves cognitive function by setting specific cognitive functions, such as memory, concentration, executive function, activities of daily living, and social skills, as treatment goals. The number of studies for each variable included 3 to 5, and the literature proving the effect on depression was the highest, with 5 studies.

According to the results of the meta-analysis, the overall effect size of the 12 studies on cognitive rehabilitation treatment appeared normal. By variable, the effect size for cognitive rehabilitation treatment appeared in the following order: sociability, memory, concentration, executive function, quality of life, and depression. Taken together, our findings show that cognitive rehabilitation treatment has an overall positive effect on the cognitive function of patients with chronic mental illness, and it has been confirmed that it is particularly effective in sociability, memory, and concentration. This may have also affected the fact that schizophrenia was the most common condition among the 12 studies included in this meta-analysis. In general, patients with schizophrenia show improved processing speed, attention, working memory, verbal and visual learning and memory, and reasoning. It has been found to have various cognitive problems, such as reasoning, problem solving, and social cognition, but among them, it is said that they show remarkable difficulties in attention, memory, and executive function[35]. In the studies included in this analysis, the effectiveness of memory and concentration among cognitive functions was confirmed through repeated application of various cognitive trainings in

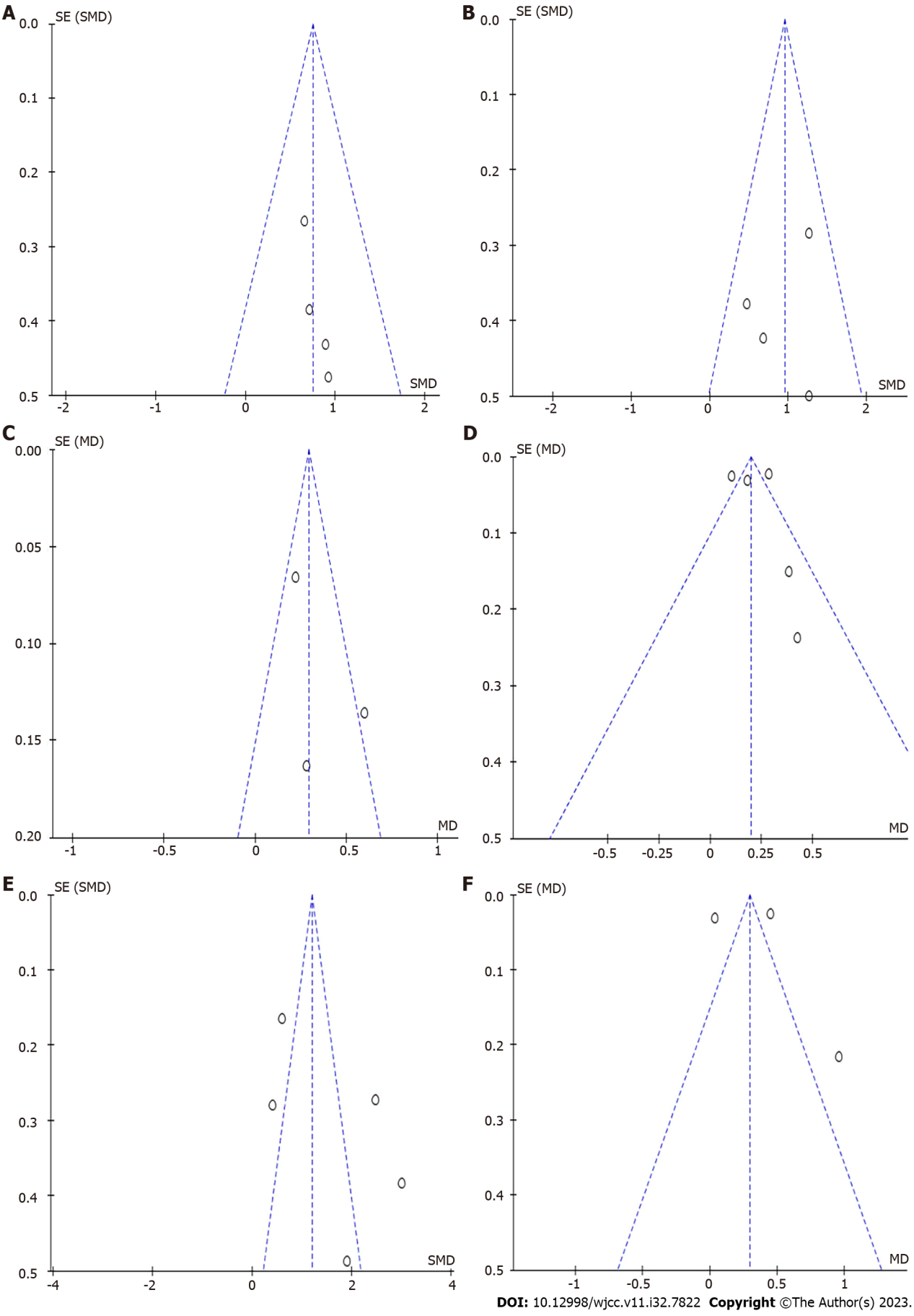

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Figure 2 Publication convenience. A: Attention; B: Memory; C: Executive function; D: Depression; E: Social skill; F: Quality of life.

the form of group and individual provisions. Studies applying social cognitive training were also included. It is thought to have a positive effect on psychological symptoms, such as sociality. According to Fett *et al*[36], social cognitive theory, rather than neurocognitive factors, is a better predictor of improvement in the quality of life of patients with schizophrenia, and social cognitive rehabilitation programs are more likely to improve social functioning than non-social cognitive rehabilitation programs. noted that there is a higher effect size. Therefore, future research should verify this by dividing it into social and nonsocial programs according to the type of intervention used for cognitive rehabilitation.

This study will provide basic data for the use of cognitive rehabilitation therapy for the purpose of improving function and alleviating symptoms of patients with chronic mental illness, and expanding the role of occupational therapy in the field of mental health. In the treatment of mental disorders, cognitive rehabilitation is mainly applied to patients with chronic mental disorders such as depression, anxiety disorders, schizophrenia, and alcoholism[10]. However, in the case of chronic mental illness, despite the fact that various factors affect symptoms, such as the type of disease, functional level of the subject, prevalence and treatment period, medication compliance, and family support[9], the selected studies were not included in this analysis. Owing to the limitations of the analysis, which provided limited information based on the data, various factors could not be fully considered. In addition, analysis of the effect size according to the evaluation tool or intervention type was insufficient. Additional studies that can address and supplement these limitations should be conducted in the future.

CONCLUSION

Through a meta-analysis, this study confirmed the effectiveness of cognitive rehabilitation therapy for improving cognitive function and alleviating behavioral and psychological symptoms in patients with chronic mental illness and confirmed which functions were mainly effective. Among the 12 articles, the level of evidence was that of randomized experimental studies. Intervention types for cognitive rehabilitation can be largely divided into cognitive behavior, cognitive training, cognitive rehabilitation, and computerized cognitive programs. Most of the subjects were studies on schizophrenia, and the measurement areas were cognitive functions such as concentration, memory, and executive function, as well as depression, sociability, and quality of life. The meta-analysis showed that cognitive rehabilitation treatment applied to patients with chronic mental illness was effective in improving cognitive function and, in particular, showed a large effect size on sociability and memory. The results of this study can be used as basic evidence to provide cognitive rehabilitation treatment for patients with chronic mental illnesses in the fields of mental health and occupational therapy.

ARTICLE HIGHLIGHTS

Research background

People suffering from chronic mental illness have cognitive impairment and inadequate cognitive processes. The effectiveness of cognitive rehabilitation was shown.

Research motivation

Previous studies on this topic have been largely limited to systematic reviews, and although some meta-analyses have been performed, generalizations are difficult due to limited interventions and targets, including computerized cognitive rehabilitation and patients with severe mental illness.

Research objectives

The effectiveness of cognitive rehabilitation according to each mental disease and symptom was investigated, and evidence data that can be applied in clinical practice were presented.

Research methods

We attempted to prove the effectiveness of cognitive rehabilitation in patients with chronic mental illness at home and abroad through a meta-analysis.

Research results

When cognitive rehabilitation was performed on patients with mental illness, a basis for intervention was established. The results of the study revealed that it is effective in improving memory and social skills. There is a need to further prove the effectiveness of variables such as memory and quality of life in the future.

Research conclusions

The meta-analysis showed that cognitive rehabilitation treatment applied to patients with chronic mental illness was effective in improving cognitive function and, in particular, showed a large effect size on sociability and memory.

Research perspectives

In the future, based on the results of this study, it should become the basis for interventions to improve social skills and

memory in patients with chronic mental illness. Additionally, the effectiveness of clinical interventions should be continuously verified based on these results.

FOOTNOTES

Author contributions: Jang JS wrote the overall paper; Kwon M wrote the introduction, discussions, and methods, and is responsible for general contact on the paper; Oh S, Lee N and Kim G revised and supplemented the manuscript, and wrote and edited the article on methods, results, and references; Song H, Park J, Lee Y, and Kim M edited and revised the manuscript.

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SCIENTOMETRICS

Emerging trends and hotspots of Nuclear factor erythroid 2-related factor 2 in nervous system diseases

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Abstract

BACKGROUND

The Nuclear factor erythroid 2-related factor 2 (NRF2) transcription factor has attracted much attention in the context of neurological diseases. However, none of the studies have systematically clarified this field's research hotspots and evolution rules.

AIM

To investigate the research hotspots, evolution patterns, and future research trends in this field in recent years.

METHODS

We conducted a comprehensive literature search in the Web of Science Core Collection database using the following methods: (((((TS=(NFE2 L2)) OR TS=(Nfe2 L2 protein, mouse)) OR TS=(NF-E2-Related Factor 2)) OR TS=(NRF2)) OR TS=(NFE2L2)) OR TS=(Nuclear factor erythroid2-related factor 2) AND (((((((TS=(neurological diseases)) OR TS=(neurological disorder)) OR TS=(brain disorder)) OR TS=(brain injury)) OR TS=(central nervous system disease)) OR TS=(CNS disease)) OR TS=(central nervous system disorder)) OR TS=(CNS disorder) AND Language = English from 2010 to 2022. There are just two forms of literature available: Articles and reviews. Data were processed with the software Cite-Space (version 6.1. R6).

RESULTS

We analyzed 1884 articles from 200 schools in 72 countries/regions. Since 2015, the number of publications in this field has increased rapidly. China has the largest number of publications, but the articles published in the United States have better centrality and H-index. Among the top ten authors with the most published papers, five of them are from China, and the author with the most published papers is Wang Handong. The institution with the most articles was Nanjing University. To their credit, three of the top 10 most cited articles were written by Chinese scholars. The keyword co-occurrence map showed that

"oxidative stress", "NRF2", "activation", "expression" and "brain" were the five most frequently used keywords.

CONCLUSION
Research on the role of NRF2 in neurological diseases continues unabated. Researchers in developed countries published more influential papers, while Chinese scholars provided the largest number of articles. There have been numerous studies on the mechanism of NRF2 transcription factor in neurological diseases. NRF2 is also emerging as a potentially effective target for the treatment of neurological diseases. However, despite decades of research, our knowledge of NRF2 transcription factor in nervous system diseases is still limited. Further studies are needed in the future.

Key Words: Nuclear factor erythroid 2-related factor 2; Nervous system diseases; Brain; Expression; Activation; Ferroptosis

Core Tip: In this paper, the research progress of nuclear factor erythroid 2-related factor 2 (NRF2) expression, activation, mechanism of action, and related targets in nervous system diseases is explored based on related articles published in the past decade. Oxidative stress plays a crucial role in their pathological process, and there have been many studies on the treatment of nervous system diseases based on oxidative stress targets. As a key factor against oxidative stress, NRF2 plays an important role in the nervous system. Through computational analysis of the literature, we will present the research hotspots and possible future research directions of NRF2 in the nervous system.

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INTRODUCTION

The physiology and pathology of the central nervous system are significantly influenced by oxidative stress[1]. Free radicals play a physiological role in neuroplasticity and communication in the healthy brain. However, an excessive buildup of free radicals can cause cell mortality and neurotoxicity[2]. Oxidative stress is an important target for the successful treatment of nervous system diseases[3]. The increased oxygen demand in the brain, the high concentration of polyunsaturated fatty acids, and the peroxidation of polyunsaturated fatty acids to create lipid peroxides all make the brain susceptible to oxidative damage. Additionally, compared to other organs, the brain has lower amounts of antioxidant enzymes[4]. Both acute and chronic inflammation interact with oxidative stress throughout the progression of nervous system diseases. Oxidative stress plays a significant role in the pathogenesis of nervous system diseases. Endogenous antioxidant protection mechanisms are numerous in cells. Among them, nuclear factor erythroid 2-related factor 2 (NRF2) mediates an important mechanism of cellular anti-oxidative damage. NRF2 is a basic leucine zipper (bZIP) cap 'n' collar transcription factor. NRF2 binds to the cytoplasmic Kelch-like epichlorohydrin-related protein 1 (Keap1) in the absence of oxidative stress, and in reaction to the E3-ubiquitin ligase complex, degrades and maintains low levels[5]. When the body is under oxidative stress, which includes proteotoxic stress and an excessive buildup of Reactive Oxygen Species (ROS) electrophilic molecules, NRF2 is released from the E3-ubiquitin ligase complex and moves into the nucleus. There, it forms a heterodimer with the small Maf protein (sMaf) and attaches to AU-rich elements (AREs) on DNA to regulate the expression of cytoprotective genes. A variety of cytoprotective genes, such as biotransformation enzymes, antioxidant proteins, drug transporters, anti-apoptotic proteins, and proteasome proteins, are synergistically activated by the NRF2/Keap1 pathway. Examples include glutamate cysteine ligase, Multidrug Resistance-associated Protein, Glutathione S-Transferase (GST), Quinone Oxidoreductase 1 (NQO1), Sulfiredoxin 1, and UDP-galactose translocator[6]. Therefore, mice lacking NRF2 are susceptible to various oxidative stress-related pathologies. NRF2 not only plays a role in maintaining proper Oxidation-Reduction (REDOX) homeostasis but also plays a role in metabolic pathways such as protein balance, iron/heme metabolism, carbohydrate and lipid metabolism, as well as apoptosis. NRF2 has also been demonstrated to regulate ferroptosis in recent years. Therefore, proper NRF2 function is essential for cell survival, particularly when oxidative or metabolic stress is increased.

NRF2 has seven highly conserved NRF2-ech homology (Neh) domains, each of which performs different functions[7]. The Neh1 domain has a conserved Cnc-bZIP motif that allows small Muscle aponeurotic fibrosarcoma (Maf) proteins or other transcriptional proteins to link NRF2 to form heterodimers, and the NRF2-Maf heterodimers can then bind to DNA sequences that encode downstream proteins. The Neh2 domain is rich in lysine, which is important for ubiquitin-binding because it contains two Keap1 binding sites, The two binding sites are the high-affinity ETGE motif and the low-affinity DLG motif, which contribute to the formation of the NRF2- Keap1 complex, so Neh2 also acts as a negative regulatory domain of NRF2. The C-terminal Neh3 region controls the transcriptional activation of ARE genes. The transcriptional activation regions include Neh4 and Neh5. It can interact with the nuclear hormone receptor transcriptional coactivator

AIB1, enhancing NRF2-ARE gene expression, and attach to co-activating cAMP response element binding protein, promoting NRF2 transcription[8]. In addition, a redox-sensitive Nuclear Export Signal in the Neh5 region regulates the intracellular location of NRF2. Neh6, a serine-rich domain with DSGIS and DSAPGS motifs, binds to proteins that contain Transduction Repetitions and serves as a substrate receptor for the E3 (substrate-specific ubiquitin ligase) complex, which is a negative regulator of NRF2 activity. The Neh7 region of NRF2 can bind to the Retinol X Receptor and prevent NRF2 transcriptional activation. With increasing research on NRF2-specific agonists, NRF2 is considered to be a potential drug target for the treatment of nervous system diseases. In recent years, research in this area has flourished. A method is needed to explore the research hotspot and progress of NRF2 in the nervous system. A time-varying map of research growth from its frontier to its knowledge base can be created using bibliometric analysis[9]. Our research seeks to provide accurate and understandable images of the evolution trends of research hotspots in this field using the bibliometric tool Cite-Space and to help researchers better comprehend research trends of NRF2 in nervous system diseases.

MATERIALS AND METHODS

Data collection

The Web of Science Core Collection (WoSCC) database was used to conduct a preliminary systematic screening of the literature. The following search method was used: TS = NFE2 L2 or TS = NFE2 L2 protein, mouse OR TS = NF-E2 associated factor 2 OR TS = NRF2 OR TS = NFE2L2 OR TS = nuclear factor erythroid 2 associated factor 2 and TS = AND TS = neurological diseases OR TS = neurological disorder OR TS = brain disorder OR TS = brain injury OR TS = central nervous system disease OR TS = CNS disease OR TS = central nervous system disorder OR TS = CNS disorder AND Language = English from 2010 to 2022. Articles and critiques were the only forms of literature allowed. To prevent the effects of database updates, all data collection was completed on October 4, 2022, in a single day. A total of 37 records, including conference abstracts, book chapters, proceedings papers, edited materials, corrected publications, and retracted publications, were removed from our collection of 1921 records. For further review and processing, data were imported into the Cite-Space program (version 6.1. R6). Figure 1 illustrates the recruitment approach.

Data analysis

Thirty-seven records, including conference abstracts, book chapters, proceedings articles, and edited books, were not included in our collection of 1884 records. The WoSCC database was used mainly for the analysis of publications per year, publication year, H-index, and subject category. The H-index obtained from WoSCC more correctly depicts academic achievement on an individual, national, or institutional level. A higher H-index shows a paper's, scholar's, or country's greater impact. Cite-Space software was used to evaluate the research institutions, nations, authors, keywords, and other relevant indicators. Authors, institutions, and contributing nations/regions were charted. In addition, phrase bursts, keyword cluster timelines, and co-occurring keywords were described. The nodes in the resulting maps correspond to particular projects like Countries, Institutions, keywords, and Authors. The quantity of literature increases with node size. Collaborative networks are represented by links between notes. The level of collaboration increases as the line becomes thicker. The significance of a node in the network is indicated by its centrality. Nodes with centrality numbers greater than 0.1 are typically thought to be more important. The greater the node's centrality and frequency of co-occurrence (Count), the more significant it is in the area. The present state of the research and its focus were determined using a keyword clustering timeline, co-occurring keywords, and highly cited literature. The keyword burst results are applied to look for new frontiers in this field and show a sharp rise in the heat of a particular research path over time.

RESULTS

Global trends in publication output

A total of 1884 articles, including 1621 articles and 285 reviews, were collected. After removing self-citations, 34995 articles were cited. The overall frequency of citations excluding self-citations was 46799. The average frequency of citations per article was 27.78 and the H-index was 91. The number of publications per year is shown in Figure 2. Before 2015, the number of articles issued per year did not reach 100; it grew rapidly from 2015, with 316 publications by 2021. The arc of growth increased significantly in 2020, and research in 2020 still focused on the anti-inflammatory and anti-oxidative stress of NRF2, which shows that NRF2 plays an important role in inflammation and oxidative stress. The main research fields included Neuroscience (585, 31.05%), Biochemical Molecular Biology (437, 23.20%), Pharmacology Pharmacy (381, 20.22%), Cell Biology 223, 11.84%), Medical Research Experimental (152, 8.07%), *etc.* The journals with the most published articles in this field were Oxidative Medicine and Cell Longevity (63, 3.344%), Frontiers in Pharmacology (44, 2.335%), Antioxidants (43, 2.282%), Molecular Neurobiology (37, 1.964%), and International Journal of Molecular Sciences (35, 1.858%). The National Natural Science Foundation of China (NSFC) provided funding for most research (517, 27.442%), followed by the United States Department of Health and Human Services (220, 11.677%) and the National Institutes of Health (NIH) United States (219, 11.624%) (Table 1).

Table 1 Top 5 research areas/journals/funding agencies according to the number of documents

Field		Record count (%)
Research areas	Neurosciences	585, 31.05
	Biochemistry Molecular Biology	437, 23.20
	Pharmacology Pharmacy	381, 20.22
	Cell Biology	223, 11.84
	Medicine Research Experimental	152, 8.07
Journals	Oxidative Medicine and Cellular Longevity	63, 3.34
	Antioxidants	43, 2.28
	Frontiers in Pharmacology	43, 2.28
	Molecular Neurobiology	37, 1.96
	International Journal of Molecular Sciences	35, 1.86
Funding agencies	National Natural Science Foundation Of China	517, 27.44
	United States Department Of Health Human Services	220, 11.68
	National Institutes Of Health United States	219, 11.62
	National Institute Of Neurological Disorders Stroke Ninds	81, 4.30
	European Commission	61, 3.24

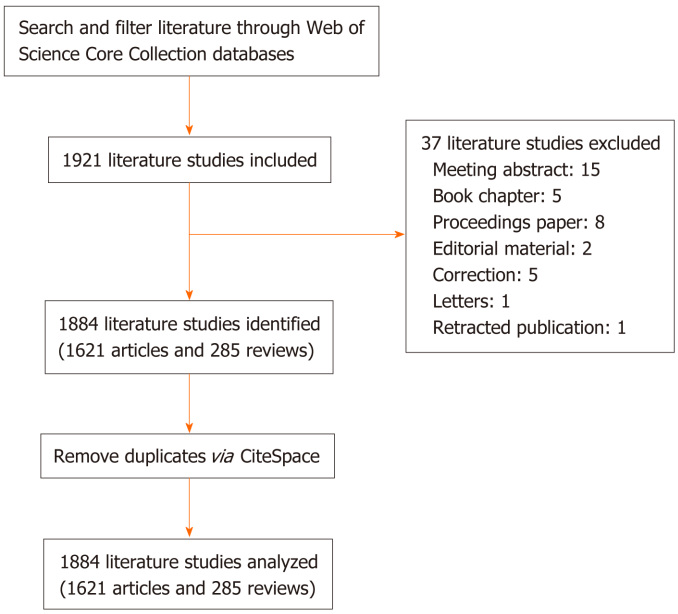

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Figure 1 Schematic for reviewing literature. One day was dedicated to data collection. (04 October 2022). The Web of Science Core Collection database yielded 1921 entries in total. 37 articles were then removed, including conference abstracts, book chapters, proceedings papers, edited materials, revised publications, and publications that had retracted earlier versions. 1884 statistics were ultimately collected. For further research, data were imported into Cite-Space software (version 6.1. R6).

Contribution of countries and institutions

Researchers from 200 institutions and 72 countries/regions took part in this study. According to Table 2, which lists 67 countries/regions, China (972, 51.592%), the United States (384, 20.382%), South Korea (106, 5.626%), Italy (87, 4.618%), and India (71, 3.769%) contributed most articles. The results and connections between the nations are shown in Figure 3. According to the connections shown in this figure, there is little cooperation between countries. As the largest country with the greatest number of articles published, China has less close cooperation with other countries. The number of articles published is related to the node size. The node's purple exterior circle reveals that its centrality is greater than 0.1, indicating that it is an important node in the network. Although China leads in the number of articles published, its

Table 2 Top 5 countries and institutions in terms of the number of documents

Field		Record count (%)	Centrality
Countries	China	972, 51.59	0.14
	United States	384, 20.38	0.78
	South Korea	106, 5.63	0.11
	Italy	87, 4.62	0.12
	India	71, 3.77	0.06
Affiliations	Nanjing University	53, 2.81	0.18
	Fourth Military Medical University	41, 2.18	0.06
	Nanjing Medical University	32, 1.70	0.04
	China Medical University	31, 1.65	0.06
	Chongqing Medical University	29, 1.54	0.01

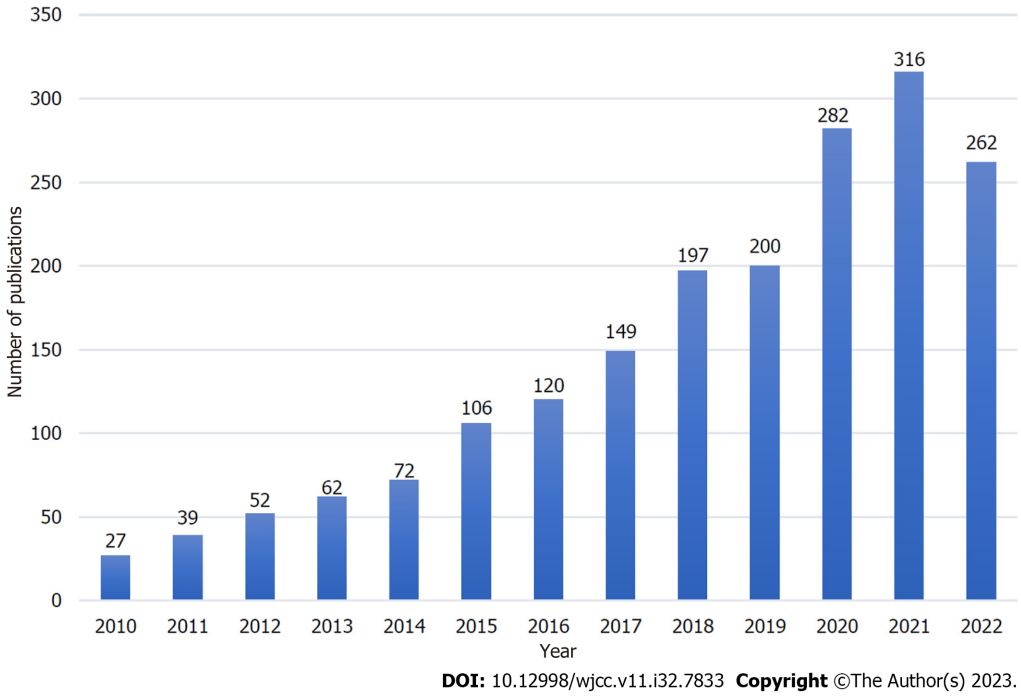

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Figure 2 Publications by year (2010-2022).

centrality is lower than that of the United States, indicating that the latter is more significant in cooperative networks. The annual number of publications are shown by nation in Figure 4. The leading five institutions are depicted in Table 2 and Figure 5, and are as follows: Nanjing University (53, 2.813%), the Fourth Military Medical University (41, 2.281%), Nanjing Medical University (32, 1.804%), China Medical University (31, 1.645%), and Chongqing Medical University (29, 1.539%). Surprisingly, the top five institutions with the largest number of publications are all from China, indicating that despite the relative lack of cooperation between China and other countries, China's output in this field cannot be ignored. Figure 5 shows only 489 links and 394 nodes indicating that there is a lack of cooperation between institutions.

Authors and co-cited authors

A total of 8482 authors were involved in the study of NRF2 function in nervous system diseases. Supplementary Table 1 lists the five most productive authors, including Handong Wang (Nanjing University, Count 39), Dore, Sylvain (Nagoya University, Count 11), Cucullo, Luca (Texas Tech University, Count 11), Ding Ke (Nanjing University, Count 10), and Aschner, Michael (Albert Einstein College of Medicine, Count 9). Of these, two authors were from China. The second most published author began to publish papers in 2015 and continued to produce papers in recent years. Figure 2 shows that the number of articles has been steadily increasing over the years.

When a paper cites two or more authors simultaneously, these two or more authors are part of a network of co-cited authors. Twenty-five of the 754 co-cited authors were cited more than 100 times. The most frequently referenced co-cited

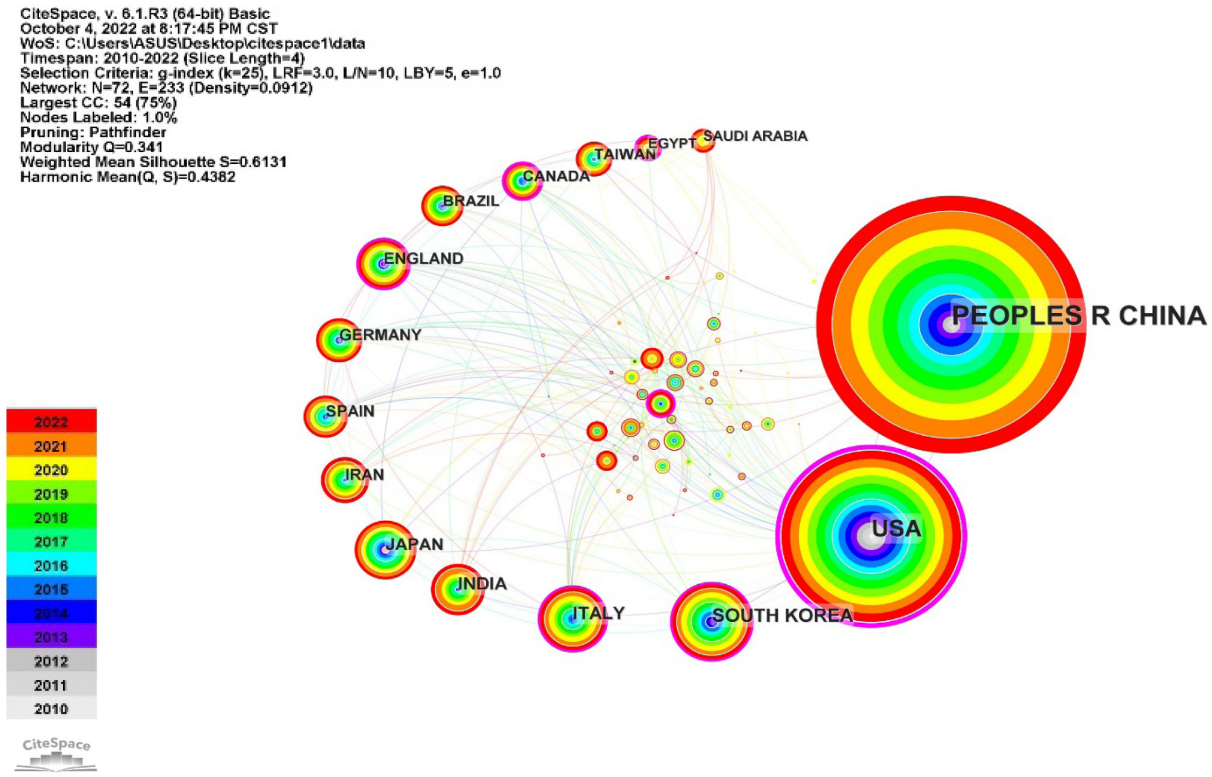

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Figure 3 Publications by country. The quantity of articles is indicated by the node size. The quantity of articles published by a nation is shown by an increase in node size. The top 20 publishing-producing nations are depicted in the graph. China tops the chart, followed by the United States, South Korea, Italy, Japan, India, Ireland, Spain, Germany, and the United Kingdom in clockwise order. The collaboration between various nations is represented by lines between nodes.

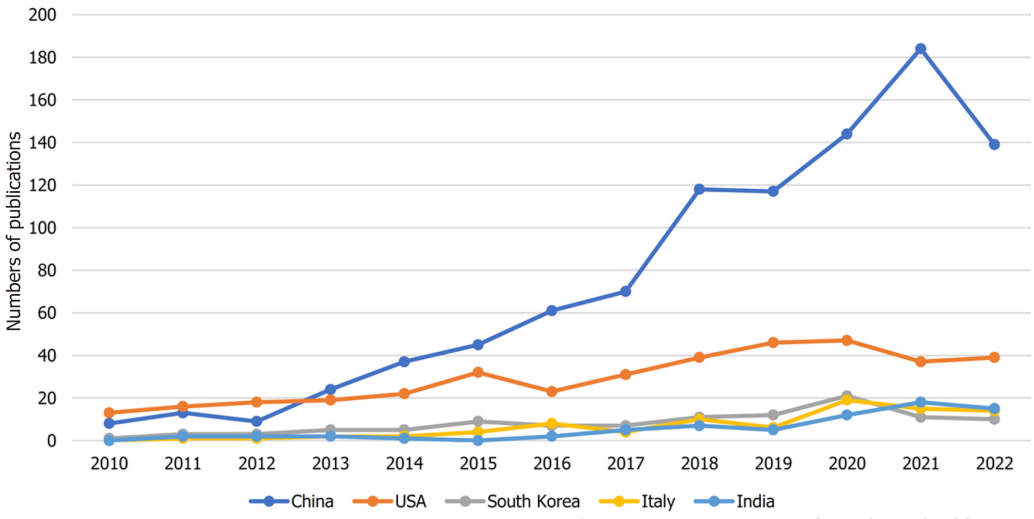

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Figure 4 The number of publications by each of the five nations each year. China, the United States, South Korea, Italy, and India were the five countries with the most articles released. Estimation of the annual quantity of publications in each of these five nations. Different hue lines denote various countries.

author was SHIH AY (186), followed by ITOH K (272) (Supplementary Table 1). The top 20 co-cited authors are shown in Figure 6, which demonstrates the writers' tight cooperation.

Research areas and frontiers

The top 10 highly cited literature: The term "highly cited literature" refers to works that have received numerous citations and have significant influence, highlighting the importance and breadth of research in this field. Supplementary Table 2 lists the top 10 most popular articles on NRF2 research in nervous system diseases from 2010 to 2022. Two of them were published in 2015. Furthermore, Figure 1 shows that there has been a steady increase in the literature

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Figure 5 Institutional publications. The quantity of articles is indicated by the node size. The quantity of articles increases with node size. Nanjing University produced most papers, followed by Fourth Military Medical University, Nanjing Medical University, China Medical University, and Chongqing Medical University. Additional nations are displayed in a counterclockwise sequence. The cooperation between various institutions is represented by lines between the nodes.

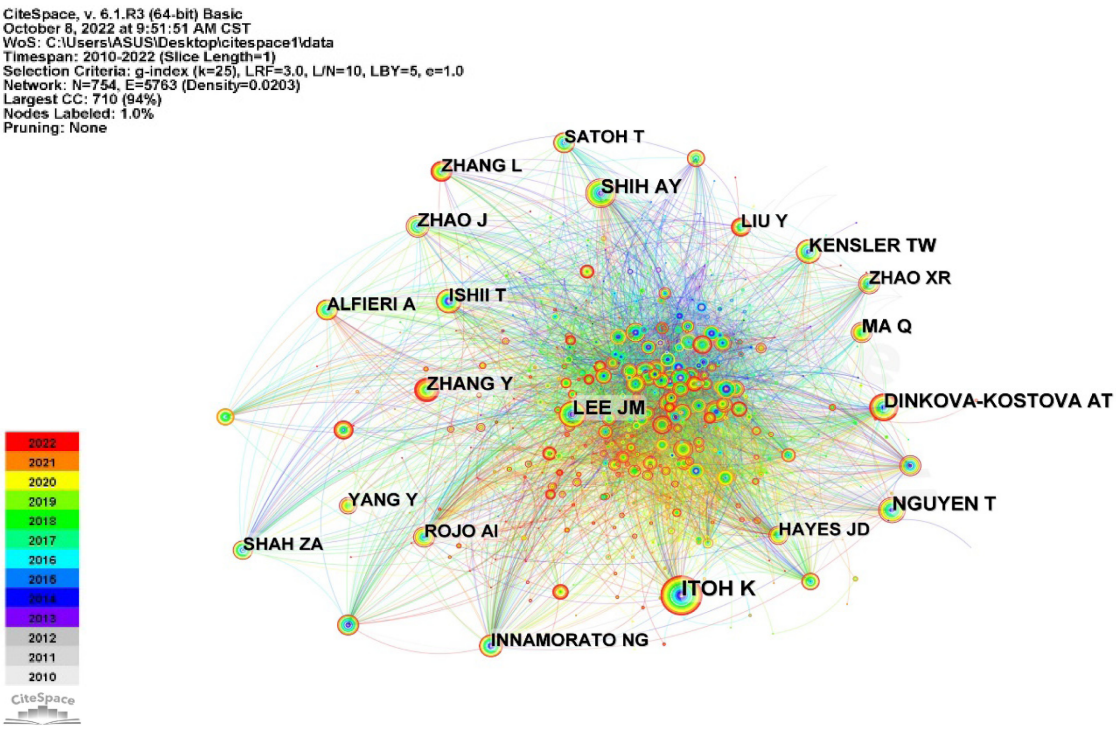

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Figure 6 Network of co-cited authors. Co-cited authors are represented by nodes. The number of citations is indicated by the size of the node. Collaboration between authors is represented by lines connecting nodes.

on this topic since 2015. It can be seen that these two articles in 2015 have a profound impact on subsequent studies. Two articles in 2015 investigated the molecular crosstalk between NRF2 and the nuclear factor-kappa B (NF-κB) pathway and the interaction between NRF2 and autophagy and the molecular regulatory mechanism, respectively. In these ten papers, Sies, H, and colleagues ranked first in the article published in the journal Nature Reviews Molecular Cell Biology with a high number of 1015 citations, This paper shows that physiological doses of ROS play a central role in REDOX signaling, but when the body is under pathological attack, excessive accumulation of ROS can aggravate the pathological process. This article also highlights the important function of NRF2 in the antioxidant system. The second and seventh-ranked articles discuss the role of NRF2 in neuroinflammation and neuroprotection, indicating that NRF2 not only plays a role in oxidative stress but also has an essential role in neuroinflammation. The fourth and fifth-ranked articles discuss the role of NRF2 in various chronic neurological and immunological diseases. These findings suggest that researchers have had a strong interest in the targets of NRF2 in the pathology of neurological diseases over the past decade.

Co-occurrence of keywords

The frequency of keyword co-occurrence in the literature is the basis for the keyword co-occurrence graph. When two or more keywords appeared in the same text, they were considered to be co-occurring. Keyword co-occurrence analysis was used to identify research hotspots and predict future research trends. High-frequency keywords are displayed in Table 3. The top 10 co-occurring keywords were Oxidative Stress (1140), NRF2 (503), Activation (400), Expression (327), Brain (271), Stroke (265), NF-κB (206), Alzheimer's Disease (195), and Pathways (192). We have created a keyword co-occurrence network figure to aid comprehension (Figure 7). NRF2 is involved in regulating the pathological processes of many central nervous system diseases, such as: "multiple sclerosis", "Alzheimer's disease", "Parkinson's disease", "stroke", and "traumatic brain injury". NRF2 is closely associated with several pathophysiological processes, as shown by the Keyword Co-Occurrence Map, such as: "apoptosis", "cell death", "inflammation", " neuroprotection "and "oxidative stress". Similarly, the focus of research in the past decade has been on the neuroprotective effects of NRF2 and its mechanism of action after activation of the corresponding signaling pathways. NRF2 may be the target of many antioxidants. The NRF2 pathway also has much crosstalk with other pathways, including but not limited to the NF-κB pathway.

Keyword clustering timeline and keyword burstiness

The grouping based on keyword relevance is called keyword clustering. "Multiple sclerosis", "subarachnoid hemorrhage", "heme oxygenase-1", "carnosic acid", "major depressive disorder", "blood-brain barrier", and "metabolism" are the seven clusters that are produced. The largest cluster in Cite-Space is Cluster 0, and the second largest cluster is Cluster 1. Keyword clustering timelines are created when drawing clusters (Figure 8). The timeline view presents the year in which keywords appeared in each cluster. The horizontal solid line which is the length of each point represents the time range in which it appeared. The timeline view is used to follow the development of research trends and visually displays the historical scope of the literature. We further used Cite-Space to draw a keyword citation burst map (Figure 9), in which the blue line indicates the cycle. The red line indicates the duration of the keyword and shows the progress of the hot topic. As shown in Figure 9, keywords with strong burst strength included the following, among which "heme oxygenase 1" (12.35) was the most intense, followed by "Gene Expression" (9.92), "*In Vivo*" (6.71) and "Antioxidant Response Element" (6.70) ". The keywords with longer duration were "Heme oxygenase 1" (2010-2016) "Arterial Occlusion" (2011-2017) and "Protection" (2011-2017), demonstrating that scholars have given these investigations a lot of thought. "Neuronal apoptosis" (2019-2020) and "goal" (2020-2022) have emerged as prominent keywords in recent research, indicating that more and more attention has been paid to its importance as a therapeutic target for diseases.

DISCUSSION

Study trends

Figure 2 shows that there has been an increase in the number of studies in this field since 2015. It is also evident from Supplementary Table 2 that the most cited literature was published in the journal Molecular Sciences for Natural Review in 2020, with an impact factor of 94.44. It can be seen that in recent years NRF2 has aroused great interest in researchers. Therefore, it is foreseeable that the number of articles on NRF2 will continue to grow after 2020, and this will broaden the depth and breadth of research in neurological diseases. From Table 2, it can be seen that in terms of the number of publications, China, the United States, South Korea, Italy, and the United Kingdom are the top five contributors. It is noteworthy that nearly half (985/1884) of the papers published on this topic were from China. The top five institutions with the largest number of articles published were from China, which were Nanjing University, the Fourth Military Medical University, Nanjing Medical University, China Medical University, and Chongqing Medical University. Authors with the largest number of articles published were also from China. Thus, China has contributed a large number of articles. The funding support for most research was from the NSFC. This suggests that high-yielding authors, important countries, institutions, and investment funds are all consistent. Thanks to significant financial support, a solid academic climate at top schools and universities, and a high author output, since 2013, China has surpassed the United States in terms of publication quantity and has consistently maintained its dominant position (Figure 4). Although the United States ranked second in the total number of publications, it ranked first in the H-index, outperforming China. In addition, although Chinese authors account for three of the top ten cited literature, they rank low. A possible reason for the lack of influence of Chinese research articles is that their research started late. This means that Chinese researchers still have great potential in this area of research, and should intensively study this research field to enhance their influence. Moreover, China has less cooperation with other countries (Figure 3). This echoes its small influence and may later

Table 3 Frequency of keyword co-occurrence (top 25 counts, 2010–2022)

Keywords	Count	Centrality
Oxidative stress	1140	0.01
NRF2	473	0.00
Activation	400	001
Expression	327	0 01
Brain	271	0 03
Stroke	265	0.02
Nf kappa B	206	0.02
Alzheimer's disease	195	0.02
Pathway	192	0.02
Apoptosis	187	0.02
Protect	186	0.02
Injury	186	003
Inflammation	169	0.03
Mechanism	168	0.02
Cell	152	0.01
Traumatic brain injury	147	0.03
Damage	143	0.02
Model	141	0.03
Heme oxygenase 1	132	0.03
Brain injury	132	0.03
Parkinson's disease	129	10.01
Antioxidant	129	0.00
Signaling pathway	124	0.01
Mouse model	119	0.04
Rat	116	0.03

NRF2: Nuclear factor erythroid 2-related factor 2.

promote its research depth and breadth by increasing cooperation with other countries. In contrast, there are fewer articles published in the United States, the United Kingdom, Canada, and Egypt, but cooperation with other countries is closer and the influence is higher, indicating that cooperation is very important.

Study focus and frontiers

According to the keyword burst diagram (Figure 9), researchers focused on the relationship between NRF2 and heme oxygenase-1 in central nervous system diseases before and after 2010, as well as the antioxidant mechanism as a transcription factor *in vivo* and the expression and activation of related signaling pathways. Therefore, keywords that appeared more frequently during this period included "oxidative stress", "activation", "expression", "nf kappa b", "pathway", "apoptosis", "inflammation", and "mechanism". It can be seen that the enthusiasm for the study on its mechanism and other pathway crosstalk only increased in the following years and the appearance of "iron" in the keywords in 2017 heralds its close connection with ferroptosis in the future. In recent years, researchers have paid more attention to the feasibility of NRF2 as a target for the treatment of central nervous system diseases. Among the many targets, apoptosis has attracted the attention of researchers. However, it can be found that attention to apoptosis began to decline after 2020, whether the reason for this phenomenon is due to researchers paying more attention to its role in iron metabolism is unclear, but what is clear is that recent studies have found that NRF2 plays a key role in iron metabolism. Currently, NRF2 is being extensively studied in central nervous system diseases such as Alzheimer's disease (AD), Parkinson's disease, hemorrhagic/ischemic stroke, and other diseases. Studies have shown that its ability to reduce inflammation and oxidative stress is the main mechanism of action in treating neurological diseases. The Keyword co-occurrence map (Figure 7) leads to similar conclusions. Molecular biology, pharmacology, cell biology, and other fields are included in the research direction of NRF2 as indicated in Table 1, which also represents the potential clinical utility of

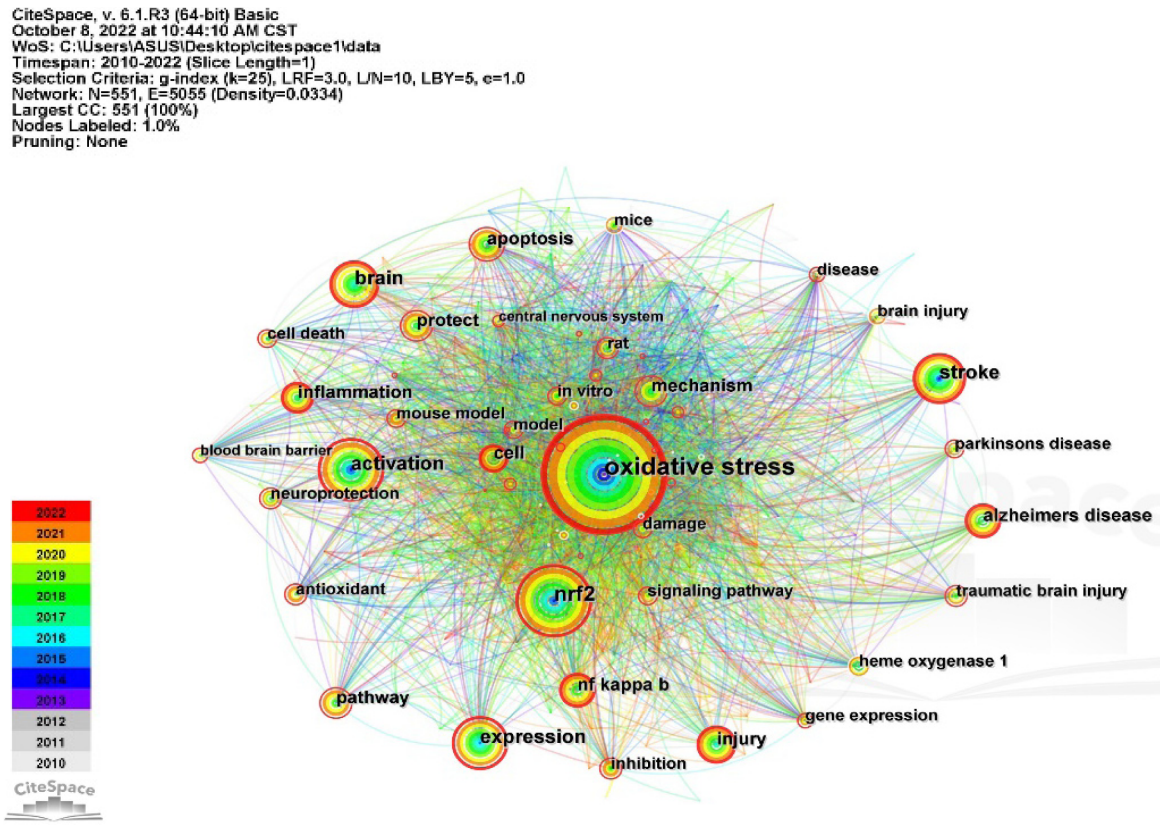

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Figure 7 Co-occurrence network of keywords. The number of keywords is indicated by the node size. Multiple sclerosis, Alzheimer's disease, Parkinson's disease, stroke, and traumatic brain injury are the top 8 comorbid keywords. The primary disorders linked to nuclear factor erythroid 2-related factor 2 (NRF2) are depicted in the right side of the diagram, including "Alzheimer's disease," "stroke," "traumatic brain injury," and "Parkinson's disease." Apoptosis, neuroprotection, and inflammation are some of the key terms associated with the mechanism of NRF2 activation that are depicted on the left side of the figure.

investigating NRF2. Traditional Chinese medicine (TCM) has the characteristics of multi-target treatment. Following further reading of the literature searched, we found that many studies involved research on TCM, and some studies discussed the efficacy of sulforaphane in the treatment of diffuse axonal injury and its ability to reduce oxidative stress. These studies revealed that sulforaphane reduced oxidative stress by activating the NRF2/heme oxygenase 1 (HO-1) pathway to reduce ROS generation and activate antioxidant factors such as superoxide dismutase (SOD) and GPX. They also found that sulforaphane prevented brain injury by inhibiting apoptosis by activating the NRF2/HO-1 pathway[10]. In addition, in diabetic patients, curcumin reduced urinary albumin excretion in type II diabetic patients by inhibiting inflammatory signaling through activating the NRF2 signaling pathway, demonstrating that curcumin alleviated the progression of diabetic nephropathy by activating the NRF2 antioxidant system in T2DM patients[11]. These experiments further revealed the regulatory effects of TCM on oxidative stress, inflammation, and apoptosis by regulating NRF2 signaling, which is shown in Figure 7.

The importance of NRF2 in regulating ferroptosis

Ferroptosis is a type of regulatory cell death, and the accumulation of iron ions and lipid peroxides are essential conditions for ferroptosis. Increases in lipid peroxides are dealt with by a range of defense mechanisms in cells, including glutathione and enzymes that use glutathione. Free iron accumulation and peroxidation of polyunsaturated fatty acids are regarded as "markers of ferroptosis". The role of glutathione peroxidase in the regulation of ferroptosis cannot be ignored, especially glutathione peroxidase 4, which catalyzes the reduction of lipid peroxides to lipid alcohols and inhibits ferroptosis. During iron metabolism, the light and heavy chains of the key iron storage protein ferritin (FTL/FTH1), as well as the Ferroportin responsible for iron efflux cells, are controlled by NRF2[12]. In addition, enzymes associated with heme synthesis and metabolism have also been shown to be up-regulated following NRF2 activation, such as heme oxygenase 1 (HMOX1, a key enzyme in heme synthesis), Ferrochelatase, and adenosine triphosphate (ATP) Binding Cassette Subfamily B Member 6, and heme transporter Solute Carrier Family 48 Member 1[13]. During glutathione anabolism, the catalytic and regulatory subunits of glutamate-cysteine ligase (GCLC/GCLM), glutathione synthase, and Solute Carrier Family 7 Member 11 (SLC7A11) have all been shown to be downstream gene products of NRF2, and these subunits are necessary for glutathione synthesis[14]. This suggests an important link between NRF2 function and ferroptosis-related molecules. This echoes "iron" and "cell death" in the keywords. Further studies should explore the effect of drugs on the NRF2 signaling pathway in multiple dimensions, as well as the effects of related drugs targeting this pathway on the ferroptosis of nerve cells and clinical outcomes of nervous system diseases.

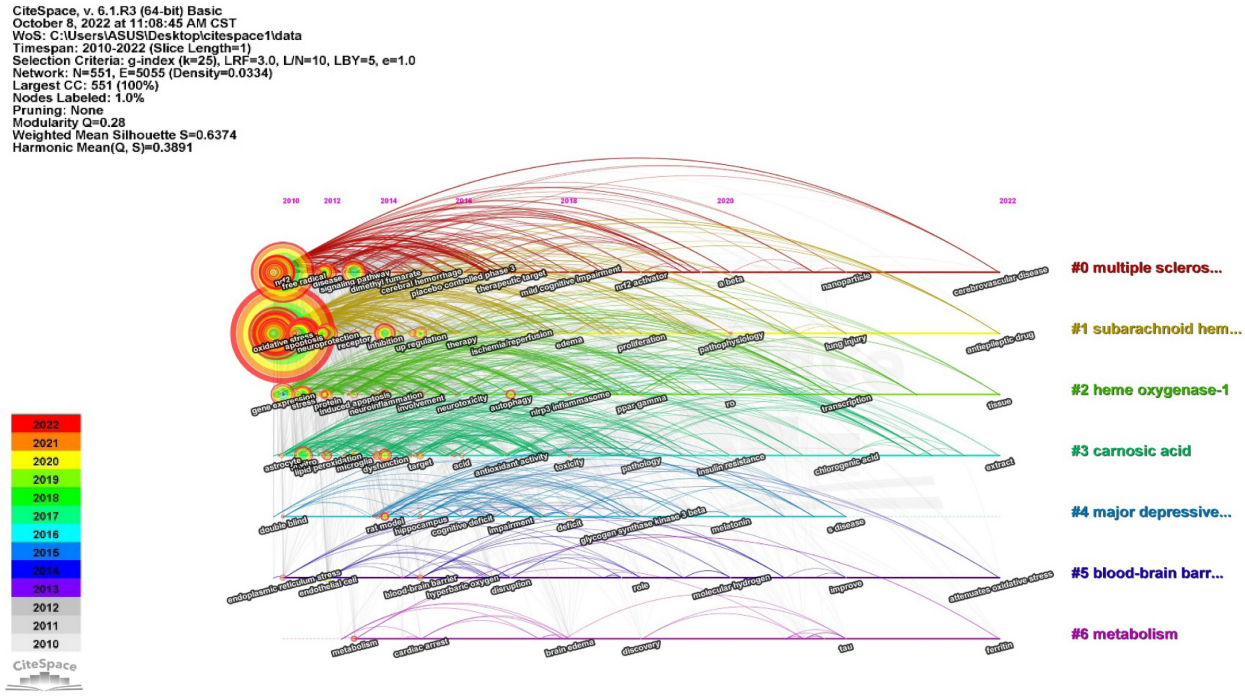

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Figure 8 Timeline analysis with keyword clustering (2010-2022). Eight clusters altogether, each identified by a unique color. The biggest cluster is cluster 0, then cluster 1, and so on. The keywords contained in the cluster are spread out by this timeline map as it forms. The label color of the cluster to which a keyword belongs is the same as that of the cluster.

Role of NRF2 in regulating autophagy

The term "Autophagy" was frequently mentioned, appearing up to 40 times. Autophagy is an important biological process for cells to achieve self-repair and control cellular homeostasis. Autophagy eliminates short-lived or improperly folded proteins, lipid droplets, and damaged organelles, and is important in cell development, metabolism, and defense against oxidative stress[15]. The autophagy pathway is typically split into three distinct types: Macroautophagy, chaperone-mediated autophagy (CMA; occurring only in mammals), and microautophagy, depending on how substances are delivered to lysosomes for degradation[16]. The most characteristic form of autophagy is macroautophagy (hereafter referred to as "autophagy"). Autophagy forms characteristic autophagosomes, which are composed of double-membrane structures enclosing cytoplasmic components. The autophagosomes then fuse with lysosomal membranes and are degraded by hydrolytic enzymes. Under nutrient deprivation, autophagy is activated, providing amino acids and ATP [17]. Large numbers of prostacyclin 62 (P62) aggregates are produced in the cytoplasm as a result of the transcription of autophagy-related gene P62 which is activated by oxidative stress, metabolic issues, and illness. P62 directly interacted with Keap1 to activate NRF2, aggregates of p62 maintain chronic activation of NRF2, and p62 induces permanent destruction of Keap1 in the specific autophagy pathway. As a result, the NRF2 signaling pathway is activated, which causes the transcription of genes encoding antioxidant enzymes to increase[18]. Additionally, intranuclear NRF2 encourages p62 gene overexpression and creates the p62-Keap1-NRF2 positive feedback axis, which leads to persistent NRF2 activation. In addition, NRF2 can promote autophagy. The autophagy-related genes Autophagy Related Protein 5 (ATG5) and Microtubule-associated protein 1 Light chain 3 beta (MAP1 LC3B), whose promoters are located in ARE nucleotide sequences, are upregulated when NRF2 is translocated into the nucleus in large quantities. This is accomplished by binding to ARE through small MAFs proteins and increasing the expression of ATG5, p62, and Microtubule-Associated Protein 1 Light Chain 3 (LC3B) proteins[19]. Recent studies have shown that NRF2 binds to ARE and can also induce the expression of the proteasome, and autophagy-related genes gastrin 2 and p62[20], and Sestrin2 can activate autophagy by inhibiting the expression of mTORC1. Therefore NRF2 can directly or indirectly trigger selective autophagy. In summary, there is a reciprocal regulatory relationship between the NRF2 pathway and autophagy through the p62-Keap1-NRF2 positive feedback loop[21]. At present, *in vivo* studies have found crosstalk between NRF2 and autophagy[22], but there is no relevant clinical data, which proves that research in this area has great potential.

Role of NRF2 in ischemic stroke

It can be seen on the right of Figure 7 that stroke occupies a very high position in the keyword co-occurrence map. Analysis by Cite-Space software showed that its occurrence frequency was up to 265 times, which also demonstrated the researchers' attention to the role of NRF2 in stroke. Ischemic stroke is marked by a sudden reduction or termination of cerebral blood flow in a specific brain region. The major ischemia-induced metabolic alteration is an insufficient level of ATP, as the brain's energy source is primarily glucose metabolism, the brain relies heavily on blood-derived glucose and oxygen to maintain the normal function of glycolysis, the tricarboxylic acid cycle, and the mitochondrial electron transport chain[23], hypoxia is particularly harmful to neurons. Although rapid reoxygenation *via* reperfusion is an

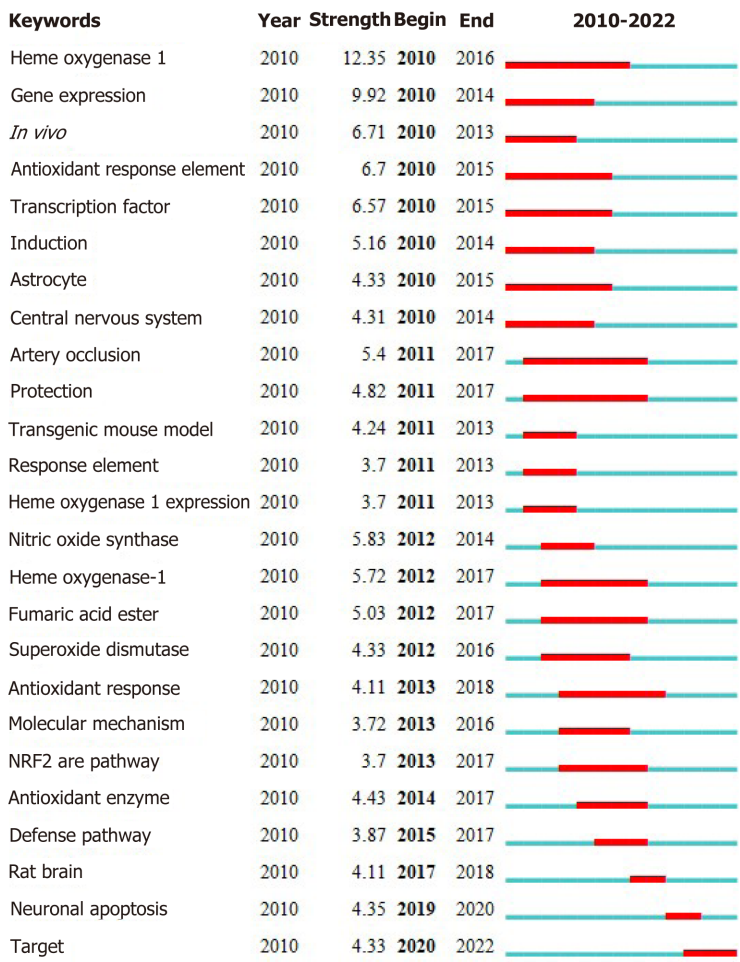

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Figure 9 Top 25 terms with the most citations. Burst data indicate an increase in citations for particular keywords over time. In other words, research in this area has received a lot of attention. This is a sign of the state of the scientific frontier at any given time. Blue lines indicate cycles and red lines indicate the duration of citation bursts. Numbers in parentheses represent higher burst strength values.

essential step to alleviate metabolic stress in ischemic stroke, reperfusion may also contribute to the generation of ROS [24], thereby exacerbating ischemia-reperfusion oxidative damage. On the other hand, increased levels of ROS following ischemia-reperfusion can up-regulate NRF2[25] and promote NRF2 downstream protein expression to mitigate the deleterious effects of excess oxidants following cerebral ischemia-reperfusion. Studies have shown that NRF2 knockout animals (NRF2 $^{-/-}$) are more likely to develop cerebral ischemic stroke after NRF2 downregulation, and the expression of cytoplasmic Thioredoxin interacting protein (TXNIP)-NOD-like receptor protein 3 inflammasome (NLRP3) and downstream elements caspase-1, interleukin-18 and interleukin-1β (IL-1β) are significantly increased[26]. At present, it is recognized that the NLRP3 inflammasome-mediated inflammatory cascade can lead to brain edema, bleeding, blood-brain barrier injury, and more neuronal death; thus, RF2 can be used as a protective mediator of NLRP3 inflammasome activation. In a randomized controlled clinical trial, patients with ischemic cardiomyopathy were randomly divided into a soybean isoflavone treatment group and a control group. It was found that soybean isoflavones significantly increased the levels of NRF2 and SOD, and decreased the levels of serum C-reactive protein, 8-isoprostane, malondialdehyde, IL-6 and tumor necrosis factor-α (TNF-α). Therefore, its clinical therapeutic effect was confirmed[27]. The *in vivo* and *in vitro* experimental studies of NRF2 in ischemic stroke are now relatively mature[28]. Although some progress has been made, there is still a lack of clinical trials. The above clinical trials based on the cardiovascular system may provide encouragement and inspiration to researchers, to facilitate people to better study the role of NRF2 targets in the clinical treatment of ischemic stroke.

Role of NRF2 in hemorrhagic stroke

NRF2 has also been shown to affect hemorrhagic stroke such as cerebral hemorrhage and subarachnoid hemorrhage (SAH). Following analysis using Cite-Space software, it was found that the two keywords "intracerebral hemorrhage" and "subarachnoid hemorrhage" appeared 65 times and 49 times, respectively, and the frequency of their occurrence was very high. As shown in Figure 8, among the 7 clusters generated, SAH occupied the second largest cluster, which was sufficient to determine the important role of NRF2 in hemorrhagic stroke. Intracerebral hemorrhage is a common clinical nervous system disease, which refers to the primary non-traumatic rupture of blood vessels in the brain parenchyma, and accounts for 15% to 30% of strokes and 20% to 30% of sudden brain deaths. It is currently a cerebrovascular disease[29].

Studies have shown that Isoliquiritigenin relieves early brain injury after experimental intracerebral hemorrhage by promoting the NRF2 antioxidant pathway to inhibit ROS or NF-κB-mediated NLRP3 inflammasome activation. NRF2 on the other hand, boosts the expression of anti-oxidant genes while lowering the expression of pro-inflammatory genes[30]. Dexmedetomidine inhibits neuroprotection by inhibiting neuronal apoptosis in rat brain tissue by activating the NRF2/HO-1/NQO1 signaling pathway in a rat intracerebral hemorrhage model[31]. Mitophagy driven by NRF2/Optineurin (OPTN) prevents intracerebral hemorrhage-induced NLRP3 inflammasome activation[32]. Through the Extracellular regulated protein kinases (ERK)/NRF2/HO-1 pathway, albumin lowers oxidative stress and neuronal apoptosis following intracerebral hemorrhage in rats[33]. Through the Sirtuin-3 (Sirt3)/NRF2/HO-1 pathway, intermittent fasting decreases neuroinflammation in intracerebral hemorrhage[34]. Aneurysmal subarachnoid hemorrhage (aSAH) is a very dangerous and devastating cerebrovascular event that has a mortality rate as high as 50%[35]. aSAH is associated with a greater social and medical burden than ischemic stroke, and patients with this disease have a lower quality of life[36]. In the SAH model, NRF2 agonist RTA408 reversed vasospasm by increasing the expression of NRF2 and decreased the expression of the cytokine TNF-α and apoptosis-related protein caspase-3 to exert neuronal protection[37]. Luteolin further inhibits the NLRP3 inflammasome signaling pathway by activating NRF2 to produce neuroprotection in mice with SAH[38]. A multicenter, randomized, double-blind, placebo-controlled clinical trial has confirmed the efficacy of SFX-01 (Evgen Pharma) in patients with SAH. SFX-01 is a novel compound consisting of α-cyclodextrin and sulforaphane that releases sulforaphane after human intake. It acts on the NRF2 signaling pathway to provide sulforaphane for SAH patients and improve their condition[39]. These experiments are sufficient to illustrate that NRF2 may be a potential therapeutic target for cerebral hemorrhage and SAH.

Role of NRF2 in multiple sclerosis

Figure 8 shows that among the seven clusters generated, multiple sclerosis (MS) was the largest cluster, showing that the research on NRF2 in MS is very hot. MS is an autoimmune disease of the central nervous system, characterized by axonal damage, demyelination, and chronic inflammation. By oxidizing lipids, proteins, and DNA, oxidative stress directly adds to demyelination and neurodegeneration. The Keap1-NRF2 signaling pathway, which is a master regulator of antioxidant and phase II detoxification genes, governs many of the functions of this tightly regulated network. This pathway has significant promise for use in the treatment of MS as it also plays a crucial role in inflammation. Autopsy studies in MS patients have shown elevated expression of NRF2 and the NRF2-responsive genes HO-1 and NQO-1 in and around the injured brain and spinal cord[40]. Experimental autoimmune encephalomyelitis (EAE) models and copper ion models are two frequently used MS animal models. NRF2 and its downstream target proteins were observed to increase after 1 to 3 wk of copper ion treatment and to decrease after 5 wk in the copper ion model[41]. This suggests that NRF2 is activated early in the disease but suppressed as the disease develops. Withametelin has significant neuroprotective potential in EAE mouse MS models by modulating NRF2-mediated oxidative stress in EAE models[42]. There are also many clinical trials related to the NRF2 agonist dimethyl fumarate (DMF) in the treatment of MS[43-47], and the efficacy of DMF in the treatment of MS has been certified by the European Medicines Agency. Since the European Medicines Agency approved the NRF2 activator DMF (brand name Tecfidera®) for the treatment of remission-relapse MS, the pharmaceutical industry's interest in NRF2 as a pharmacological target for other diseases has also increased[48].

Role of NRF2 in Alzheimer's disease

As shown in Figure 7 and Table 3, "Alzheimer's disease" is prominent in this figure, with a high frequency of 195 times. AD, a neurological disorder that worsens with age, is the most typical cause of dementia. The hallmark signs of AD include amyloid-peptide aggregation, increased levels of hyperphosphorylated tau protein (p-tau), and the absence of redox homeostasis. As all proposed treatments that target p-tau have so far failed in clinical trials, it is imperative to identify new therapeutic targets. The pathogenic features of AD are numerous. Examples include significant lipid peroxidation, high levels of neurotoxic trace elements, and increased Aβ levels[49-51]. All of these elements contribute to an increase in ROS or free radicals. In AD brains, reduced expression of NRF2 and its driver genes NQO1, HO-1, and GCLC were observed. NRF2 is crucial for preserving cellular redox homeostasis and controlling inflammatory reactions. Spatial memory impairment and neuronal death are reduced by NRF2 activation[52]. Oxyphylla A ameliorated cognitive deficits and neuropathology in mice through the NRF2-Keap1-HO-1 pathway *in vitro* and *in vivo* AD mouse models[53]. Via the NRF2- TXNIP- thioredoxin (TrX) axis, DL-3-n-butylphthalide suppresses NLRP3 inflammasomes and reduces pathology similar to AD[54]. By inhibiting the Keap1/NRF2 and mitogen-activated protein kinases (MAPK)-38p/ERK signaling pathways, vitamin D analogs reduce the neurodegenerative effects of rat AD[55]. Also, it has been demonstrated that the NRF2/ARE signaling pathway is involved in the protective effects of 3H-1, 2-dithio-3-thione in AD cell models. By working on the Phosphatidylinositol 3-kinase (PI3K)/ Protein Kinase B (Akt)/NRF2/HO-1 pathway, anthocyanin supplements added to a natural diet reduces oxidative stress in mouse models of AD[56]. According to a study published in 2020, artemether activates the AMPK- Glycogensynthasekinase3β (GSK3β) -NRF2 signaling pathway and inhibits β-amyloid-induced neurotoxicity in a mouse model of AD[57]. Inducing NRF2 expression in AD model mice can improve cognitive impairment by reducing oxidative stress and neuroinflammation[58]. The *in vivo* and *in vitro* experiments on the therapeutic effect of NRF2 in AD have been relatively mature, but clinical trials are still relatively scarce. In the future, researchers can further study the application value of NRF2-related drugs in the clinical treatment of AD.

Role of NRF2 in Parkinson's disease

As shown in Figure 7 and Table 3, the keyword "Parkinson's disease" also appeared many times, up to 129 times. It can be seen that research on Parkinson's disease (PD) is no less hot than stroke. Following AD, PD is the second most common

neurodegenerative disease. PD is frequently distinguished by progressive dyskinesia (rigidity, resting tremor, postural instability, hypokinesia, and bradykinesia), as well as variable degrees of cognitive dysfunction and dementia[59]. Typical PD symptoms are mediated by the loss of dopamine neurons in the SN. However, the cause of PD is still not fully known. According to studies, oxidative stress plays a significant role in the development and progression of PD, notably by accelerating membrane lipid peroxidation and protein degradation[60]. We have reason to believe that NRF2 regulates a large number of cytoprotective genes with anti-inflammatory and antioxidant properties and is a potential target for PD-related neuronal cell death. In the rotenone-induced rodent PD model, dapagliflozin may significantly alleviate neuronal oxidative stress by reducing lipid peroxides *via* activation of the DJ-1/NRF2 pathway. Ultimately, it reduces neuronal damage and motor dysfunction[61]. Celastrol's neuroprotective effects in PD are mediated by the NRF2-NLRP3-caspase-1 pathway[62]. The DJ1-NRF2-STING axis regulates ingested solanine A's neuroprotective impact in PD[63]. Polydatin controls the AKT/GSK3-NRF2/NF-κB signaling pathway to protect against PD brought on by lipopolysaccharide[64]. In the 6-hydroxydopamine model of PD, the induction of NRF2 in astrocytes protects against brain injury[65]. In the postmortem brain of PD patients, proteins p62 and NQO1 are partially sequestered in Lewy bodies, indicating that NRF2 neuroprotective capacity is impaired. In the same study, pharmacological activation of NRF2 by DMF protected SN neurons from α-synuclein toxicity in a mouse PD model, but was not significant in NRF2 knockout mice[66]. Earlier studies also found that NRF2 activation up-regulated brain HO1 and NQO1 expression and prevented MPTP-induced SN neuron death in a neurotoxin PD model[67]. Related clinical trials have also studied the clinical treatment effect of NRF2-related drugs in PD, and DMF has a good effect on the treatment of Parkinson's symptoms in patients with psoriasis[68]. All the above studies indicate the widespread use of NRF2 in PD.

Role of NRF2 in traumatic brain injury

As shown in Figure 7 and Table 3, the study of traumatic brain injury (TBI) has also recently gained popularity among scholars. TBI has emerged as a significant public health issue in modern society as the primary cause of death and disability in the young adult population[69]. TBI results in primary mechanical damage to brain cells and triggers secondary brain injury, such as oxidative stress, inflammation, and apoptosis, which occur immediately after primary injury. Secondary brain injury exacerbates the effects of TBI, which is the major factor affecting prognosis. The prognosis for TBI patients is still poor despite decades of collaborative efforts and improvements in surgical and therapeutic procedures. New, efficient treatment alternatives must be created immediately. Studies have revealed that in mice with TBI, loss of NRF2 activity worsens endoplasmic reticulum (ER) stress-induced apoptosis[70]. A study has shown that tert-butylhydroquinone, a novel NRF2 activator, significantly improves neurological function and reduces brain edema in mice with TBI[71,72]. In addition, it has been shown that atorvastatin prevents ER stress-mediated apoptosis through the NRF2/HO-1 signaling pathway in mice with TBI[73]. The possible mechanisms of NRF2 action in TBI may be as follows: First, by interacting with ARE, up-regulation of the antioxidant enzyme SOD to activate HO-1, NQO-1, and NOX-2 inhibits cellular and mitochondrial oxidative stress. Astrocyte-derived exosomes protect hippocampus neurons following traumatic brain damage by reducing mitochondrial oxidative stress[74]. Evodiamine reduces oxidative stress by blocking the PGK1/NRF2 pathway, which protects against TBI[75]. Another study reported that SOD activity was dramatically reduced in NRF2 (−/−) mice after TBI compared to NRF2 (+/+) animals, but nicotinamide adenine dinucleotide phosphate oxidase (NOX2) protein expression and MDA levels were significantly elevated[76]. Melatonin receptor activation attenuates oxidative stress and inflammation through the NRF2 signaling pathway, thereby providing brain protection after TBI[77]. Second: reduces apoptosis by reducing cell foaming, chromosomal DNA fragmentation, and apoptotic body formation[70]; third, inhibits inflammation and attenuates inflammatory responses by reducing inflammatory factors such as NF-κB, TNF-α, IL-1β, IL-6, ICAM-1, and Matrix metalloproteinase-9 (MMP-9). Jin *et al*[78] found that NRF2(−/−) mice had higher levels of inflammatory factors than NRF2(+/+) mice, and reported the role of NRF2 in inhibiting inflammation in TBI for the first time. In addition, they suggested that NRF2 depletion also worsens inflammatory responses in the lung and intestine of mice with TBI in their subsequent study[76]. In *in vitro* TBI models, NRF2 deletion increased the expression of TNF-α, IL-1β, IL-6, and MMP-9, further aggravating brain injury. Astaxanthin improves neurological status after TBI injury by up-regulating the expression of NRF2 and HO-1 mRNA and the levels of NRF2, HO-1, and NQO1 protein[74]. Fourth: Reduces the loss of endothelial cell markers and tight junction proteins including GST3, GPx, and HO-1 to maintain the blood-brain barrier's function[79]. Although both *in vivo* and *in vitro* experiments have emphasized the importance of targeting NRF2 in the treatment of TBI, there is still a lack of clinical studies in this area. Given the abundant *in vitro* and *in vivo* studies, researchers should next focus on the clinical efficacy and significance of NRF2 agonists in TBI.

Future studies

Animal experimentation has produced a wealth of evidence that NRF2 is emerging as a new target for the treatment of central nervous system diseases. However, the clinical application of NRF2-related drugs in neurological diseases remains to be further explored. TBHQ is carcinogenic, so we have to reconsider drugs acting on this target. For reasons of safety, another Phase 3 investigation of the promising candidate CDDO-Me was stopped. However, it is gratifying that in 2008, the NRF2 activator DMF was approved by the FDA as a new first-line oral drug for the treatment of patients with relapsing MS. It is exciting that many Chinese herbal components and plant extracts have been shown to act on the central nervous system by activating NRF2. Resveratrol is a polyphenol complex extracted from natural plants, and is mainly present in red grape skin and wine. Resveratrol enhances the signaling of NRF2 by blocking Keap1 thereby regulating NRF2 expression and nuclear translocation[80]. Studies have shown that resveratrol can improve the antioxidant capacity of AD models *via* the NRF2/HO-1 signaling pathway[81] with beneficial effects in oxidative stress-mediated cerebral ischemic injury[82], which are closely related to the regulation of NRF2. The active ingredient dl-3-n-butylphthalide (Dl-NBP) has been isolated from Chinese herbal celery seeds, and has been used to treat ischemic stroke.

In recent years, great progress has been made in the study of Dl-NBP in the central nervous system. Dl-NBP therapy improves oxidative stress injury in APP/PS1 mice by improving neuronal apoptosis, decreasing TXNIP-NLRP3 interaction, and inhibiting NLRP3 inflammasome-mediated inflammation[54]. Given the few toxic side effects of Chinese herbal medicines, it may provide new perspectives in the treatment of central nervous system diseases.

Intensity and limitations

In comparison to conventional literature reviews, analysis of the bibliometric tool Cite-Space can provide more in-depth information on the development of research hotspots and trends as well as fairly thorough and impartial data analysis. Although our study is the first to bibliometrically analyze NRF2 in neurological illnesses, it is not without certain restrictions. Initially, the Web of Science database was used to access the literature data. Nevertheless, due to the database's ongoing updates, the study's findings may not accurately reflect the number of publications that are actually in existence. Second, the search topic is only chosen to appear in the title, abstract, and keywords due to Web of Science's technical restrictions; the pertinent terms in the text are not searched. Also, as only articles and reviews were chosen for this study, there is a range in the caliber of the publications that were gathered. The aforementioned factors might prevent our analysis from being thorough. Notwithstanding such drawbacks, we think that our visual analysis can still help researchers evaluate the state of the field's overall research and its future directions.

CONCLUSION

In this study, the role of NRF2 in central nervous system diseases was systematically assessed by bibliometric analysis. The bibliometric analysis of 1884 papers from the Web of Science database in the past decade showed that China had the largest number of papers published in this field, while Western scholars represented by Kimura *et al*[83] and Ishii *et al*[84] had a greater influence in this field. In summary, the important role of NRF2 inflammasomes in central nervous system diseases has been fully recognized. Experimental trials and animal models have both demonstrated the therapeutic benefits of NRF2 activators in neurological disorders. However, more research is required to demonstrate their effectiveness and allow for their use in the treatment of illnesses of the central nervous system while taking into account their low risk of side effects. New possibilities for challenging disorders are provided by traditional Chinese medicine and ingredients derived from plants. We think that in the future, tailored therapy against NRF2 might be an effective way to treat conditions of the central nervous system and that it will be promptly implemented in clinical practice to benefit patients.

ARTICLE HIGHLIGHTS

Research background

As a key transcription factor in the antioxidant network, the nuclear factor erythroid 2-related factor 2 (NRF2) plays an important role in nervous system diseases that are susceptible to oxidative damage. In recent years, research on a variety of new cell death modes in nervous system diseases has been very popular. A large number of studies have explored the regulatory role of NRF2 in these cell death modes and its clinical application in nervous system diseases.

Research motivation

Although a large number of studies have explored the potential value of NRF2 in neurological diseases, there is still a lack of large-scale bibliometric analyses to summarize its research hotspots and future research trends.

Research objectives

Based on the bibliometric analysis, this paper summarizes the research hotspots and future research trends of NRF2 in nervous system diseases, in order to provide enlightenment for subsequent researchers.

Research methods

We searched and screened the literature related to NRF2 and nervous system diseases in the past decade, and then analyzed the literature using the bibliometric tool Cite-Space, read the literature, and summarized the research progress, hotspots, and research trends in this field.

Research results

China ranks first in both the number of articles published and the amount of funds invested. In addition, the author with the largest number of publications is also from China, which shows that China's influence in this field cannot be ignored. In recent years, research on the application of traditional Chinese medicine in neurological diseases by acting on NRF2 targets has become more and more popular. In addition, NRF2 not only regulates inflammation, apoptosis, autophagy, and oxidative stress of nerve cells, but also plays a crucial regulatory role in the ferroptosis of nerve cells.

Research conclusions

The role of NRF2 in nervous system diseases is mainly focused on its anti-oxidative stress, anti-inflammation, and anti-

apoptosis action. Although China has published the greatest number of papers, its centrality is low and its influence is small compared with the United States and other countries. The cooperation between China and other countries is also less, indicating that cooperation can identify breakthroughs. In recent years, research on the therapeutic effect of traditional Chinese medicine on nervous system diseases by acting on the NRF2 pathway has become more and more popular. However, although some progress has been made in related clinical trials, clinical research on the NRF2 pathway in nervous system diseases is still lacking. Researchers should perform more clinical studies to explore the clinical significance of NRF2-related drugs.

Research perspectives

More attention should be paid to the role of NRF2 in regulating ferroptosis. Most importantly, researchers should pay more attention to the clinical efficacy of NRF2 agonists in neurological diseases. More high-quality randomized controlled trials should be conducted to promote the clinical application of NRF2 agonists.

FOOTNOTES

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CASE REPORT

Transcatheter embolization for hemorrhage from aberrant testicular artery after partial nephrectomy: A case report

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Abstract

BACKGROUND

Arterial bleeding typically involves the renal artery following partial nephrectomy; in this study, we present a case of bleeding originating from the testicular artery that has not been reported in previous studies.

CASE SUMMARY

A 52-year-old man suffered hemorrhage from a perinephric branch of the aberrant left testicular artery after an open nephron-sparing surgery for renal cell carcinoma. Clinical signs of bleeding were manifested by the patient, such as fresh blood drainage from the catheter, decreased hemoglobin levels, and significant vital sign changes. Since computed tomography did not show evidence of active bleeding, transcatheter angiography was conducted to identify the bleeding site. Fluoroscopic spot images confirmed bleeding derived from a perinephric branch of the testicular artery originating from the segmental artery of the left renal artery. Using n-butyl-2-cyanoacrylate, successful transcatheter arterial embolization of the affected branch was performed. Immediately after the embolization procedure, the bleeding ceased, and the patient experienced complete recovery devoid of complications.

CONCLUSION

In patients with postoperative arterial hemorrhage after partial nephrectomy, the testicular artery can be a rare but notable source of bleeding. Accurate bleeding site localization *via* angiographic evaluation, followed by transcatheter arterial embolization, can be instrumental for safe, prompt, and effective hemostasis.

Key Words: Partial nephrectomy; Hemorrhage; Testicular artery; Angiography; Embolization; Case report

Core Tip: Arterial hemorrhage, one of the complications associated with post partial nephrectomy, primarily arises from an injury to the distal end of the renal artery located at the kidney's resection margin. Herein, we present a rare case of hemorrhage following partial nephrectomy that originated from a perinephric branch of the testicular artery, arising from the segmental artery of the renal artery. Despite the absence of active bleeding on computed tomography scan, preemptive angiographic evaluation based on a strong clinical suspicion of hemorrhage was performed. This afforded precise bleeding site identification, followed by successful transcatheter arterial embolization. It is noteworthy that arterial hemorrhage after partial nephrectomy can originate not only from the renal artery but also from the perinephric branches of nonrenal arteries, including the testicular artery.

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INTRODUCTION

Partial nephrectomy (PN), also known as nephron-sparing surgery, is preferred for surgical removal of renal tumor owing to its ability to preserve renal function[1-3]. However, the abundant renal tissue vascularity poses a potential risk of vascular complications associated with PN compared to radical nephrectomy[2,3]. Hemorrhage resulting from arterial injury following PN primarily occurs at the renal artery, located at the kidney's resection margin[1,2,4,5]. In the literature, no documented cases have been reported regarding hemorrhage secondary to testicular artery injury following PN. While this may be attributed to the rarity of bleeding as a result of testicular artery injury, it is also plausible that the potential for hemorrhage originating from the testicular artery has been overlooked or underestimated. In arterial bleeding, spontaneous hemostasis is difficult to anticipate, and it can hinder postoperative recovery due to massive blood loss. Thus, prompt intervention, including surgical or endovascular treatment, is crucial. Transcatheter arterial embolization has been established as a safe and efficacious treatment strategy for managing post-PN bleeding[1,2,4,5]. However, to attain immediate and effective embolization, accurate bleeding site localization *via* angiography is necessary.

In this report, we present a case of active bleeding from a perinephric branch of the aberrant testicular artery following PN, and the diagnosis was established through angiographic evaluation, which was successfully managed using transcatheter embolization.

CASE PRESENTATION

Chief complaints

A 52-year-old male patient was referred to the Department of Interventional Radiology for angiographic evaluation and endovascular management to control postoperative bleeding after open PN.

History of present illness

He underwent nephron-sparing surgery as an indication for left renal cell carcinoma (T1b) (Figure 1). Immediately after surgery, a continuous discharge of fresh blood was noted in the Jackson–Pratt drain, with a total drainage volume of 600 mL within 24 h postoperatively.

History of past illness

He had no underlying medical conditions or diseases that may indicate a coagulopathy.

Personal and family history

His personal and family history was unremarkable.

Physical examination

His hemodynamic status was relatively stable as follows: Systolic blood pressure of 115 mmHg, diastolic blood pressure of 63 mmHg, and heart rate of 99 beats per minute. However, compared to his preoperative status, a decrease in blood pressure and a significant increase in heart rate were observed (systolic blood pressure of 145 mmHg, diastolic blood pressure of 86 mmHg, and heart rate of 66 beats per minute). He did not manifest with gross hematuria; however, he experienced abdominal and flank pain and tenderness, which are considered typical following renal surgery.

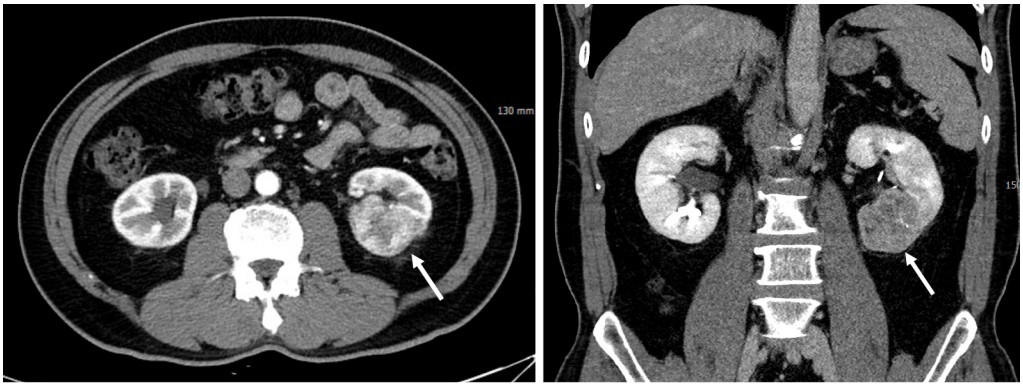

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Figure 1 Pre-operative computed tomography. Pre-operative computed tomography images demonstrating a heterogeneously enhancing mass (arrows) located in the lower polar area of the left kidney, suggestive of renal cell carcinoma.

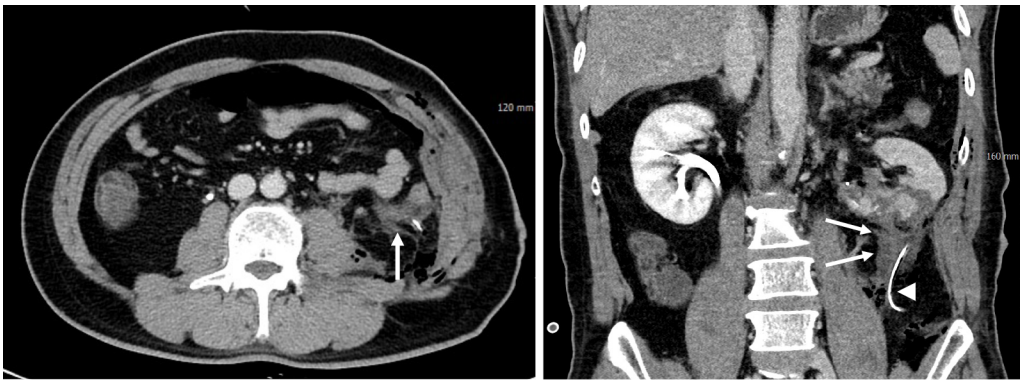

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Figure 2 Post-operative computed tomography. Post-operative computed tomography images obtained 1 d after partial nephrectomy revealing a small amount of fluid (arrows) in the inferior aspect of the left kidney, adjacent to the drainage tube (arrowhead), without evidence of contrast extravasation.

Laboratory examinations

Laboratory examinations revealed a decline in the hemoglobin level from 13.4 g/dL to 11.4 g/dL, even after receiving transfusion of three units of packed red blood cells following surgery. Other laboratory findings were unremarkable.

Imaging examinations

Minimal amount of fluid adjacent to the operative site of the left kidney was demonstrated in the abdominal contrast-enhanced computed tomography (CT); however, no signs of contrast extravasation or pseudoaneurysm indicative of active bleeding were observed (Figure 2). The patient was referred to the interventional unit for angiographic evaluation and endovascular treatment due to clinical suspicion of active bleeding despite the absence of radiologic evidence.

Selective digital subtraction angiography (DSA) was conducted for the left renal artery using a cobra catheter (Cook Medical Inc., Bloomington, IN, United States). Angiographic opacification of left renal artery did not show any positive findings indicative of ongoing bleeding (Figure 3A). After catheterization of the left testicular artery (Figure 3A), which originated from the segmental artery of the left renal artery in the renal hilar shadow, contrast medium was injected using a microcatheter (Progreat; Terumo, Tokyo, Japan) with a coaxial technique. Subsequently, extravasation of the contrast medium was noted on the fluoroscopic spot images (Figure 3B).

FINAL DIAGNOSIS

Hemorrhage from a perinephric branch of an aberrant testicular artery originating from the renal artery following open PN.

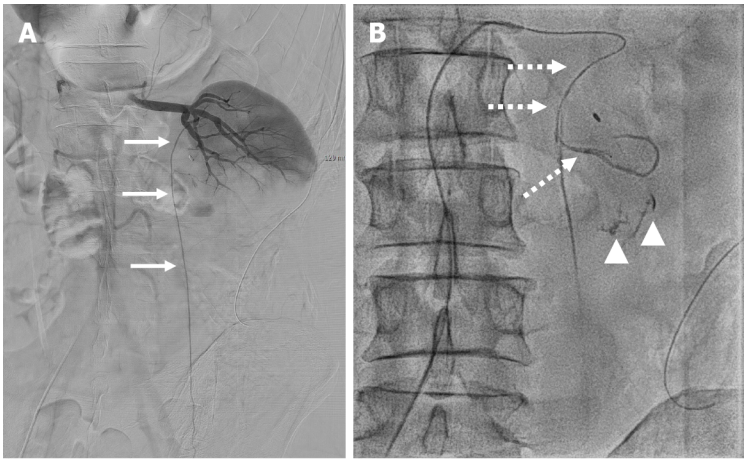

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Figure 3 Transcatheter angiography. A: Digital subtraction angiography of the left renal artery demonstrating no evidence of active bleeding and revealing the left testicular artery (arrows) arising from the middle segmental artery of the renal artery; B: Fluoroscopic spot image obtained following super-selective catheterization (dashed arrows) of the suspected branch arising from the testicular artery, revealing contrast extravasation (arrowheads).

TREATMENT

Transcatheter embolization was conducted for the culprit branch using a mixture of n-butyl-2-cyanoacrylate (NBCA) (Histoacryl, B. Braun, Melsungen, Germany) diluted 1:3 in iodized oil (Lipiodol, Guerbet, Paris, France). The NBCA and iodized oil mixture was carefully injected into the bleeding site to achieve hemostasis while avoiding nontarget embolization of the testicular artery and renal artery. Subsequent fluoroscopy demonstrated a cast formation of the embolic material in the bleeding site (Figure 4).

OUTCOME AND FOLLOW-UP

Immediately after transcatheter embolization, bleeding from the Jackson–Pratt drain ceased, with no further decline in the hemoglobin levels. During the 6-mo clinical follow-up, the patient attained full recovery without any complications, such as renal or gonad dysfunction, indicating the absence of nontarget embolization.

DISCUSSION

For early stage renal cell carcinoma, PN has become the gold standard treatment, specifically T1a and some T1b cases[3]. While hemorrhage following PN is rare, it can potentially be fatal and is typically associated with renal bleeding. Unilateral open PN is performed *via* several steps, including a flank incision, kidney dissection inside the Gerota's fascia, clamping of the renal arteries and veins, renal lesion resection, and renorrhaphy[3]. Renal tumor resection conveys a potential bleeding risk due to the abundant vascular tissue in the kidneys[2].

A retrospective study analyzing 1187 patients undergoing PN, approximately 3% of patients required embolization due to bleeding-related complications, all of which were related to renal bleeding[5]. Prior studies on endovascular treatment of post-PN bleeding have primarily highlighted on renal bleeding[1,2,4,5]. However, hemorrhage may also occur from the perinephric space or nearby retroperitoneum[3], particularly during the preresection stage of the PN. In our case, the perinephric fat presented with denser characteristics and a stronger attachment to the renal capsule than usual. This probably led to arterial injury supplying the perinephric fat tissue during kidney dissection from the perinephric fat inside the Gerota's fascia.

The clinical features of post-PN bleeding include hematuria secondary to renal hemorrhage, flank pain, or renal dysfunction due to bleeding in the perirenal compartment, bleeding from suction drains, or decreased hemoglobin level [1]. In our case, since it was nonrenal bleeding, hematuria was not present. However, continuous drainage of fresh blood through the drainage tube, along with persistent hemoglobin decline despite transfusion, strongly raised clinical suspicion of active bleeding.

Radiologically, active bleeding is demonstrated through contrast medium extravasation, pseudoaneurysm, and arteriovenous fistula. In our case, CT and initial DSA findings did not provide evidence of active bleeding. This could be attributed to continuous drainage of blood through the drainage tube inserted during surgery. Finally, the bleeding site was identified on fluoroscopy by superselectively accessing each suspected vessel *via* a microcatheter and injecting a contrast agent.

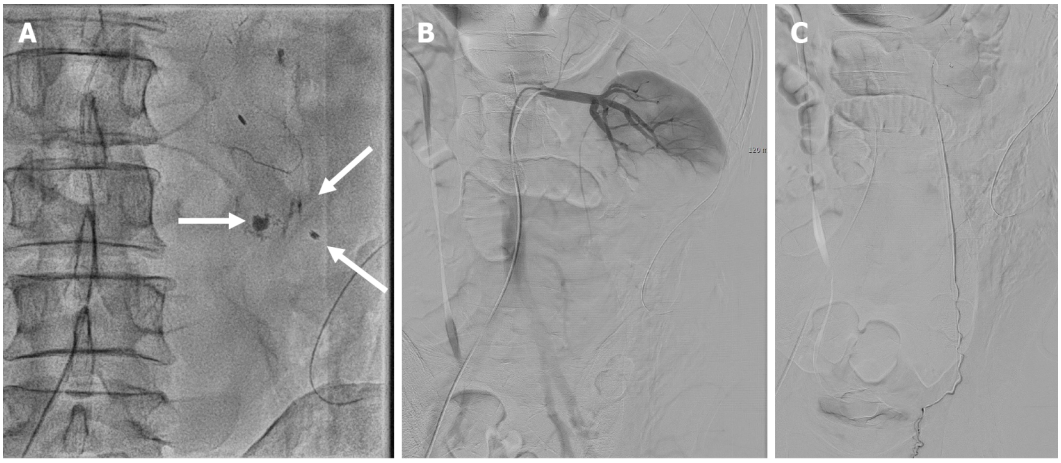

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Figure 4 Post-embolization images. A: Fluoroscopic spot image obtained after transcatheter embolization, demonstrating cast formation (arrows) of n-butyl-2-cyanoacrylate and iodized oil mixture at the bleeding site; B and C: Post-embolization digital subtraction angiography illustrating preserved distal flow of the renal artery (B) and testicular artery (C).

A systemic approach to differential diagnosis is crucial in evaluating post-PN patients with suspected hemorrhage. Distinguishing between different potential sources of bleeding, such as renal artery bleeding, perirenal compartment bleeding, or other vascular abnormalities, is essential. Initial imaging examinations, including contrast-enhanced CT and selective DSA, may not always provide evidence of active bleeding. Therefore, to accurately guide diagnosis and intervention decisions, combining clinical symptoms, laboratory findings, and angiographic evaluation is crucial.

Compared to surgery, transcatheter embolization is less invasive but involves a crucial procedural step that needs to be employed. In contrast to the surgical approach, which allows direct visualization and control of the bleeding site, an endovascular approach requires an initial and essential step of identifying the parent artery of the bleeding vessel to achieve immediate and effective hemostasis.

To date, no cases of post-PN bleeding originating from the testicular artery branches have been reported, indicating that this possibility has been overlooked rather than deemed unlikely. The testicular artery leads to numerous branches that supply blood to the perinephric fat and ureter as it descends toward the pelvis and inguinal ring[6].

Our case report not only underscores the importance of accurate localization and timely intervention but also has significant implications for clinical practice. The possibility of testicular artery-related hemorrhage in post-PN patients should be considered by interventional radiologists and urologists when traditional sources of bleeding have been ruled out. Early recognition of such cases can lead to more targeted angiographic evaluations and timely transcatheter embolization, decreasing the risk of massive blood loss and expediting patient recovery.

The origin of the testicular artery from the renal artery is another noteworthy aspect of our case. The testicular artery usually originates directly from the lateral side of the abdominal aorta at the L2-L3 Level, just below the renal arteries' ostium[6,7]. Nallikuzhy *et al*[6] reported the anomalous origin of the testicular artery by conducting a meta-analysis of variations in the testicular vasculature. In their study, a total of 2,396 testicular arteries were analyzed, and they found that 4.55% of cases (56 out of 1229) on the right side and 4.97% of cases (58 out of 1167) on the left side had the testicular artery originating from the renal artery or its associated arteries, such as an accessory renal artery. In this present case, the left testicular artery originated from the middle segmental artery of the left renal artery in the renal hilar portion.

NBCA is a permanent liquid embolic material that undergoes rapid polymerization upon contact with blood[8,9]. One particular advantage of NBCA is that it is not affected by the patient's coagulation state[9]. In cases where it is challenging to advance the microcatheter adequately due to a tortuous vessel course or small-vessel diameters, embolization can be performed by adjusting the NBCA and iodized oil mixing ratio[9]. However, the use of this embolic material requires proficiency in its application by the operators. In our case, caution was exercised to prevent reflux into the peripheral portion of the renal artery and the testicular artery, ensuring that the embolic material was accurately and appropriately injected into the bleeding site.

CONCLUSION

This case elucidates that post-PN hemorrhage can be attributed to a perinephric branch originating from the testicular artery. Angiographic exploration plays a crucial role in the accurate identification of the bleeding site, allowing for a safe, prompt, and effective hemostasis through transcatheter arterial embolization.

FOOTNOTES

Co-first authors: Juyoun Youm and Min-Jeong Choi.

Author contributions: Youm J and Choi MJ contributed equally to this work; Youm J, Choi MJ, and Seo Y contributed to manuscript writing and editing, and data collection; Choi MJ contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

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CASE REPORT

Persistent left superior vena cava in right hemiarch replacement under deep hypothermic circulatory arrest: A case report

Ze-Yu Mi, Gang He, Hong-Li Gao, Chao Li

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Abstract

BACKGROUND

Persistent left superior vena cava (PLSVC), a relatively rare thoracic vascular malformation, can inconvenience perfusionists and operators when encountered during deep hypothermic circulatory arrest (DHCA).

CASE SUMMARY

Herein, we describe the case of a patient with concurrent giant aortic arch aneurysm, aortic stenosis, and PLSVC. To treat these conditions, we performed right hemiarch and aortic valve replacements under DHCA. Notably, we applied "bilateral superior vena cava retrograde cerebral perfusion (RCP)" for cerebral protection, which significantly optimized the surgical procedure and reduced the risk of postoperative complications. The patient was discharged 14 d after surgery with no complications.

CONCLUSION

Surgical intervention for PLSVC under DHCA can be performed using the bilateral superior vena cava RCP approach.

Key Words: Persistent left superior vena cava; Aortic arch aneurysm; Hemiarch replacement; Deep hypothermic circulatory arrest; Retrograde cerebral perfusion; Case report

Core Tip: Persistent left superior vena cava (PLSVC) is a malformation that can coexist with the right superior vena cava without causing an imbalance in the hemodynamics, thereby concealing its detection during clinical consultation. We describe the case of a patient with an aortic arch aneurysm who also had PLSVC. When replacing the right hemiarch under deep hypothermic circulatory arrest, we utilized a "bilateral superior vena cava retrograde cerebral perfusion (RCP)" approach to PLSVC. The patient was discharged 14 d postoperatively without any complications. To the best of our knowledge, RCP *via* the bilateral superior vena cava has not previously been reported.

Citation: Mi ZY, He G, Gao HL, Li C. Persistent left superior vena cava in right hemiarch replacement under deep hypothermic circulatory arrest: A case report. *World J Clin Cases* 2023; 11(32): 7858-7864
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INTRODUCTION

Persistent left superior vena cava (PLSVC) is one of the most prevalent venous malformations of the superior vena cava vessels, occurring in approximately 0.3%-0.5% of individuals[1]. PLSVC with agenesis of the right superior vena cava (RSVC) is also known as isolated PLSVC[2]. In approximately 80%-90% of cases, PLSVC returns to the right atrium (RA) *via* the coronary sinus (CS), coexisting with the RSVC without causing an imbalance in the hemodynamics, thereby making detection difficult during clinical consultation[3]. PLSVC is usually detected incidentally during cardiovascular surgery[4]. However, PLSVC can cause extracorporeal circulation drainage, retrograde cerebral perfusion (RCP), and retrograde arrest fluid perfusion failure, presenting challenges during cardiac surgery.

Herein, we present the case of a patient with an aortic arch aneurysm combined with PLSVC who required a right hemiarch replacement under deep hypothermic circulatory arrest (DHCA). Cerebral protection was achieved by DHCA and RCP. To the best of our knowledge, this is the first report of RCP *via* the bilateral superior vena cava in the literature.

CASE PRESENTATION

Chief complaints

On June 20, 2022, a 55-year-old male patient presented with cough and shortness of breath that had persisted for 3 mo.

History of present illness

Three months prior to admission, the patient had presented with cough and shortness of breath without any obvious trigger, accompanied by the coughing up of white foamy sputum. These symptoms were aggravated by activity and could be relieved by rest. There was no diagnosis nor treatment at that time.

History of past illness

Prior to this visit, the patient had been in good health with no underlying diseases.

Personal and family history

The patient had no history of familial hereditary diseases.

Physical examination

At the time of admission, the patient's blood pressure was 90/64 mmHg, there was no cyanosis in the lips, there was no protuberance in the precordial area, the apical beat point was located 0.5 cm medial to the intersection of the left fifth intercostal space and the midclavicular line, there was no pericardial friction, the heart rhythm was neat, a systolic ejective murmur was heard at the auscultation area of the aortic valve, and there was no abnormal murmur at the other auscultation areas of the heart valves.

Laboratory examinations

The results of all of biochemical tests were within normal limits.

Imaging examinations

Multislice computed tomography revealed a significant aortic arch aneurysm with a maximum diameter of approximately 68 mm (Figure 1). The PLSVC returned to the CS and collected venous flow from the left internal jugular, left subclavian, and azygos veins (Figure 2). The diameter of the PLSVC was 11 mm (Figure 3). Echocardiography revealed severe aortic stenosis (AS) with an aortic annular diameter of 21.8 mm, annular area of 6.16 cm^2, maximum aortic antegrade flow velocity of 4.83 m/s, and mean pressure difference of 41 mmHg. The patient's left ventricular ejection fraction was 70%, and the atrial and ventricular sizes were within the normal range. Notably, we observed enlargement

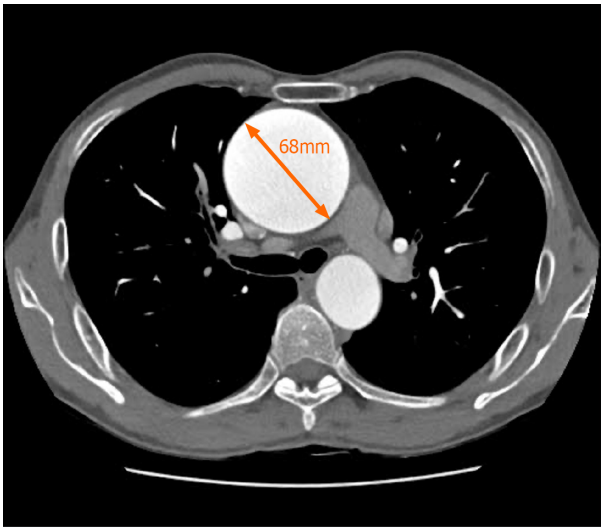

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Figure 1 Aortic arch aneurysm with a maximum diameter of 68 mm.

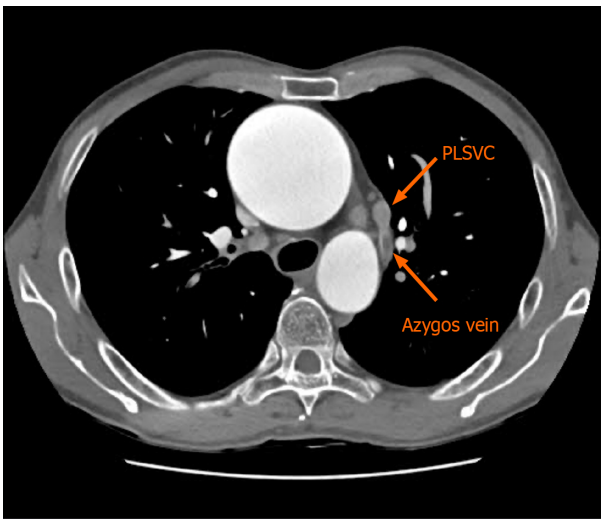

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Figure 2 Preoperative spiral computed tomography showing azygos vein reflux to the persistent left superior vena cava. PLSVC: Persistent left superior vena cava.

of the CS on echocardiography to approximately 2.5 times the normal size.

FURTHER DIAGNOSTIC WORK-UP

We further performed saline-contrast echocardiography. Saline contrast was injected through the left arm vein, and the order of contrast injection was the PLSVC, CS, and RA; no contrast was present in the RSVC. Upon injection of saline contrast through the right arm vein, in the order of the RSVC and RA, we noted the absence of a bridging vein (BV) connected between the PLSVC and RSVC[5].

FINAL DIAGNOSIS

Bicuspid aortic valve, severe AS, aortic arch aneurysm, PLSVC, and New York Heart Association Class IV status.

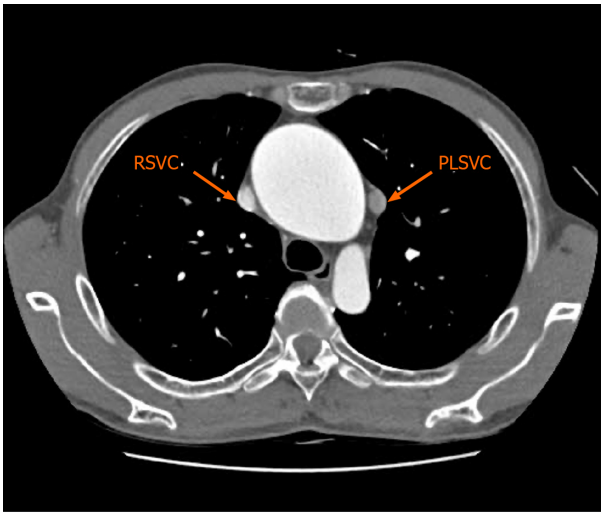

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Figure 3 Aortic arch aneurysm. The arrows indicates the bilateral superior vena cava. PLSVC: Persistent left superior vena cava; RSVC: Right superior vena cava.

TREATMENT

We performed aortic valve replacement and right hemiarch replacement under DHCA after diagnosis, and the procedure was as follows. While sawing through the sternum to expose the heart and right aortic arch, our surgical exploration revealed the absence of the innominate vein, and a giant aneurysm in the right aortic arch. The heart was lifted to expose the PLSVC crossing the anterior aspect of the left pulmonary artery and flowing downward into the CS (Figure 4).

The right femoral artery was cannulated and connected to an arterial perfusion tube, and venous drains were inserted in the superior and inferior vena cava lumens. A 1.5 cm incision was made on the surface of the RA, an inflatable balloon cannula was inserted into the PLSVC *via* the CS, and the left and RSVC drains were connected to the superior vena cava drains of the extracorporeal circulation machine *via* a T-tie to initiate extracorporeal circulation.

After gradual lowering of the circulatory temperature (Figure 5), we clamped the distal ascending aorta with a blocking clamp, and the ascending aorta was transected at 1 cm above the sinotubular junction. Myocardial protection was achieved by cascade perfusion and aortic valve replacement. We continued to lower the circulatory temperature to 20 ℃, at which point the extracorporeal circulation was stopped, the ascending aortic blocking clamp was opened, and RCP was performed *via* the bilateral superior vena cava, with the perfusion pressure maintained at 20-25 mmHg (Figure 5). We subsequently excised the aortic arch aneurysm and anastomosed the artificial vessel with the distal aorta. The proximal artificial vessel was clipped after completion of the anastomosis, and the side of the head was lowered to remove residual gas from the blood vessels. Extracorporeal circulation was restarted, and the circulatory temperature was gradually restored to 30 ℃, while anastomosing the proximal end of the ascending aorta with the artificial vessel. Subsequently, we opened the artificial vessel blocking clamps, and the heart resumed beating by itself. Then strict hemostasis and suturing of the surgical incision were performed.

OUTCOME AND FOLLOW-UP

After the operation, the patient was sent to the intensive care unit for continued treatment, with 800 mL of intraoperative bleeding. The DHCA duration was 16 min. The duration of the aortic block was 90 min. Postoperatively, the patient was mechanically ventilated for 7 h without complications and was discharged after 12 d.

DISCUSSION

PLSVC is caused by the degenerative failure of the left anterior cardinal vein that forms the Marshall ligament[1]. Its incidence is relatively rare in the general population. As PLSVC usually has no hemodynamically significant consequences, it is difficult to recognize in a clinical setting[6], and can only be detected during specific surgical procedures such as cardiac catheterization, cardiovascular interventions, and placement of permanent pacemakers[7,8].

With the increased awareness of PLSVC and the continuous development of imaging techniques in medicine, the diagnosis of PLSVC is becoming increasingly common. Experienced imaging physicians can now identify the presence of a PLSVC using multilayer spiral computed tomography of the chest, which can show the drainage pathway of the PLSVC in its entirety. The detection of a dilated CS upon echocardiography suggests the presence of PLSVC[9]. Saline contrast echocardiography can confirm the diagnosis of PLSVC and the BV connection between PLSVC and RSVC[10]. In

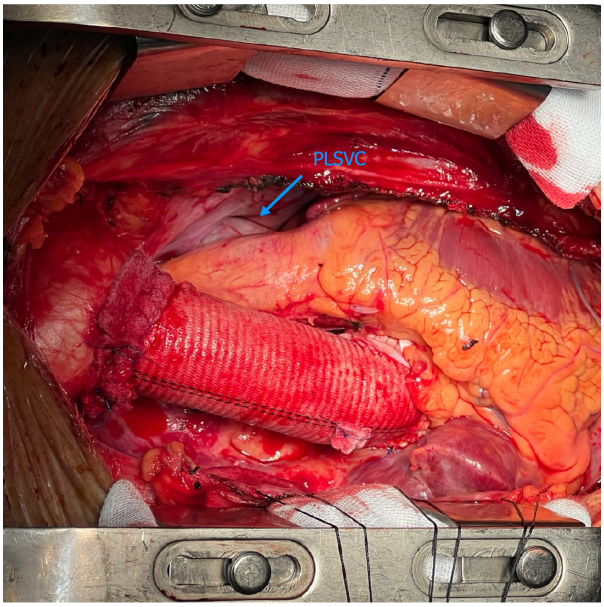

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Figure 4 Intraoperative photograph. The arrow indicates the persistent left superior vena cava. PLSVC: Persistent left superior vena cava.

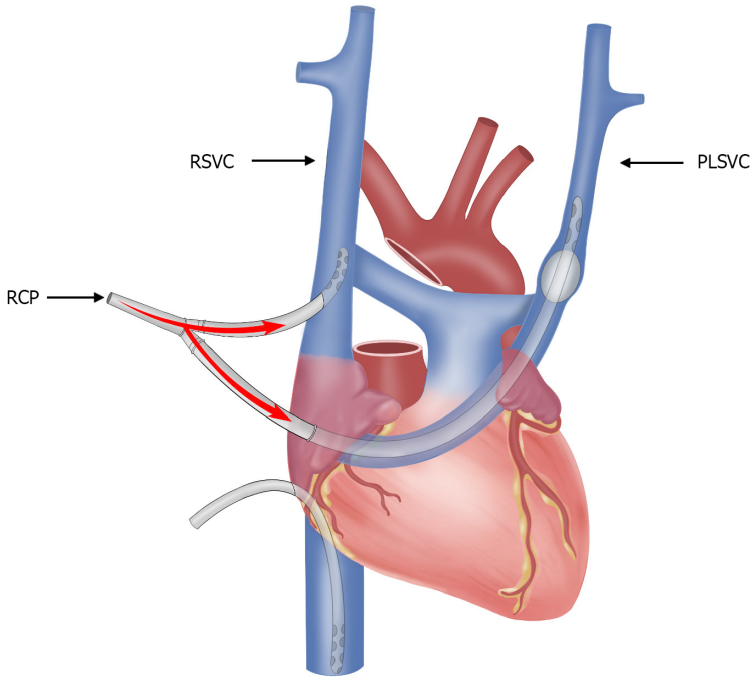

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Figure 5 Schematic diagram showing an intravenous cannula inserted into the persistent left superior vena cava. Schematic diagram of the "bilateral superior vena cava retrograde cerebral perfusion" is shown. PLSVC: Persistent left superior vena cava; RSVC: Right superior vena cava. RCP: Retrograde cerebral perfusion.

addition, widening of the left upper mediastinum on chest radiography and leftward deviation of the electrocardiographic electrical axis are indicators of PLSVC[11]. It has further been suggested that an enlarged CS can compress the atrioventricular node and hippocampus, leading to arrhythmias, which can also indicate a diagnosis of PLSVC[12].

DHCA and RCP can be used for cerebral protection during aortic arch surgery. RCP is one of the key factors affecting clinical outcomes. Ensuring a moderate perfusion pressure (20-25 mmHg) during RCP can prevent the development of postoperative cerebral edema[12]. Several reports have confirmed that PLSVC occurrence in general cardiac surgery leads to retrograde arrest fluid perfusion failure[13]. However, no incidences of PLSVC encountered during DHCA surgery have been reported to date. Previous studies have shown that a DHCA duration of > 25 min is a risk factor for transient neurological deficits, and that the duration of DHCA correlates linearly with the incidence of transient neurological deficits, which significantly increase when the duration of ischemia exceeds 50 min[14]. Therefore, in this case, we used a

single pump and two tubes to perform "bilateral superior vena cava RCP", which prevented the prolongation of DHCA time due to RCP failure. In cases with an abundant BV connection between the PLSVC and RSVC, surgeons may also block the PLSVC with an intravenous sleeve and perform RCP using the RSVC. Preoperative verification of BV connections between the PLSVC and the RSVC can be performed using saline-contrast echocardiography[10].

CONCLUSION

In conclusion, when PLSVC is encountered during the DHCA procedure, the bilateral superior vena cava RCP technique ensures stable perfusion pressure and adequate perfusion flow and is safe and effective. The preoperative identification of PLSVC is particularly critical in DHCA surgery. Further, preoperative planning of the surgery involving a reasonable RCP approach can shorten DHCA time, allowing optimization of the surgical procedure. With this approach, major complications can be prevented, and a satisfactory clinical outcome can be achieved.

FOOTNOTES

Author contributions: Mi ZY contributed to manuscript writing and editing, and data collection; He G and Gao HL contributed to data analyses; Li C contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

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CASE REPORT

Type II Abernethy malformation with cystic fibrosis in a 12-year-old girl: A case report

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Abstract

BACKGROUND

Abernethy malformation, also known as congenital extrahepatic portosystemic shunt, is an uncommon malformation resulting from aberrant development of the portal venous system. Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutations in the *CFTR* gene. It mainly affects the exocrine glands of the respiratory, digestive and reproductive systems. It is considered extremely rare in the Asian population. We present a clinical case involving a pediatric patient of Asian descent who was diagnosed with Abernethy malformation and CF.

CASE SUMMARY

A 12-year-old girl presented with a medical history of recurring respiratory infections and hemoptysis, and chest computed tomography (CT) showed bronchiectasis. Whole exome sequencing was performed for the patient, yielding findings that revealed a compound heterozygous variant of the *CFTR* gene: c.233_c.234insT/p.Trp79fsTer3 (maternal origin); c.2909G>A/p.Gly970Asp (paternal origin). CF was diagnosed. The physician's attention was drawn to the presence of splenomegaly during disease progression. Abdominal enhanced CT revealed splenomegaly, compression of the left kidney, and multiple tortuous dilated vascular shadows were seen at the splenic hilum, which flowed back into

the left renal vein and portal vein, suggesting Abernethy malformation type II. Intraoperatively, the abnormal blood flow was seen to merge into the inferior vena cava through the left renal vein without hepatic processing, and the pathology of liver biopsy showed hypoplastic, dilated or absent portal vein branches, both of which supported the diagnosis of Abernethy malformation type II. This represents the initial documented instance of Abernethy malformation accompanied by a *CFTR* gene mutation in the existing body of literature.

CONCLUSION
Coexisting Abernethy malformation and CF are rare. Detailed medical history information, abdominal enhanced CT, venography and genetic testing contribute to diagnosis as well as differential diagnosis.

Key Words: Abernethy malformation; Cystic fibrosis; *CFTR* gene; Case report

Core Tip: Abernethy malformation, also referred to as congenital extrahepatic portosystemic shunt, is an uncommon malformation resulting from anomalous development of the portal venous system. Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the *CFTR* gene, which is rare in Asian populations. We present an Asian child with type II Abernethy malformation coexisting with CF and discuss the diagnosis and treatment of Abernethy malformation and CF.

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INTRODUCTION

Abernethy malformation, alternatively referred to as congenital extrahepatic portosystemic shunt, is a congenital anomaly that arises from aberrant embryonic development of the umbilical and yolk veins[1,2]. This condition leads to an anomalous connection between the portal vein and vena cava, which exhibits a low occurrence rate, affecting approximately 1 in every 30000 live births[3]. Cystic fibrosis (CF) is a hereditary disorder characterized by autosomal recessive inheritance, resulting from mutations in the *CFTR* gene located on chromosome 7, which mainly affects the respiratory, digestive and reproductive systems[4,5]. CF exhibits a higher prevalence among individuals of Caucasian descent, while it is extremely rare in Asian populations[6,7]. We present an Asian girl with type II Abernethy malformation coexisting with CF. Compound heterozygous mutations of the *CFTR* gene were detected. We discuss the key points of diagnosis and treatment of Abernethy malformation and CF.

CASE PRESENTATION

Chief complaints

A 12-year-old girl was admitted to the respiratory department of our hospital on October 3, 2021, presenting with the chief complaints of cough with hemoptysis and dyspnea persisting for 4 d.

History of present illness

Four days previously, the individual presented with symptoms of a cough accompanied by hemoptysis and dyspnea subsequent to exposure to cold temperatures.

History of past illness

The patient has a medical history of recurrent respiratory tract infections dating back to early childhood. The patient had a history of patent foramen ovale and was admitted to our cardiothoracic surgery department 1 year previously. Cardiac ultrasound revealed a 2-mm echogenic interruption in the atrial septum, confirming the presence of a patent foramen ovale. Due to the small size of the defect and low platelet count (89×10^9/L), surgical intervention was not pursued.

Personal and family history

The patient was G3P3, born at term with a birth weight of 3.5 kg. The Apgar score at birth was unknown, and there was no reported history of postnatal asphyxia. The patient's parents were healthy and not blood relatives. The patient had a 25-year-old brother and a 14-year-old sister; neither of whom had any history of similar medical conditions.

Physical examination

Physical examination at admission showed body temperature 36.4°C, pulse rate 98 bpm, respiratory rate 24 breaths/min, and blood pressure 98/65 mmHg. The patient exhibited clear mental status, stable breathing, absence of cyanosis in the lips, no signs of aspiration, coarse breathing sounds in both lungs with audible wet rales, and the absence of clubbing of the fingers. The abdomen was found to be soft with no evidence of pressure or rebound pain. On palpation, the liver was located 3 cm below the rib cage, while the spleen was found to be 8 cm below the rib cage.

Laboratory examinations

Laboratory test results were as follows: white blood cell count 3.28 × 10^9/L, platelet count 84 × 10^9/L; fecal occult blood, negative; blood biochemistry: alanine aminotransferase 28.0 U/L, aspartate aminotransferase 38.0 U/L, creatine kinase-MB 15.0 U/L; positive for Mycoplasma antibodies; sputum culture: *Pseudomonas aeruginosa*; bone marrow smear: normal proportions and morphology of the erythroid, myeloid, megakaryocytic, and lymphoid populations; tumor tests: a-fetoprotein 1.66 ng/mL, carcinoembryonic antigen 1.63 ng/mL, nonspecific enolase 10.87 ng/mL, carbohydrate antigen 19-9 90.95 ng/mL; fiberoptic bronchoscopy alveolar lavage: numerous erythrocytes and inflammatory cells, 74% neutrophils, 6% lymphocytes, and 20% macrophages.

Imaging examinations

Chest computed tomography (CT) (Figure 1A and B) showed a flocculent shadow with multiple cystic translucent shadows in both lungs, and bronchiectasis with infection was considered. Ultrasound of the portal venous system showed that the internal diameter of the main trunk of the portal vein was 8 mm, with a maximum blood flow velocity of 19.3 cm/s, and a slightly tortuous course. The internal diameter of the splenic vein was 11 mm, with a tortuous course, slowed blood flow velocity, and tortuous vascular echoes around the fundus of the stomach, suggesting that the portal vein had a slightly tortuous course, and the splenic vein was thickened with a tortuous course. The whole abdomen was enhanced on CT imaging (Figure 1C-E). The liver was irregular in shape, with a large caudate lobe and no abnormal density shadows in the parenchyma. The gallbladder was not significantly abnormal in shape or size, and no abnormal density shadows were seen. The spleen was enlarged, the left kidney was compressed, and multiple tortuous dilated vascular shadows were seen at the splenic hilum, which flowed back into the left renal and portal veins. The findings were suggestive of Abernethy malformation type II.

Genetic analysis

The diagnosis of CF was based on a combination of recurrent respiratory infections, hemoptysis, splenomegaly and bronchiectasis. Prior to conducting full epigenetic testing, the parents were engaged in preoperative communication and provided written informed consent. The testing was carried out at our hospital by the Beijing Full Spectrum Medical Testing Laboratory. Whole-exome sequencing of the patient identified two compound heterozygous mutations, c.233_c.234insT (p.Trp79fsTer32) and c.2909G>A (p.Gly970Asp), in the *CFTR* gene, associated with CF (OMIM:219700). The c.233_c.234insT and c.2909G>A mutations were inherited from the mother and the father of the patient, respectively, as confirmed by Sanger sequencing (Figure 2). In exons 3 and 18 of the *CFTR* gene, a frameshift mutation (c.233_c.234insT) and a missense mutation (c.2909G>A) were identified, respectively. The mutation c.233_c.234insT caused a frameshift and premature stop codon 32 amino acids downstream (p.Trp79fsTer32), theoretically leading to the production of a truncated protein. According to the American College of Medical Genetics and Genomics guidelines (2019), both mutation classes are pathogenic. Sanger sequencing confirmed that the father carried a c.2909G>A/p.Gly970Asp missense mutation, while the mother was a carrier of a c.233_c.234insT heterozygous mutation. These findings are consistent with an autosomal compound heterozygous mutation inheritance pattern, known as autosomal stealth inheritance. The compound heterozygous mutation observed in the aforementioned case is the first reported instance in China, following a thorough review of the relevant literature and databases.

FINAL DIAGNOSIS

The diagnosis of CF was determined through an analysis of medical history, chest CT, and whole exon gene detection. Additionally, the diagnosis of Abernethy malformation type II was established through enhanced abdominal CT, intraoperative portography, and liver biopsy. Ultimately, the patient was diagnosed with Abernethy malformation type II concurrent with CF.

TREATMENT

After the pulmonary infection improved, the patient was transferred to the general surgery department and underwent ligation of abnormal branches of the portal vein and liver biopsy on October 20, 2021 after excluding the relevant contraindications. During the intraoperative period, observations revealed hepatic shrinkage, significant splenic enlargement, and tortuous alterations in the splenic vessels. The inferior margin of the spleen exhibited looseness, accompanied by an abnormally thickened vessel measuring ~0.8 cm in diameter, which was observed to be draining into the left renal vein. The central venous catheter remained *in situ via* the terminal jejunal vein, and portal vein pressure measurements recorded values of 17.1 and 23.1 cmH_2O before and after occlusion of the abnormal shunt, respectively.

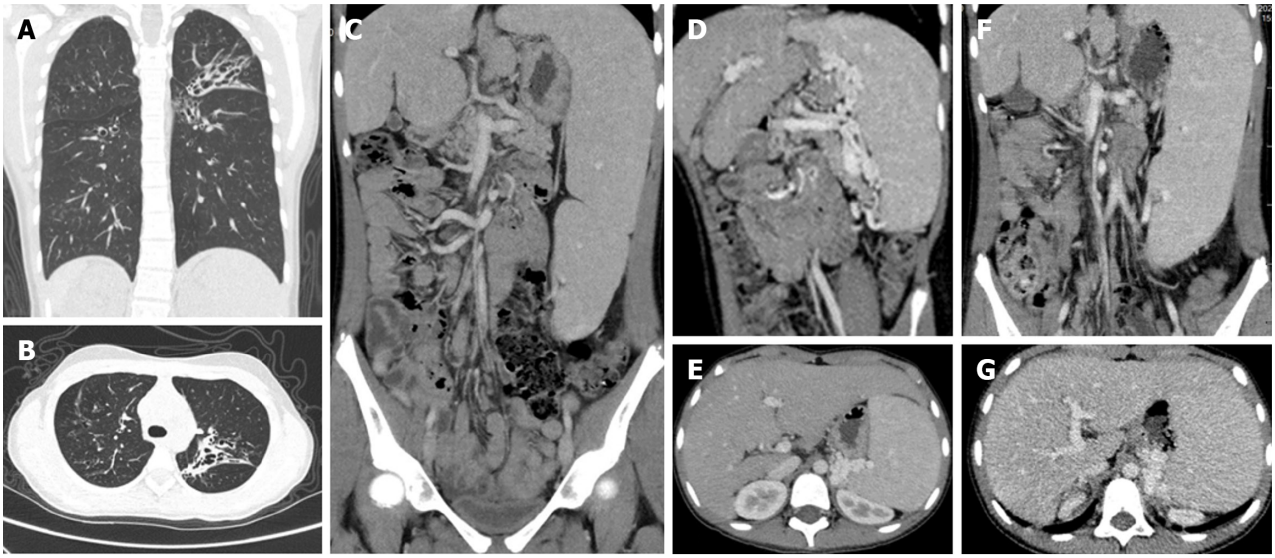

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Figure 1 Chest and abdominal computed tomography. A and B: Chest computed tomography (CT) showed bronchial dilatation and flocculent shadow with multiple cystic translucency in both lungs; C-E: Preoperative whole abdominal enhanced CT showed splenomegaly, multiple tortuous dilated vessels at the splenic hilum, irregular liver morphology and pancreatic atrophy; F and G: 17-month postoperative whole abdomen enhanced CT showed irregular liver morphology, splenomegaly, multiple tortuous dilated vessels at the splenic hilum, and pancreatic atrophy.

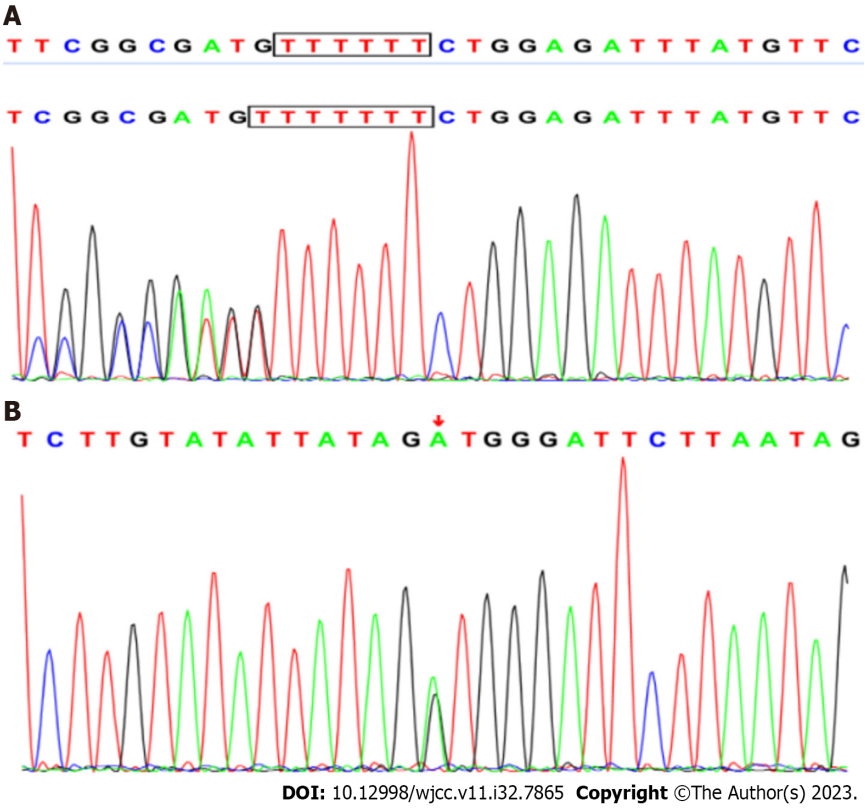

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Figure 2 *CFTR* gene sequencing. A: The mother of the proband was a carrier of *CFTR* gene c.233_c.234insT heterozygous mutation compared with the standard sequence; B: The father of the proband carried *CFTR* gene c.2909G>A/p.Gly970Asp heterozygous mutation.

Twenty minutes after blocking, no stasis was seen in the intestinal canal, kidney and spleen, and the branches of the portal vein were seen on portal venography. The abnormal shunt vessels were ligated, and no abdominal organ stasis was seen, and some tissues of the right lobe of the liver were taken for pathological examination. Pathological analysis showed that portal vein branches were dysplastic, dilated or absent, which was consistent with Abernethy malformation type II (Figure 3).

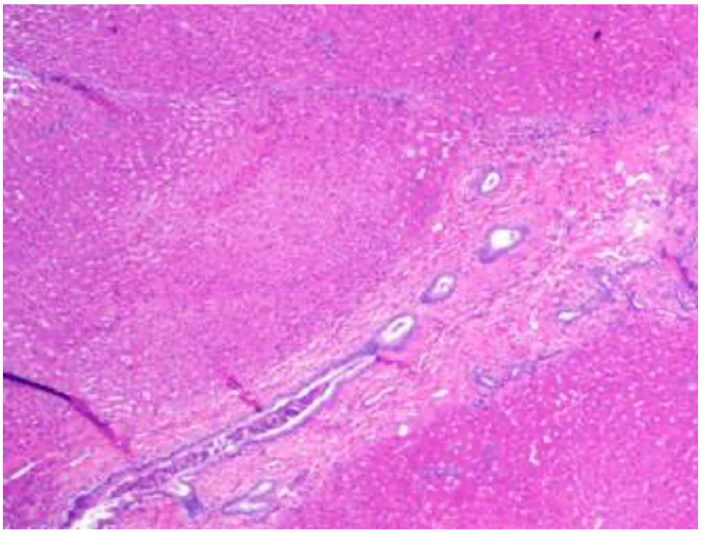

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Figure 3 Pathology of liver biopsy. Pathological findings of the liver biopsy showed poorly developed, dilated or absent portal vein branches.

OUTCOME AND FOLLOW-UP

Postoperative anti-infective therapy, rehydration, hemostasis, liver protection, and nutritional support were provided. Subsequently, cardiac enzymes were reassessed: Troponin I 0.005 ng/mL, myoglobin 141.7 ng/mL, creatine kinase isoenzyme 1.3 ng/mL, and B-type natriuretic peptide 33 pg/mL. Additionally, liver function assessed on postoperative days 1, 3 and 7 showed no abnormalities.

The patient had a satisfactory postoperative recovery and was subsequently discharged from the medical facility. However, during routine outpatient follow-up, she was admitted to the respiratory department on two separate occasions in November 2021 and February 2023 for the treatment of recurring cough and hemoptysis, respectively. Sputum bacterial culture revealed the presence of *Pseudomonas aeruginosa* infection. Subsequent re-evaluation of the abdominal enhanced CT scan revealed irregular liver morphology, splenomegaly, multiple tortuous dilated blood vessels at the splenic hilum, and pancreatic atrophy (Figure 1F and G).

DISCUSSION

Coexistent Abernethy malformation and CF are infrequent, and a comprehensive examination of the pertinent academic sources yielded no documented occurrences. Intraoperative venography showed multiple tortuous dilated vessels in the splenic hilum, abnormal blood flow into the inferior vena cava through the left renal vein, and portal vein branches and side branches were present, which supported the diagnosis of Abernethy malformation type II[8,9].

There is evidence suggesting a potential association between Abernethy malformation and CF with the occurrence of splenomegaly. Abernethy malformation results in splenomegaly due to obstruction of blood return from the splenic vein as a result of portal vein hypoplasia and abnormal blood shunting. CF is a monogenic disorder resulting from mutations in the *CFTR* gene, which encodes the epithelial ion channel responsible for the transportation of chloride and bicarbonate ions. These mutations lead to impaired mucus hydration and clearance, resulting in the obstruction of lumens of the respiratory, pancreatic, and biliary tracts, as well as abnormal secretion from exocrine glands[10]. Cystic fibrosis liver disease (CFLD) frequently manifests with hepatic steatosis, cholestasis, and progressive cirrhosis, leading to portal hypertension and subsequent splenomegaly[11,12]. Additionally, non-cirrhotic portal hypertension can arise in CFLD, potentially attributed to inflammatory and fibrotic paracaval portal vein lesions[13]. Therefore, it is hypothesized that the splenomegaly observed in this child was a result of a combination of both diseases.

Splenomegaly may cause secondary hypersplenism, which is clinically manifested by hypoplasia of one or more blood vessels. Complications such as infection, anemia, and hemorrhage can easily arise. In the present case, the child exhibited splenomegaly, reduced peripheral leukocyte count, and thrombocytopenia, indicating the presence of hypersplenism, and bone marrow aspiration was performed to exclude the possibility of hematological disorders. The respiratory system of this child with CF exhibited manifestations such as recurrent respiratory infections and hemoptysis following birth, with imaging indicating the presence of bronchiectasis[14]. In this particular instance, postnatal asphyxia was not observed, and the child had a history of serum transfusion and electrolyte disorders at the age of 2 mo. The diagnostic value of chloride concentration in the sweat test for CF is substantial[15]. Although the child's serum electrolyte examination before and after hospitalization and surgery did not reveal any significant abnormalities, the sweat electrolyte examination was regrettably not conducted during the hospitalization period. Consequently, the diagnosis of CF was based on clinical manifestations and genetic test results. The genetic analysis indicated that the patient's father and mother possessed heterozygous alleles for the causative gene. The specific mutations were identified at positions

c.233_c.234insT and c.2909G>A, which have not been documented in the pertinent databases. In accordance with Mendelian inheritance patterns, the likelihood of the disease manifesting in the patient's siblings was 1/4. However, it is important to note that the patient's brother and sister had no similar history of the disease, and no genetic testing was conducted on them.

Misdiagnosis and underdiagnosis are common occurrences in cases of Abernethy malformation and CF. A comprehensive medical history and meticulous physical examination are invaluable in enhancing diagnostic accuracy. In the presence of splenomegaly, varices of the digestive tract, and hepatic encephalopathy, it is imperative to consider the potential occurrence of Abernethy malformation. Similarly, when encountering a patient with recurrent respiratory tract infections, alongside a history of hemoptysis and abnormal sweating, it is crucial to contemplate the possibility of CF. Patients with Abernethy malformation accompanied by upper gastrointestinal varices may have hematemesis after food stimulation, and CF may also have massive hemoptysis due to bronchiectasis. When inquiring about the history, it is imperative to exercise caution in accurately identifying the two conditions.

The management of Abernethy malformation encompasses both conservative approaches and surgical interventions aimed at rectifying abnormal blood flow[16,17]. Conversely, CF is primarily addressed symptomatically to mitigate respiratory infections, impede disease advancement, and the advent of genetic testing technology has emerged as a valuable tool to enhance diagnosis and treatment precision[10,18]. Consequently, patients exhibiting clinical suspicion of CF necessitate routine genetic testing.

CONCLUSION

Coexisting Abernethy malformation and CF is rare. In cases where patients present with unexplained thrombocytopenia, splenomegaly, and hypersplenism, it is advisable to perform enhanced abdominal CT to detect Abernethy malformation. In instances where children exhibit symptoms such as hemoptysis, recurrent respiratory infections, and bronchiectasis, it is crucial to raise awareness regarding the possibility of CF, and genetic testing may be conducted to establish a conclusive diagnosis. The co-occurrence of Abernethy malformation and CF is a clinically infrequent phenomenon that necessitates a detailed clinical history, as well as comprehensive laboratory and imaging evaluation to improve diagnostic accuracy.

FOOTNOTES

Author contributions: Yin HQ and Xu ZY designed the work and revised the manuscript; Zhang LJ was responsible for writing the original draft; Liu XY and Che TF collected and analyzed the patient data; All authors approved the final version to be submitted.

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CASE REPORT

Glucocorticoid reduction induced chorea in pediatric-onset systemic lupus erythematosus: A case report

Yan-Qiu Xu, Miao Wang, Ying Zhang

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Abstract

BACKGROUND

Pediatric-onset systemic lupus erythematosus (SLE) is typically more severe than adult-onset SLE, with a higher incidence of nervous system involvement. Chorea is a relatively rare neurological complication reported in 2.4%-7% of SLE patients. In particular, chorea induced by glucocorticoid dose reduction is even rarer. Herein, we report the case of a girl with SLE, who developed chorea during the process of glucocorticoid therapy reduction.

CASE SUMMARY

We describe a 14-year-old girl who was diagnosed with SLE. She was treated with methylprednisolone and rituximab, and her symptoms improved. On the second day after the methylprednisolone dose was reduced according to the treatment guidelines, the patient developed chorea. Her condition improved after adjusting her glucocorticoid regimen.

CONCLUSION

This case is a reminder that extra attention to chorea is required in SLE patients during glucocorticoid dose reduction.

Key Words: Glucocorticoid; Chorea; Pediatric systemic lupus erythematosus; Case report

Core Tip: Chorea can be induced by glucocorticoid dose reduction in patients with pediatric-onset systemic lupus erythematosus (SLE). Patients with SLE should be closely monitored during glucocorticoid reduction.

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INTRODUCTION

Pediatric-onset systemic lupus erythematosus (SLE) is generally more severe and has a higher incidence of neurological involvement than adult-onset SLE. The most prevalent neuropsychiatric syndrome manifestations include headache, cognitive dysfunction, and mood disorders[1]. Chorea is a relatively rare neurological complication reported in approximately 2.4%-7% of SLE patients (Table 1), and is rarer in SLE patients undergoing glucocorticoid therapy reduction. We report a pediatric patient with SLE, who improved after treatment with glucocorticoid and immunosuppressants. When the patient's condition was assessed as stable, the glucocorticoid was reduced according to routine treatment. Unfortunately, the glucocorticoid reduction induced chorea. With an increase in glucocorticoid dosage, the symptoms of chorea improved. This case is a reminder that extra attention to chorea is required in pediatric-onset SLE patients during drug dose reduction.

CASE PRESENTATION

Chief complaints

A 14-year-old female with fever, facial erythema, facial ulcers, mouth ulcers and alopecia was admitted to our rheumatology department.

History of present illness

Two months before admission, the patient began to develop facial ulcers with swelling, and no improvement was observed following treatment with clindamycin and metronidazole. Fever occurred one month before admission, and routine blood examination showed that the white blood cell count and red blood cell count were decreased. C-reactive protein (CRP) was normal, erythrocyte sedimentation rate (ESR) was 96 mm/h, and her body temperature continued to rise after dexamethasone and cefuroxime administration. One week previously, facial erythema accompanied by gaze (Video 1), fever, facial and oral ulcers, ulceration and bleeding on the ulcer surface, internal and external genital ulcers, severe hair loss, pharyngitis, and erythema on the fingertips of both hands and toes were observed.

Physical examination

A body temperature of 37.6 ℃, blood pressure of 108/76 mmHg, heart rate of 126 beats/min, and respiratory rate of 20 times/min were noted. Ulceration and scabbing can be seen in the oral cavity. Facial erythema, ulcers at the fingertips of both hands and toes, vulvar ulcers and scar alopecia were observed. No joint tenderness. The remaining physical examinations showed no significant abnormalities.

Laboratory examinations

The results of laboratory examinations were as follows: ANA1: 1000, natural anti-SSA antibody, anti-dsDNA antibody, anti-nucleosome antibody, anti-cardiolipin antibody, and P-ANCA were positive. CRP was 9.78 mg/L, ESR was 68 mm/h, complement 3 (C3) was 0.11 g/L, and complement 4 (C4) was 0.01 g/L. The white blood cell count, red blood cell count, platelet count and hemoglobin were decreased, and a bone marrow biopsy showed no abnormalities. Respiratory virus, Mycoplasma infection, and procalcitonin results were negative. Given the patient's clinical symptoms, she was diagnosed with SLE. The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2000) was 13 and we evaluated the activity as medium level. Following intravenous methylprednisolone 80 mg/d administration over five days and rituximab 500 mg once, the child's symptoms improved. C3 and C4 increased (C3 0.29 g/L, C4 0.02 g/L) and routine blood levels were normal. CRP and ESR decreased to within the normal range. The SLEDAI-2000 was 2. On the sixth day, methylprednisolone was reduced to 60 mg/d. The patient's body weight was 60 kg. The dosage of glucocorticoid as prednisone was 1.25 mg/kg/d due to decreased disease activity. Unfortunately, new symptoms emerged after one day of glucocorticoid reduction, her limbs and head exhibited involuntary dance-like movements, such as, turning of the neck, intermittent flexion and extension of fingers, waving the hand, and stretching of the arm (Videos 2 and 3). Further examination of the cerebrospinal fluid (CSF) including CSF biochemistry, next-generation sequencing of CSF, and autoimmune encephalitis antibody were negative. Anti-streptolysin O was negative. Thus, infectious encephalitis and autoimmune encephalitis were excluded.

Imaging examinations

Cranial magnetic resonance imaging revealed acute cerebral infarction in the left centrum semiovale.

Table 1 Prevalence of chorea in systemic lupus erythematosus

Year	Study	Prevalence
1987	Chorea in systemic lupus erythematosus and "lupus-like" disease: association with antiphospholipid antibodies	2.4%
2001	The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus	2%
2002	The incidence and prevalence of neuropsychiatric syndromes in pediatric onset systemic lupus erythematosus	7%
2006	Neuropsychiatric manifestations in pediatric systemic lupus erythematosus: a 20-year study.	7%
2007	Neuropsychiatric involvement in pediatric systemic lupus erythematosus	Approximately 5%

FINAL DIAGNOSIS

Based on the patient's manifestations which included involuntary dance like movements of her limbs and head, and positive anti-cardiolipin antibody, she was diagnosed with chorea.

TREATMENT

As the SLEDAI-2000 changed to 27, we decided to administer more glucocorticoid. The patient received methylprednisolone (80 mg/d), intravenous immunoglobulin (20 g/d) for 3 d, cyclophosphamide (0.2 g every other day), low molecular weight heparin (2050 IU/d), sertraline (25 mg/d), and olanzapine (5 mg at night).

OUTCOME AND FOLLOW-UP

The patient's chorea symptoms improved significantly and she was able to move normally and answer questions clearly (Video 4).

DISCUSSION

SLE is an invasive autoimmune disease characterized by multiple system injury including the central nervous system. Among the neurological manifestations, chorea is rare in pediatric SLE patients[2]. The distinguishing feature of SLE is the production of autoantibodies, with the formation of immune complexes that precipitate at the vascular level, causing organ damage[3].

Previous studies have found that chorea can appear at any time in pediatric SLE, during the entire process of disease activity and clinical remission, and even several months after the onset of symptoms[4]. Glucocorticoid is the most important therapeutic agent in SLE patients with chorea. In this case, we treated pediatric lupus erythematosus with the standard glucocorticoid dosage. As the patient's condition improved, we gradually reduced the dosage of glucocorticoid according to the treatment guidelines[5]. However, the patient developed chorea symptoms on the second day of glucocorticoid reduction. As reported in the literature[6], the occurrence of chorea in SLE may be caused by the action of immune complexes, cytokines, and antiphospholipid antibodies (aPL) on cerebral blood vessels, which cause vascular occlusion, and corresponding brain dysfunction. Glucocorticoid dose reduction may lead to intensification of the inflammatory storm, and an increase in immune complexes which block cerebral blood vessels. Therefore, SLE should be fully re-evaluated when the glucocorticoid dose is reduced.

Chorea in SLE has been strongly associated with aPL. The positivity of aPL in SLE patients varies from 12% to 30%[7]. In a 50-patient study, among patients with positive aPL and chorea, 58% were diagnosed with SLE[8]. The pathophysiology of positive aPL with chorea in SLE has not been clearly identified. It may be involved in activation of aPL leading to neuronal disorders. aPL may pass through the blood-brain-barrier and connect to unknown antigens in the central nervous system, or to microthrombi that disturb local circulation in small cerebral vessels, causing disruption of the blood-brain-barrier, which normally protects the central nervous system from plasma proteins and cells[9]. Glucocorticoid dose reduction may lead to re-activation of aPL and result in brain thrombosis.

CONCLUSION

The emergence of chorea can be induced by glucocorticoid dose reduction in patients with pediatric-onset SLE. As shown by our case, we remind clinicians that when SLE patients have positive aPL, they should be particularly careful when reducing the dosage of glucocorticoid.

FOOTNOTES

Author contributions: Xu YQ contributed to the collection of medical record data and writing the first draft; Wang M and Zhang Y contributed to critically reviewed the paper; all authors actively contributed to the writing and reviewing of the article and approved the final version.

Informed consent statement: This study was conducted with the approval of the ethics committee of Chongqing Hospital of Traditional Chinese Medicine (approval No. 2023-GAKY-KS-XYQ). The patient gave explicit informed consent to report her clinical case.

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CASE REPORT

Primary pulmonary lymphoepithelioma-like carcinoma misdiagnosed as lung squamous cell carcinoma: A case report

Chang-Jie Yin, Guang-Jie Wang, Xiao-Mei Su, Dong Li

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Abstract

BACKGROUND

Primary pulmonary lymphoepithelioma-like carcinoma (PPLELC) is an uncommon subtype of squamous cell carcinoma (SCC) of the lung, closely associated with Epstein-Barr virus (EBV) infection. The pathological features of PPLELC closely resemble those of SCC, which makes it prone to misdiagnosis. Surgical intervention constitutes the primary treatment approach for PPLELC.

CASE SUMMARY

This report describes a 44-year-old woman who was hospitalized for 1 mo due to left chest pain. Computed tomography revealed a mass shadow in the anterior basal segment of the left lower lobe, and a subsequent needle biopsy suggested SCC. The patient underwent radical tumor resection in the lower left lobe of the lung, and postoperative pathological examination indicated lymphoepithelial carcinoma, and the test for EBV encoded small RNA was positive. Following surgery, the patient was scheduled to receive four cycles of adjuvant chemotherapy, using the paclitaxel + carboplatin regimen, but the patient refused further treatment.

CONCLUSION

PPLELC is an exceptionally rare subtype of lung SCC and is prone to misdiagnosis.

Key Words: Primary pulmonary lymphoepithelioma-like carcinoma; Lung cancer; Squamous cell carcinoma; Misdiagnosis; Epstein-Barr virus; Case report

Core Tip: Primary pulmonary lymphoepithelioma-like carcinoma (PPLELC) is a rare subtype of squamous cell carcinoma (SCC) of the lung, closely associated with Epstein-Barr virus infection. The pathological features of PPLELC bear similarities to those of SCC, which makes it prone to misdiagnosis. Surgery is the primary treatment for PPLELC. Here, we present a recent case of PPLELC at our hospital, initially misdiagnosed as SCC of the lung.

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INTRODUCTION

Lung cancer has the highest incidence rate among cancers worldwide. Non-small cell lung cancer is the most common type, accounting for about 85% of cases[1], including squamous cell carcinoma (SCC) and adenocarcinoma. Among subtypes of lung SCC, primary pulmonary lymphoepithelioma-like carcinoma (PPLELC) is rare and its specific pathogenesis remains unknown, but it may be associated with Epstein-Barr virus (EBV) infection[2,3]. PPLELC displays a higher incidence rate in Southeast Asia compared with Europe and the United States[4]. PPLELC lacks specific clinical manifestations, and its pathological changes are similar to those of lung SCC. Typical features include extensive lymphocyte infiltration and better prognosis in comparison with other types of non-small cell lung cancer[5]. Currently, surgery is the primary treatment method for PPLELC, and there is no universally accepted standard for postoperative adjuvant treatment. In this report, we present a case of PPLELC initially misdiagnosed as lung SCC, highlighting a rare subtype prone to misdiagnosis. This case report might serve as a valuable reference for improving diagnosis and treatment of PPLELC.

CASE PRESENTATION

Chief complaints

Dull pain in the left chest for 1 mo.

History of present illness

The patient developed dull pain in the left chest in February 2023, with no other accompanying discomfort such as chest tightness or breathing difficulties. However, the patient did not seek further examination or treatment at that time.

History of past illness

The patient had rheumatoid arthritis for > 7 years that was effectively managed with stable control through oral medication.

Personal and family history

No history of smoking or drinking.

Physical examination

The performance status score was 1, and there was no peripheral lymphadenopathy. Additionally, no positive signs were found in the heart, lungs, or abdomen.

Laboratory examinations

Tumor markers: α-fetoprotein 3.86 ng/mL; carcinoembryonic antigen 0.68 ng/mL; carbohydrate antigen (CA)199 5.20 U/mL; CA125 79.70 U/mL; CA153 27.90 U/mL.

Imaging examinations

Computed tomography (CT) showed a lobulated mass shadow in the anterior basal segment of the left lower lobe, with a size of approximately 3.3 cm × 3.6 cm × 3.5 cm. There was adjacent pleural thickening and adhesion, indicating the possibility of a neoplasm. However, no tumors were detected during magnetic resonance imaging (Figure 1).

Pathological findings

On March 10, 2023, the patient underwent a needle biopsy, and the pathological diagnosis indicated SCC (Figure 2), with CD56(-), cytokeratin (CK)8/18(+), chromogranin A (CgA)(-), Ki-67 (+, 30%), P40(+), synaptophysin (Syn)(-), and thyroid transcription factor 1 (TTF-1)(-) on immunohistochemistry. According to the results, the patient underwent radical lung cancer surgery on March 18, 2023. Postoperative pathology suggested no lymph node metastasis. The findings showed

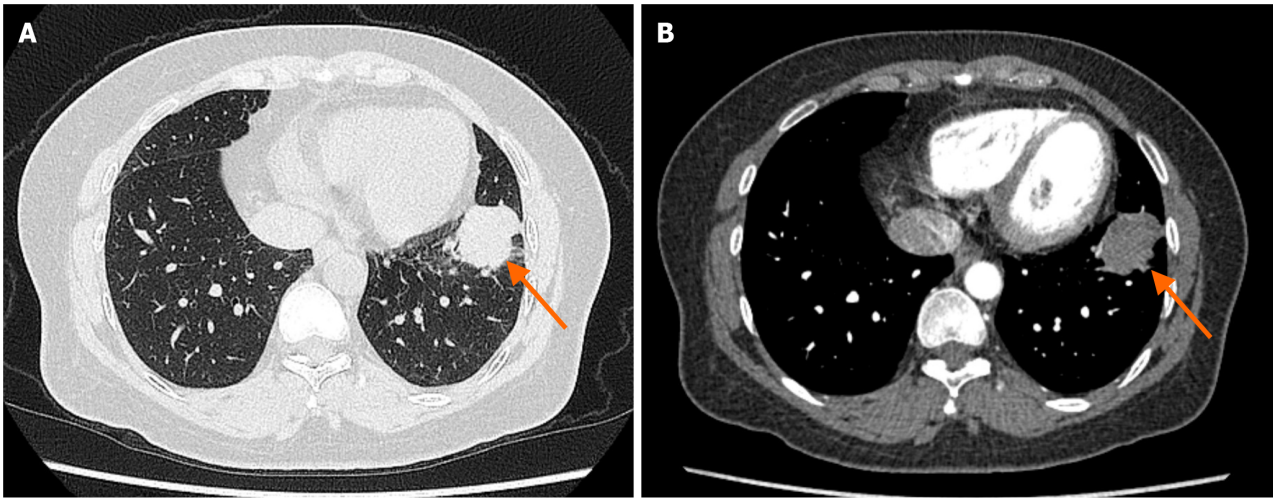

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Figure 1 Computed tomography images of the chest. A and B: The tumor size was approximately 3.3 cm × 3.6 cm × 3.5 cm (orange arrow).

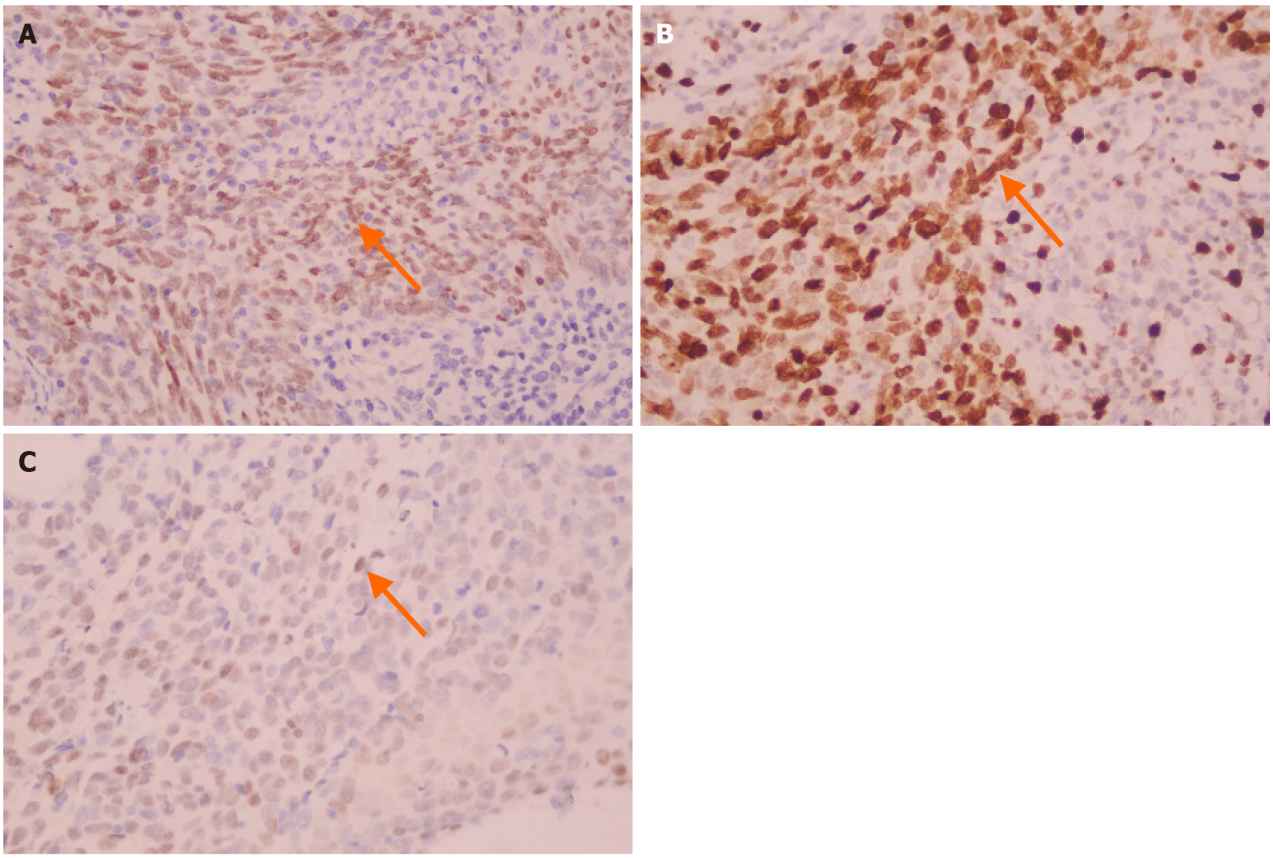

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Figure 2 Immunohistochemistry staining of biopsy specimens and Epstein-Barr virus encoded small RNA testing indicate primary pulmonary lymphoepithelioma-like carcinoma (magnification 400 ×). A: Immunohistochemistry (IHC) staining of needle biopsy specimens (orange arrow); B: IHC staining of postoperative specimens (orange arrow); C: Presence of Epstein-Barr virus encoded small RNA in postoperative specimens (orange arrow).

positivity for EBV encoded small RNA (EBER), CK5/6, CK8/18, Ki-67 (60%), and P40, while TTF-1 was negative (Figure 2), leading to a diagnosis of PPLELC.

FINAL DIAGNOSIS

Based on the pathological examination results, the patient was diagnosed with PPLELC (pT2aN0M0 IB).

TREATMENT

The patient was scheduled to undergo four cycles of postoperative adjuvant chemotherapy. The chosen protocol for chemotherapy was paclitaxel + carboplatin.

OUTCOME AND FOLLOW-UP

The patient refused further treatment and examination, and no further follow-up was carried out.

DISCUSSION

PPLELC is a rare type of lung cancer, accounting for about 0.92% of all lung malignancies[6]. It was first reported in the 1980s[3], and was classified as other unclassified cancer by the World Health Organization (WHO) in 2015. However, in the current 2021 5th edition of WHO classification of thoracic tumors, lymphoepithelial carcinoma of the lung is defined as a subtype of SCC [International Classification of Diseases for Oncology code: 8082/3]. The incidence of PPLELC is low in Western countries, but it has a higher prevalence in Asia, particularly in Taiwan, Hong Kong, and Guangdong, China[6, 7]. This disease primarily affects young nonsmoking patients, with a higher prevalence among women. Clinical manifestations of PPLELC are mostly nonspecific, and in the early stage, patients typically exhibit no obvious symptoms. As the tumor progresses, symptoms such as cough, phlegm, hemoptysis, and chest pain may manifest[8].

Most Asian patients with PPLELC are diagnosed with EBV infection, suggesting a strong correlation between EBV and PPLELC[6]. In this report, we performed *in situ* hybridization of EBER on patient specimens, and the results were positive, further indicating the association between EBV infection and PPLELC. However, the specific pathogenic mechanism of EBV has not been fully elucidated to date.

Typical PPLELC is a solitary nodule near the pleura, and the lesion is generally < 3.5 cm. The CT imaging features often include a burr sign and a lobed sign[9]. Although the imaging manifestations are not distinct from those of other types of lung malignancies, lymph node metastasis is uncommon[10]. In this case, PPLELC grew under the pleura, with a size of approximately 3.3 cm × 3.6 cm × 3.5 cm as measured by CT. No lymph node metastasis was observed, and the imaging findings were consistent with typical PPLCLE characteristics.

The histopathological manifestations of PPLELC closely resemble those of nasopharyngeal carcinoma. A distinctive feature of PPLELC is the presence of a large number of tumor-infiltrating lymphocytes in the tumor background[2], and positivity for EBER. However, in biopsy specimens, these characteristics may not be obvious due to the small sample size. Research has identified common immune markers for PPLELC, such as P40, P64, and CK5/6, which are similar to those seen in SCC, leading to a potential risk of misdiagnosis[11]. In this case, the patient underwent lung biopsy, which yielded a small gray-white tissue sample of about 1.5 cm. The immune markers observed were: CD56(-), CK8/18(+), CgA(-), Ki-67 (+, 30%), P40(+), Syn(-), and TTF-1(-). Due to the limited amount of biopsied tissue, the typical microscopic characteristics of PPLELC were not observed, and the immune markers appeared to align with SCC, resulting in a misdiagnosis. However, during surgical treatment, a larger specimen was obtained, and the postoperative pathological examination revealed a significant number of tumor-infiltrating lymphocytes. The immune markers observed were CK5/6(+), CK8/18(+), Ki-67(+,60%), P40(+), and TTF-1(-). Additionally, the *in situ* hybridization examination suggested EBER(+). These findings ultimately led to the correct diagnosis of lymphoepitheliomatous carcinoma. It is notable that EBER, a crucial diagnostic test that distinguishes SCC from PPLELC, is highly affordable, costing approximately 240 Chinese yuan, making it accessible to the majority of patients.

The treatment approach for PPLELC currently lacks unified guidelines, and there are no specific National Comprehensive Cancer Network guidelines for its management. However, radical surgery is usually considered the primary treatment method. According to a study involving 52 PPLELC patients who underwent radical surgery alone, only six experienced relapse, with recurrence developing between 10.6 and 41.1 mo[8]. Overall, the prognosis was favorable. Currently, it is believed that early-stage patients usually do not require postoperative adjuvant therapy, while chemotherapy can extend the overall survival of advanced-stage patients. In clinical practice, platinum-based dual-drug combination chemotherapy is commonly used as the first-line treatment for advanced PPLELC[7]. Therefore, in this case, we suggested the patient to undergo four cycles of postoperative adjuvant chemotherapy with the paclitaxel + carboplatin regimen, but the patient refused further treatment and examination, and no further follow-up was carried out.

CONCLUSION

PPLELC is a rare subtype of lung cancer that is frequently misdiagnosed due to its microscopic appearance and immune markers closely resembling those of SCC. Currently, there are no standardized treatment guidelines for PPLELC. Surgical intervention is a common treatment approach, and patients may benefit from postoperative adjuvant chemotherapy.

FOOTNOTES

Author contributions: Yin CJ collected all the data related to the case report and drafted the manuscript; Wang GJ and Su XM collected and produced the relevant pictures; Li D provided expert analysis and revised the manuscript; and all authors have read and approved the final manuscript.

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CASE REPORT

Median arcuate ligament syndrome complicated with gallbladder stones: A case report

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Abstract

BACKGROUND

Median arcuate ligament syndrome (MALS) is a rare disease caused by compression of the celiac trunk artery by the median arcuate ligament (MAL). It can cause symptoms of postprandial abdominal pain, weight loss, and nausea and vomiting.

CASE SUMMARY

A 55-year-old woman was admitted due to abdominal pain, nausea and vomiting. On admission, the patient presented with epigastric pain that worsened after eating, without signs of peritoneal irritation. Computed tomography angiography of the upper abdomen showed compression of the proximal segment of the abdominal trunk, local luminal stenosis with angular "fishhook" changes, which changed significantly during forceful inspiration and expiration; gallbladder stones; and multiple cysts in the liver. Abdominal duplex ultrasonography showed that peak systolic velocity was 352 cm/s. After diagnosis of MALS was confirmed, an arch ligament release procedure was performed. MALS has no specific symptoms and can be misdiagnosed as other abdominal diseases. Awareness of MALS should be improved to avoid misdiagnosis. The commonly used treatment option is MAL release and resection of the peripheral ganglion of the celiac trunk artery.

CONCLUSION

The diagnosis and treatment of MALS must be individualized, and MAL release is effective and provides immediate symptomatic relief.

Key Words: Median arcuate ligament syndrome; Celiac artery compression syndrome; Operative decompression; Case report

Core Tip: Median arcuate ligament syndrome (MALS) is a rare disorder caused by compression of the median arcuate ligament against the celiac trunk. Patients with MALS often present with chronic postprandial abdominal pain, nausea, vomiting, diarrhea, and unexplained weight loss. Imaging examination is the preferred screening method. MALS is confused with many common diseases, and definitive diagnosis requires exclusion of other causes of abdominal pain. In this case, combination of gallbladder stones and chronic cholecystitis made it easy to miss diagnosis of MALS. Clinicians should be more aware of MALS. Surgery can provide immediate symptomatic relief and can be an effective treatment for MALS.

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INTRODUCTION

Median arcuate ligament syndrome (MALS), also known as celiac artery compression syndrome or Dunbar syndrome, is due to the celiac trunk artery or celiac ganglion being compromised by the fibrous ligaments that connect the fibrous crus of the diaphragm on both sides (forming the anterior edge of the aortic hiatus). Caused by external compression of the median arcuate ligament (MAL). The MAL is usually located above the starting point of the celiac trunk, and 10%–24% of people have MAL located in the front and upper part of the celiac trunk, so it is easy to compress arteries or adjacent nerves and cause chronic, recurrent abdominal pain and other clinical symptoms. The typical symptoms of MALS are postprandial abdominal pain, weight loss, nausea, and vomiting[1]. The aim of this report is to document a case of MALS treated with surgical decompression. This case report was elaborated in accordance with the SCARE criteria.

CASE PRESENTATION

Chief complaints

A 55-year-old female patient presented with intermittent epigastric pain for 20 d, and the postprandial abdominal pain was aggravated without other specific manifestations.

History of present illness

Symptoms started 20 d before presentation with postprandial abdominal pain. Abdominal pain was intermittent and did not radiate from the back or perineum. She visited the local hospital and underwent computed tomography (CT) examination, which suggested: (1) Gallbladder stones (Figure 1A); (2) MALS; and (3) multiple hepatic cysts (Figure 1B). Treatment with anti-inflammatory and choleretic drugs and nonsteroidal analgesic drugs, but the abdominal pain was not significantly relieved. For further treatment, she came to our hospital.

History of past illness

The patient had a past history of right upper abdominal pain, did not go to the hospital for examination, and the abdominal pain was relieved by self-administration of anti-inflammatory and choleretic drugs.

Personal and family history

The patient denied any family history of abdominal pain.

Physical examination

On physical examination, the vital signs were: Body temperature, 36.5 ℃; blood pressure, 120/78 mmHg; heart rate, 76 beats/min; respiratory rate, and 18 breaths/min. There was no yellow sclera, flat and soft abdomen, upper abdominal tenderness, and no rebound tenderness. No vascular murmur was heard in the upper abdomen. The visual pain score was 6.

Laboratory examinations

Before the surgical procedure, routine blood analysis, liver and kidney function tests, amylase, blood coagulation function, inflammatory indexes (C-reactive protein, high-sensitivity C-reactive protein and procalcitonin) and tumor markers (carbohydrate antigens 19-9 and 125, carcinoembryonic antigen) were normal.

Imaging examinations

Upper abdominal B-ultrasound and abdominal contrast-enhanced magnetic resonance imaging showed multiple gallbladder stones and multiple liver cysts. No obvious abnormality was found in esophagogastroduodenoscopy. CT

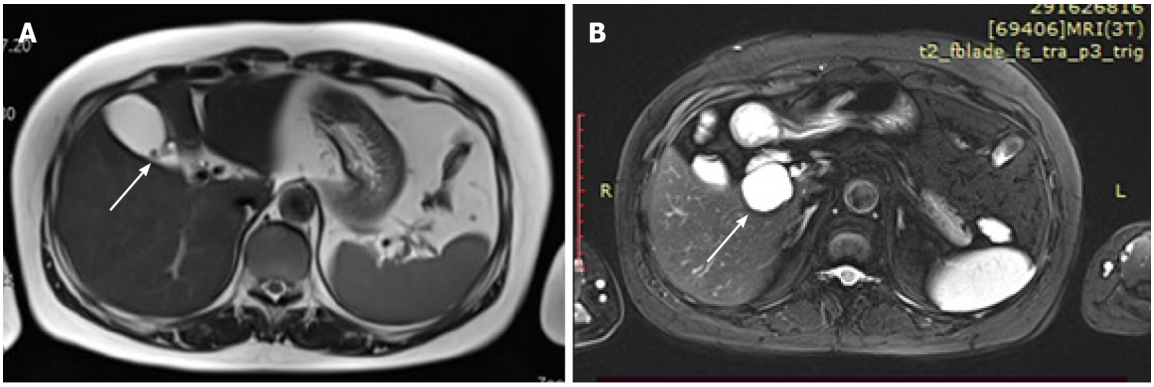

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Figure 1 Upper abdominal magnetic resonance imaging showing gallbladder stones and multiple liver cysts. A: Gallbladder stones and cholestasis. Arrow indicates gallbladder stones; B: Arrow indicates caudate lobe cyst of liver about 3 cm × 3 cm in size.

angiography (CTA) showed that the origin of the celiac trunk was high, and the adjacent MAL compressed the initial segment of the celiac trunk with severe V-shaped stenosis (Figure 2A-C). When exhaling hard, the degree of stenosis was aggravated.

FURTHER DIAGNOSTIC WORK-UP

Giving antispasmodic, analgesic, cholagogic and other symptomatic treatment, the symptoms of abdominal pain were not significantly improved. Abdominal duplex ultrasound (DUS) was performed, which showed hemodynamically significant extrinsic compression of the abdominal trunk (> 70% reduction of the lumen) with peak systolic velocity of 352 cm/s.

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was: (1) MALS, (2) gallbladder stones with chronic cholecystitis; and (3) multiple liver cysts.

TREATMENT

After diagnosis of MALS was confirmed and since the patient's symptoms remained unimproved (epigastric pain and worsening after meals), MAL release was recommended. Under general anesthesia, the patient was placed in a supine position, and a median epigastric incision was made to enter the abdomen layer by layer. Exploration showed multiple cysts in the liver, full gallbladder, slightly thickened cyst wall, and no other abnormalities. The lesser sac was opened to reveal the superior margin of the pancreas, the No.8a lymph node was removed to expose the common hepatic artery, and the proximal dissection revealed the left gastric artery and splenic artery. The anterior wall of the celiac trunk was dissected toward the root to reveal the dense and thickened fibrous tissue compressing the celiac trunk, and the ligament was freed and severed (Figure 3A and B), and the celiac trunk to the anterior wall of the abdominal aorta was fully exposed. The lateral and posterior aspects of the celiac trunk were exposed, the surrounding fibrous tissue and celiac ganglion were removed, and the junction of the abdominal trunk and abdominal aorta was skeletonized (Figure 3C). The gallbladder was resected in the conventional way, and a large hepatic cyst (3.1 cm × 3 cm) on the surface of the caudate lobe of the liver (Figure 1B) was drained by opening the cyst. The patient had an uneventful operation with intraoperative bleeding of 50 mL. The postoperative recovery was smooth, with significant relief of self-perceived abdominal pain symptoms, and she was discharged 10 d later.

OUTCOME AND FOLLOW-UP

Postoperative pathological results showed chronic cholecystitis and liver cyst. The VAS score was 2 again before discharge, and the patient was free of epigastric pain symptoms at the 3 mo follow-up.

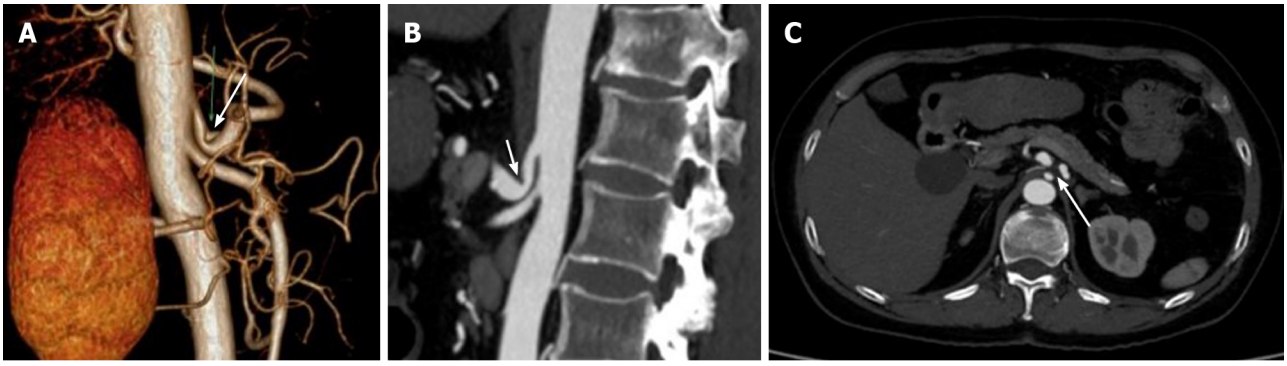

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Figure 2 Imaging examination of median arcuate ligament syndrome. A and B: computed tomography (CT) angiography coronal images showed a V-shaped stenosis at the beginning of the celiac trunk (the arrow indicates) and distal expansion; C: CT showed compression at the beginning of the celiac trunk (indicated by arrow).

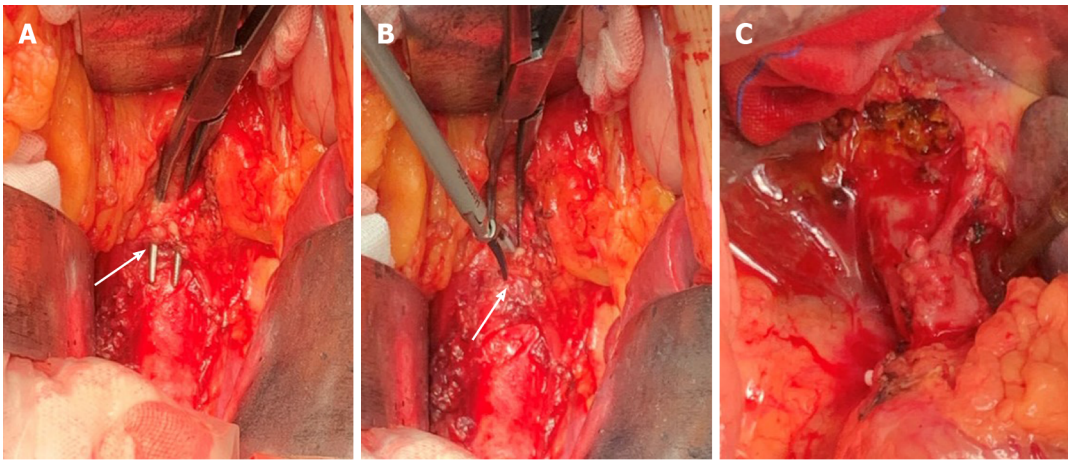

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Figure 3 Intraoperative imaging of median arcuate ligament release surgery. A: Freeing the arcuate ligament (indicated by arrow); B: Ultrasonic knife cut the arcuate ligament (indicated by arrow); C: Ligament release + end of celiac trunk peripheral ganglion resection.

DISCUSSION

MALS, also known as mid-foot of the diaphragm compression syndrome, celiac artery compression syndrome, celiac artery cord syndrome, and Dunbar syndrome, is a rare disorder caused by compression of the celiac trunk by the MAL [2]. The MAL is a tough fibrous arch that connects the right and left aortic fissures (T12–L1) at the level of the diaphragmatic feet on both sides and crosses anterior to the aorta above the root of the celiac trunk. The origin of the celiac trunk is in approximately 85% of the anterior wall of the abdominal aorta between the upper third of the T11 vertebral body and the upper third of the T12 vertebral body[3]. Compression of the celiac trunk can result from a high starting point of the celiac trunk or a low attachment point of the MAL diaphragm foot. In 1971, Lindner *et al*[4] carried out 75 autopsy studies and noticed the anatomical variation of MAL. Harjola reported for the first time that MALS, Dunbar *et al*. passed angiography, summarized and reported 15 cases of MALS[5]. However, the pathophysiological mechanism of MALS is still controversial, and the related theories are as follows. (1) Compression of the celiac trunk by MAL leads to a reduction in its blood flow. Long-term compression of MAL can lead to narrowing of the arterial lumen, and histological studies have shown that arterial smooth muscle, elastic fibers and inner and outer membrane proliferation in patients with MALS may lead to complete occlusion of the artery, resulting in organ ischemia and epigastric pain[2]. (2) When the blood flow within the larger collateral circulation is inhibited by the celiac trunk stenosis, the collateral vessels proliferate to compensate for part of the blood supply. For example, blood is supplied to the celiac trunk *via* the collateral vessels such as the pancreaticoduodenal artery arch. Clinical symptoms are caused by a decrease in blood flow shunted to the celiac trunk supply area after feeding due to dilatation of the superior mesenteric artery[6]. (3) Neuropathic factors: long-term chronic compression and overstimulation of the nerve tissues around the celiac stem can lead to abdominal pain symptoms. This neurological compression can directly stimulate sympathetic pain fibers, and combined with sympathetic excitation causes visceral vasoconstriction, resulting in local ischemia. Pathological studies have shown that the compressed nerve fibers and perineural fibrosis with small nerve fiber proliferation, and that blockade targeting the celiac ganglion relieves abdominal pain symptoms[7]. Therefore, it has been hypothesized that

neuropathic pain is one of the causes of MALS.

The true prevalence of MALS is not known due to the diverse clinical presentation. However, it is more common in women aged 30–50 years (female: male: 4:1) and in patients with a lean body mass[6], and has been reported in pediatric patients. The symptoms of MALS are: chronic abdominal pain after meals; nausea, vomiting, diarrhea and unexplained weight loss. Clinical signs include epigastric tenderness, abdominal vascular murmur and an increased end-expiratory murmur[2]. In a study of 43 patients with surgically treated MALS, 91% of patients presented with abdominal pain[8]. Of these, 62% presented with postprandial pain, 32% with postexercise pain, and 6% had abdominal pain of unknown origin. In addition, 40% of the patients had significant weight loss, 30% had nausea and vomiting, and 47% had an audible epigastric vascular murmur. Since the symptoms of MALS are similar to those of other abdominal diseases, the diagnosis of MALS requires the exclusion of other causes of abdominal pain. As in the present case, gallbladder stones were found on physical examination for > 1 year, and there was a history of epigastric pain that was relieved by oral anti-inflammatory and choleretic drugs, during which she did not seek medical attention in the hospital. The patient had no specific abdominal symptoms, no epigastric paroxysmal severe pain and radiating pain in the right back or shoulder, and abdominal symptoms did not improve after administration of antispasmodic, analgesic and choleretic drugs. Therefore, this patient's abdominal pain may have had another cause. A thorough examination of the digestive system is required to rule out other conditions that more commonly cause abdominal pain. This includes various imaging tests: upper gastrointestinal endoscopy, colonoscopy, abdominal ultrasound (US), abdominal CT, CTA or angiography, and related laboratory tests. In this case, imaging (CT and magnetic resonance imaging) confirmed gallbladder stones and cholestasis (Figure 1). CT of the upper abdomen suggested (Figure 2C) compression and narrowing of the abdominal trunk, and further CTA and DUS examination confirmed diagnosis of MALS.

When MALS is clinically suspected, abdominal DUS can be used as the screening tool of choice. DUS during maximal inspiration and expiration can dynamically demonstrate the site and extent of celiac arterial stenosis[9]. DUS is cheaper and radiation-free compared to CTA, which has the advantage of 3D reconstruction to obtain images of the celiac arteries, facilitating the observation of the compressed arteries from different angles. The CTA features of MALS include a sharp V-shaped depression or a characteristic hook-like appearance of the proximal wall of the celiac trunk[10]. This hooked appearance is helpful in differentiating the stenosis from atherosclerotic and aortitis stenosis. CTA also allows dynamic observation of arterial compression, and the degree of arterial compression stenosis in MALS patients varies with respiration, with heavier luminal stenosis in the expiratory phase than in the inspiratory phase. CTA can also show the establishment of collateral circulation after celiac trunk stenosis, and studies have shown that collateral circulation can be established when the degree of celiac trunk stenosis exceeds 65%, including pancreaticoduodenal artery arch type, dorsal pancreatic artery type, and intrahepatic type (phrenic artery). It is important to note that the presence of typical stenosis on imaging does not necessarily have clinical symptoms[11]. In a retrospective observational study, only one of eight patients with > 50% stenosis of the celiac artery was symptomatic[12].

Due to the rich collateral circulation between the superior mesenteric artery and the celiac trunk, abdominal trunk stenosis does not necessarily cause ischemic manifestations in the organs. In the diagnosis of gastrointestinal ischemia, gastric exercise tonometry (GET) has a high sensitivity (76%) and specificity (92%)[13]. Mensink *et al*[14] found that 29 (67.4%) of 43 patients with celiac trunk compression (> 70%) with significant abdominal pain had positive GET, 22 with MAL release alone, and seven with MAL release combined with celiac artery reconstruction. Follow-up at 39 mo revealed normal GET results in asymptomatic patients (83%) and abnormal GET results in patients with persistent symptoms (25%). This suggests that MALS is an ischemic syndrome with a good surgical outcome. Despite its high diagnostic accuracy, GET is a complex and time-consuming procedure that is not easily used as a routine test.

The treatment of MALS focuses on its possible pathophysiological mechanisms, which involves MAL release to relieve compression of the celiac trunk, combined with or without abdominal lymph node dissection. The combination of MAL release with peripheral ganglionectomy of the celiac trunk may be an option for treating the neurological cause of pain. In contrast, MAL release combined with periceliac trunk ganglionectomy is effective and is currently a widely accepted treatment[15]. Traditionally, MALS is treated by open surgery. After dissecting and separating the MAL and celiac trunk, the MAL is cut and the proximal part of the celiac trunk is completely exposed to release the compression; at the same time, the peripheral ganglion of the celiac trunk is removed. In recent years, there has been a trend to release the pressure on the celiac trunk through laparoscopy, and laparoscopic and surgical robots have been reported abroad for the treatment of MALS[16]. Jimenez *et al*[17] retrospectively analyzed data from 400 patients who underwent surgical treatment for MALS. Of these, 279 underwent open surgery and 121 underwent laparoscopic surgery. Overall, 85% of the patients experienced postoperative symptom relief. Postoperative symptom recurrence rates were 6.8% and 5.7% for patients in the open and laparoscopic groups, respectively; 9.1% of laparoscopic procedures were intermediate to open due to bleeding. There were no surgery-related deaths in either group. The laparoscopic group had the advantages of shorter hospital stay, shorter fasting time, less risk of postoperative complications, less intraoperative bleeding, better postoperative pain relief, and smaller incisions. Intraoperative US multispectral or angiography can visualize the effect of postoperative abdominal stem decompression, which can be addressed by arterial reconstruction if stenosis persists. These include: Abdominal aortic bypass or peritoneal artery patch angioplasty. Percutaneous transluminal angioplasty with or without stenting provides an adjunctive treatment for persistent stenosis after MAL release. However, endovascular intervention alone does not address extrinsic compression of the celiac artery and, therefore, intervention alone is ineffective in the treatment of MALS. One report found that patients who had a percutaneous peritoneal plexus block preoperatively and whose symptoms were relieved had a better postoperative outcome. However, high-quality evidence to support this claim is lacking[18].

CONCLUSION

MALS is a rare clinical syndrome for which there is no general consensus on diagnostic and therapeutic criteria. MALS can be easily confused with many common diseases. In this case, the patient also had gallbladder stones with chronic cholecystitis (which was confirmed by postoperative pathology). Gallbladder stones can also cause epigastric pain and intolerance to fried or high-fat foods (characterized by nausea and bloating), making it likely that the diagnosis of MALS will be missed. Clinicians should raise awareness of MALS, especially in patients with chronic abdominal pain, and consider it earlier. Surgery can provide immediate relief and can be an effective treatment for MALS. However, there is no consensus on the best surgical treatment. As for whether there is an intrinsic pathological link between gallstones and MALS, it remains to be confirmed by more similar cases.

FOOTNOTES

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CASE REPORT

Uterine rupture due to adenomyosis in an adolescent: A case report and review of literature

Nah Ihm Kim, Ji Shin Lee, Jong Hee Nam

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Abstract

BACKGROUND

Uterine rupture is a fatal medical complication with a high mortality rate. Most cases of uterine rupture occur in late pregnancy or during labor and are mainly related to uterine scarring due to previous surgical procedures. Adenomyosis is a possible risk factor for uterine rupture. However, spontaneous uterine rupture due to severe adenomyosis in a non-gravida-teenaged female has not been reported in the literature to date.

CASE SUMMARY

A 16-year-old girl was referred to our hospital for acute abdominal pain and hypovolemic shock with a blood pressure of 90/50 mmHg. Radiologic studies revealed a huge endometrial mass with multiple nodules in the lung, suggesting lung metastasis. The patient underwent an emergency total hysterectomy and wedge resection of the lung nodules. Histologically, the uterus showed diffuse adenomyosis with glandular and stromal dissociation. Lung nodules were endometrioma with massive hemorrhage. Immunohistochemistry demonstrated that the tumor cells were positive for PAX8, ER, and PR expression, leading to a final diagnosis of pulmonary endometriosis and uterine adenomyosis. Following surgery, the patient remains in good condition without recurrence.

CONCLUSION

This is the first case of spontaneous uterine rupture due to adenomyosis in a non-gravida adolescent.

Key Words: Uterus; Adenomyosis; Malignancy; Endometrioma; Case report

Core Tip: Uterine adenomyosis is rare in adolescents but can lead to massive menorrhagia. Differential diagnoses, early detection, and therapeutic care must be provided to avoid hysterectomy in adolescents.

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INTRODUCTION

Adenomyosis is a commonly encountered estrogen-dependent disease in women across the lifespan, causing heavy menstrual bleeding, intense pelvic pain, and infertility[1]. Adenomyosis is associated with an increased risk of many obstetrical complications, such as uterine rupture, postpartum hemorrhage and fetal growth restriction[2].

Spontaneous uterine rupture due to adenomyosis in an adolescent and non-gravida female is extremely rare, with no cases reported in the literature. Here, we describe a unique case of uterine rupture due to adenomyosis with coexisting pulmonary endometriosis and review previously reported, similar cases[3-11].

CASE PRESENTATION

Chief complaints

A 16-year-old female visited the emergency department in hypovolemic shock.

History of present illness

The patient was obese (150 cm, 78 kg, body mass index 34.7 kg/m^2) and complained of dysmenorrhea that suddenly occurred a month ago.

History of past illness

The patient was suffering from irregular menstrual period, heavy menstrual bleeding and was on ferrous sulfate medication for anemia (hemoglobin levels 9.2 g/dL). She had no history of taking other medications, including oral contraceptives or hormonal agents.

Personal and family history

The patient was a virgin. She had no other significant personal or family history or previous surgical history. Menarche began at the age of 12.

Physical examination

Physical examination revealed a distended abdomen with diffuse abdominal tenderness. A palpable mass was not detected.

Laboratory examinations

Laboratory findings showed decreased hemoglobin levels (6 g/dL). LDH (1476 U/L), CA-125 (1063 U/mL), and CA19-9 (1347 U/mL) levels were significantly increased. An hCG blood test was negative.

Imaging examinations

An enhanced computed tomography (CT) scan of the entire abdominal pelvic cavity revealed a 13 cm × 12.5 cm × 10 cm heterogeneously enhancing mass in the uterine corpus, suggesting a uterine malignancy (sarcomatous change of uterine myoma with lung metastasis), such as rhabdomyosarcoma or leiomyosarcoma (Figure 1). The chest CT also revealed enhancing lesions in the right lower lung (3.5 cm) and left lower lung (1.5 cm), suggesting metastatic lesions.

FINAL DIAGNOSIS

The preoperative differential diagnosis was uterine malignancy, such as rhabdomyosarcoma or leiomyosarcoma, with lung metastasis. However, there was no histologic evidence of malignancy in the resected surgical specimen. The final diagnosis was diffuse adenomyosis with extensive hemorrhage. Histopathology after a wedge resection confirmed

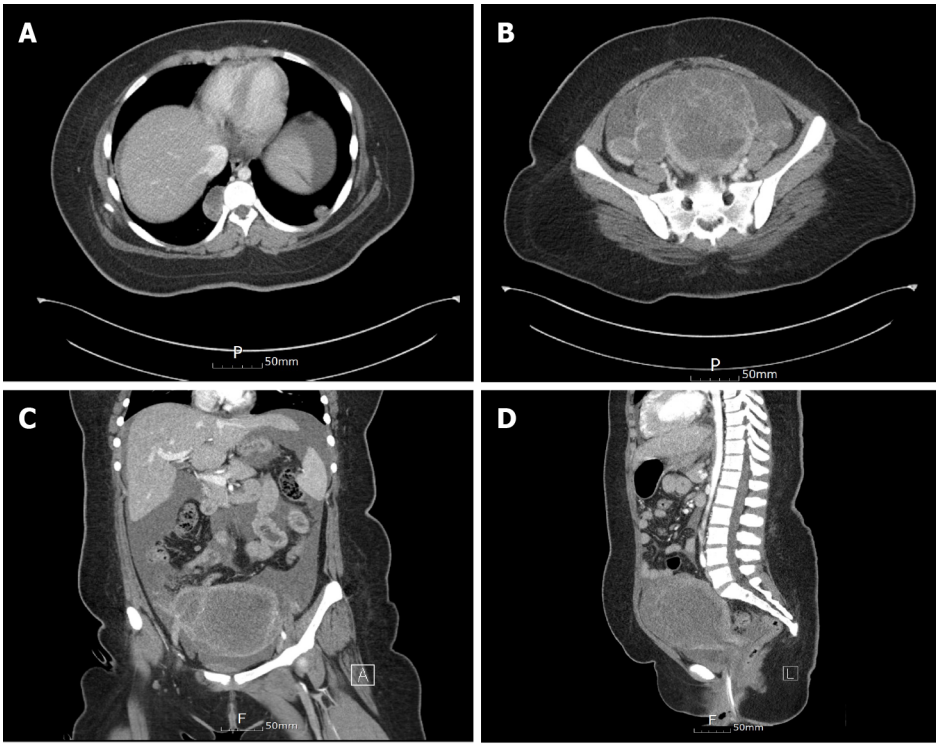

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Figure 1 Radiologic findings. A: Chest computed tomography scan revealed two nodules, suggesting metastatic lesions; B-D: Abdominal computed tomography scan demonstrated a huge mass in the uterine corpus, suggesting a uterine malignancy (B: Axial; C: Coronal; D: Sagittal).

pulmonary endometrioma of both lung nodules.

TREATMENT

The patient underwent a total hysterectomy with bilateral salpingectomy and wedge resection of the lung nodules. Intraoperative findings revealed a 4 L blood-filled abdominal cavity, a 15 cm sized huge necrotic tumor filling the uterus with blood, and multiple uterine perforations (Figure 2).

Macroscopic examination of the resected surgical specimen demonstrated an enlarged uterus with extensive hemorrhagic necrosis and hematoma. There were no definite mass-like lesions in the uterine corpus. Under low-power microscopy, the uterus showed extensive necrosis from the endometrium to the entire myometrium due to hemorrhage (Figure 3). Pathologic evaluation revealed diffuse adenomyosis with hemorrhagic necrosis and glandular and stromal dissociation.

While there was no evidence of malignancy in the uterine specimen, histology of the two lung nodules showed hemorrhagic cystic lesions lined by the cuboidal epithelium and surrounded by hemosiderin-laden macrophages. The cuboidal epithelium showed no cytologic atypia or mitotic activity. Immunohistochemistry was positive for CD10, PAX8, ER, and PR and negative for TTF-1. Ectopic endometrial glands outside the uterine cavity confirmed a final diagnosis of pulmonary endometriosis.

OUTCOME AND FOLLOW-UP

All elevated blood tests normalized after surgery. Following surgery, radiologic studies revealed no specific abnormalities. The patient is currently taking Diengest (Visanne) and is doing well without any side effects or recurrence.

DISCUSSION

Adenomyosis is a gynecologic disorder, associated with a high risk of obstetric complications and adverse pregnancy outcomes[12]. Uterine rupture is an obstetric emergency with a high incidence of morbidity and mortality. It mostly occurs during the third trimester of pregnancy or delivery, with a prevalence rate of 0.05% in pregnant women[13]. A history of surgery, such as a cesarean section or myomectomy, is the most common risk factor for uterine rupture[14]. Advanced maternal age, multiparity, uterine malformation, excessive uterine pressure, and rare intrauterine manipu-

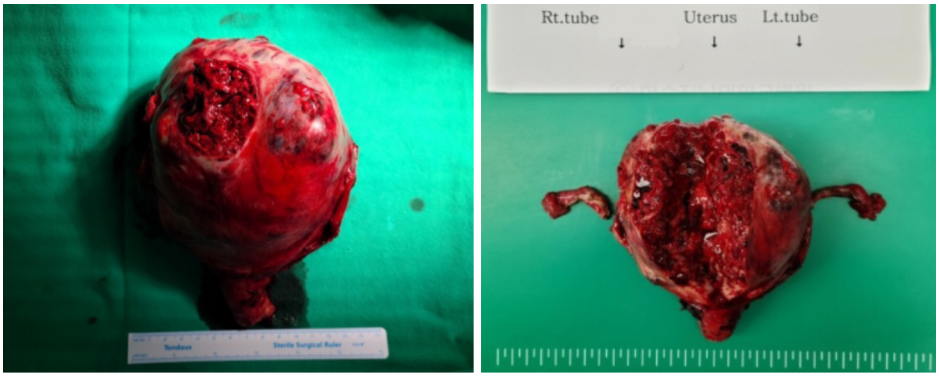

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Figure 2 Operative findings. Intraoperative findings revealed a huge necrotic mass with multiple uterine perforations.

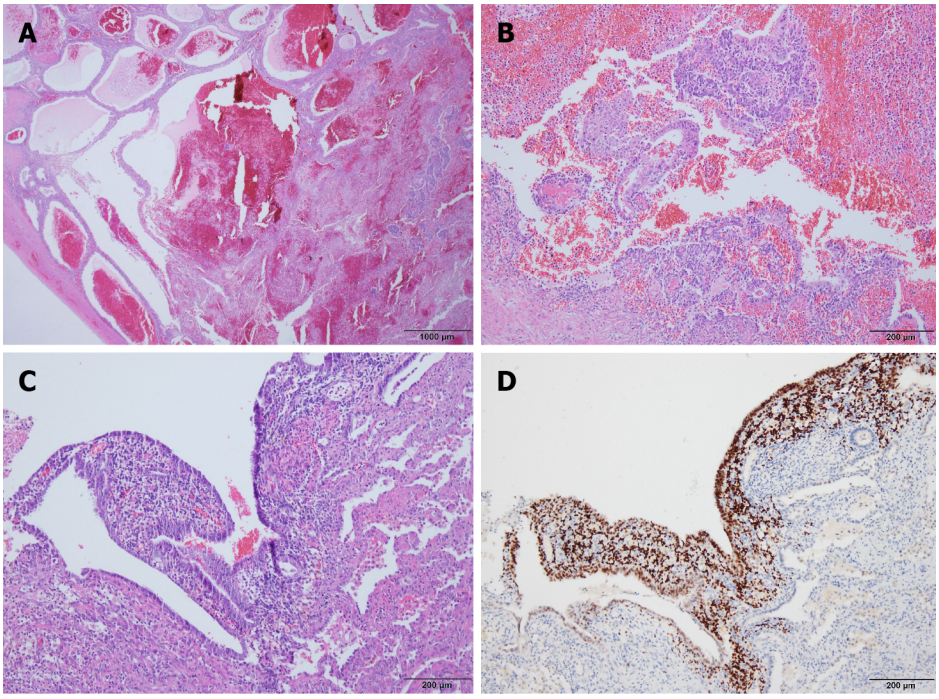

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Figure 3 Microscopic findings. A: Under low-power microscopy, the uterus showed diffuse adenomyosis with extensive hemorrhagic necrosis [Hematoxylin-and-eosin stain (H&E), × 20]; B: At a higher magnification, pathologic evaluation revealed glandular and stromal dissociation with necroinflammatory exudates (H&E, × 100); C: Histology of lung nodules demonstrated Müllerian type epithelium surrounded by endometrial stroma (H&E, × 100); D: Immunohistochemistry revealed positivity for ER in the tumor cells (immunohistochemistry, × 100).

lation are other important risk factors that may precipitate uterine rupture[15]. Spontaneous uterine rupture of an unscarred primigravid uterus is an extremely rare event[13,16]. Nikolaou *et al*[8] reported that nine of 12 cases of spontaneous uterine rupture were associated with adenomyosis.

Uterine adenomyosis involves the endometrial tissue growing into the uterine muscle wall of the uterus. This can cause painful menstrual periods, heavy bleeding, and pelvic pressure or discomfort. While adenomyosis mostly occurs in adult life, it can also involve adolescents in a mild to moderate form[17-23]. The exact cause of adenomyosis is unknown, but hormonal imbalances, uterine abnormalities, and certain medical conditions may increase the risk of this condition. Exacoustos *et al*[17] suggested using ultrasound as a diagnostic tool for adenomyosis could avoid the need for histologic diagnosis and facilitate appropriate management. Adenomyosis treatment may include medication or surgery in severe cases[1,22,24,25].

Obesity is associated with a higher risk of endometriosis and adenomyosis, although the exact relationship is unclear. The increasing incidence of adenomyosis and endometriosis in adolescents may be due to obesity[26]. Adenomyosis and endometriosis may increase the risk of obstetric complications[12]. Obesity can increase the risk of uterine rupture by increasing uterine pressure and may complicate the diagnosis of adenomyosis due to increased estrogen levels. Hormonal imbalances and inflammation may play a role in the development of both of these conditions in obese individuals[27].

Table 1 Cases of spontaneous uterine rupture due to adenomyosis

Ref.	No.	Age	Gravida/Para	Endometriosis	Pregnancy	Hysterectomy
Azziz[3] (1986)	1	41	NA/P10	NA	Yes	NA
	1	NA	NA	NA	Yes	NA
	1	25	NA/P0	NA	Yes	NA
	1	38	NA/P1	NA	Yes	NA
	1	33	NA/P0	NA	Yes	NA
	1	25	NA/P1	NA	Yes	NA
	1	26	NA/P3	NA	Yes	NA
Bensaid *et al*[4] (1996)	1	22	G1/P1	NA	Yes	No
Mueller *et al*[5] (1996)	1	30	G1/P0	No	Yes	Total hysterectomy
Pafumi *et al*[6] (2001)	1	30	G3/P2	No	Yes	Total hysterectomy
Villa *et al*[7] (2008)	1	30	G1/P1	Rectovaginal endometriosis	Yes	Total hysterectomy
Nikolaou *et al*[8] (2013)	1	33	G1/P1	Ovarian endometriosis	Yes	Subtotal hysterectomy
Indraccolo *et al*[9] (2015)	1	37	G2/P0	No	Yes	No
Li *et al*[10] (2021)	1	32	G1/P0	No	Yes	No
Vimercati *et al*[11] (2022)	1	27	G0/P0	No	Yes	Total hysterectomy
Present case	1	16	G0/P0	Pulmonary endometriosis	No	Total hysterectomy

NA: Not available.

However, hormones could cause different reactions to the adenomyotic stroma, especially in pregnant individuals. The adenomyotic stroma has two response patterns to pregnancy-related hormones. One is the superficial foci of adenomyosis, which are located within the endometrium's basal layer with no to minimal decidualization. In the second pattern, deeper adenomyosis foci could exhibit prominent decidualization[3]. Higher expression of progesterone receptors in the stromal components of adenomyosis is likely related to stromal decidualization, supporting the theory that adenomyosis is a response to progesterone during pregnancy[8]. Furthermore, abundant decidual transformation of stromal cells in adenomyosis results in atrophy and necrosis of muscle cells[7]. Necrosis of the uterine muscles causes atony and muscle cell separation, leading to life-threatening rupture[28].

This could explain the spontaneous uterine rupture due to adenomyosis in pregnant women. About 15 cases of spontaneous uterine rupture due to adenomyosis have been reported to date (Table 1). Azziz[3] reviewed 11 cases of uterine rupture, seven of which were associated with adenomyosis. Uccella *et al*[29] reviewed the literature and found that 1 in 25 reported cases of prelabor spontaneous uterine rupture involved adenomyosis. Mueller *et al*[5] reported a primigravida woman who experienced spontaneous uterine rupture at 18 wk of gestation due to heavily decidualized adenomyosis. Nikolaou *et al*[8] reported a case of rupture of an unscarred uterus caused by multiple foci of adenomyosis with a marked decidual reaction in the adenomyotic stroma. Indraccolo *et al*[9] also reported a woman with uterine rupture caused by adenomyosis.

However, all previously reported cases were related to pregnancy, and the current case in a nulligravida juvenile patient is the first reported to date. The spontaneous uterine rupture in this nulligravida adolescent girl may be due to increased uterine pressure and changes in estrogen due to her obesity. We believe that transmural adenomyotic foci with significant hemorrhage and subsequent splaying of the myometrial smooth muscle fibers may have weakened the myometrium, ultimately rupturing the uterus.

Uterine rupture, a rare adenomyosis complication, can be fatal if not treated immediately. It can be difficult to diagnose adenomyosis, as the symptoms are similar to those of other conditions, such as endometriosis[30,31]. A preoperative diagnosis of spontaneous uterine rupture is also challenging, especially in a juvenile patient with nulligravida. Unrecognized adenomyosis is particularly problematic in younger patients[32]. The standard workup for all women who present with severe dysmenorrhea and heavy menstrual bleeding should include an evaluation for adenomyosis, regardless of their age and health conditions. Regular monitoring is key to managing the risks associated with adenomyosis, especially in obese, nulliparous teenagers. Early detection may lower the risk of associated infertility and adverse obstetric outcomes, including uterine rupture[11].

The present case highlights the importance of considering a spontaneous uterine rupture diagnosis in women with a history of adenomyosis, regardless of their parity. Extensive adenomyosis may contribute to uterine wall weakness and increase the risk of uterine rupture, even in women who are not pregnant. If adenomyosis is detected early, fertility can be preserved with medical treatment and hysterectomy avoided.

CONCLUSION

Here we present an extraordinary case of spontaneous uterine rupture due to adenomyosis in a nulliparous adolescent. Uterine rupture should be considered for all female patients with adenomyosis, regardless of gestational status and history. It should be distinguished from other neoplastic conditions and early detection may lower the risk of adverse obstetric outcomes, including uterine rupture.

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FOOTNOTES

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CASE REPORT

Multiple therapies relieve long-term tardive dyskinesia in a patient with chronic schizophrenia: A case report

Liang Lv, Ping Guo, Min Feng, Yu Fang, Shi-Kai Wang, Huan-Xin Chen

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Abstract

BACKGROUND

Tardive dyskinesia (TD) is a serious and disabling movement disorder; it impairs social function and quality of life and increases the mortality rate. TD is usually induced by the use of antipsychotic drugs; however, the underlying mechanism remains unclear. Pharmacotherapy of TD includes cholinergic drugs, benzodiazepines, ginkgo biloba extract (GBE), antioxidants, amantadine, propanolol, botulinum toxin, valbenazine, and deutetrabenazine, whereas the non-pharmacotherapy approach includes modified electroconvulsive therapy (MECT) and deep brain stimulation. We successfully treated a chronic schizophrenia patient with comorbid long-term severe TD using deutetrabenazine, clozapine, and MECT.

CASE SUMMARY

A 69-year-old woman who was diagnosed as having schizophrenia 16 years ago developed severe TD after 6-mo prescription of risperidone oral solution. Her TD symptoms did not resolve despite various treatments, such as GBE, vitamin E, trihexyphenidyl, promethazine, benzodiazepines, and switching to quetiapine and olanzapine. After admission, she was given deutetrabenazine 6 mg bid. Her buccal tremor was slightly resolved 3 d later; however, her tongue remained protruded and could not be retracted. Quetiapine was switched to clozapine on day 4, and the buccal tremor remarkably resolved, and the tongue could be retracted into the mouth from day 6 onward. After three sessions of MECT, the buccal tremor resolved further. Since then, she has been able to take a semifluid diet, and her quality of life improved remarkably during 6 mo of follow-up.

CONCLUSION

TD is a serious condition which could be caused by antipsychotic medications; however, the best strategy against TD is prevention and monitoring during using antipsychotics. For patients with TD caused by antipsychotic medication use,

multiple measures should be considered like switching to clozapine, adjunction with deutetrabenazine, or even MECT.

Key Words: Tardive dyskinesia; Antipsychotics; Clozapine; Deutetrabenazine; Electroconvulsive therapy; Case report

Core Tip: Tardive dyskinesia (TD) is a serious and disabling movement disorder, and its pathogenesis remains unclear. This report describes the treatment of TD caused by risperidone in a schizophrenia patient, which could not be improved by switching to the other second-generation antipsychotics like quetiapine and olanzapine, neither by adjunction with medications like benzodiazepines, ginkgo biloba extract, or antioxidants. Her TD symptoms were relieved remarkably after multiple measures like switching to clozapine, adjunction with deutetrabenazine, and modified electroconvulsive therapy. Multiple measures are therefore recommended for TD treatment.

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INTRODUCTION

Tardive dyskinesia (TD) is a serious and disabling movement disorder, which usually occurs after long-term use of antipsychotic drugs. TD is defined as the involuntary tic or dance-like movement (lasting for at least several weeks) of the tongue, lower jaw, as well as the extremities[1]. It is evaluated with tools like the abnormal involuntary movement scale (AIMS)[2]. TD impairs social function and quality of life and increases the mortality rate[1,3].

Common risk factors for TD include first-generation antipsychotics (FGAs), age, sex, and long-term exposure to dopamine receptor blocking agents. In patients with schizophrenia, the prevalence of TD induced by antipsychotics is 20%-25%[4]. Although FGAs are much more likely to induce TD than second-generation antipsychotics (SGAs), the incidence of TD has been increasing with the widespread use of SGAs, including their off-label use[5].

Although the mechanism underlying TD pathogenesis remains unclear[6], there are three pathophysiological hypotheses for TD, namely, dopamine hypersensitivity, gamma-aminobutyric acid deficiency, and oxidative stress. The treatments for TD include pharmacotherapy and non-pharmacotherapy[7]. Pharmacotherapy includes the administration of cholinergic drugs, benzodiazepines, ginkgo biloba extract (GBE), antioxidants, calcium channel blockers, amantadine, propanolol, and botulinum toxin, whereas non-pharmacotherapy includes modified electroconvulsive therapy (MECT) and deep brain stimulation[8]. However, only valbenazine and deutetrabenazine (Austedo) have been approved by the United States Food and Drug Administration for treating TD. We successfully treated a chronic schizophrenia patient with comorbid long-term severe TD using deutetrabenazine, clozapine, and MECT. We herein report the details on this case.

CASE PRESENTATION

Chief complaints

Uncontrollable, abnormal, and repetitive movements of the tongue and lower jaw for 16 years.

History of present illness

A 69-year-old woman, who was diagnosed as having schizophrenia 16 years ago, was treated with risperidone oral solution for delusion and auditory hallucination. Six months later, her psychotic symptoms remitted, but she developed TD with abnormal involuntary movement in the mouth, tongue, and cheek. She was hospitalized twice since these symptoms appeared; however, her TD symptoms did not resolve despite various treatments, which included adjunction with GBE, vitamin E, trihexyphenidyl, promethazine, and benzodiazepines, as well as switching to quetiapine and olanzapine (Table 1). She has been on a liquid diet for many years because her teeth had to be removed due to severely worn tongue.

History of past illness

The patient was diagnosed as having schizophrenia 16 years ago. She was found to be hypertensive 2 years ago, which has been well controlled with valsartan 80 mg/d and amlodipine besylate 10 mg/d.

Table 1 Timelines of patient events and medications in current admission and follow-up

Date	Event	Medication/s	Comment
July 2008	Hospitalization	ROS 4 mg/d	First onset with delusion and auditory hallucination
November 2009	TD	ROS 4 mg/d + Alp 0.4 mg qn + GBE	Psychotic symptoms resolved, but her bucco-linguo-masticatory syndrome appeared and could not be relieved by GBE
November 09-18, 2010		Que 0.2 g/d + Alp 0.4 mg qn + GBE 1 tab bid + Vit E 0.1/d	TD was not relieved by switching ROS to Que and combining it with GBE and Vit E
November 19, 2011		Ola 10 mg/d + Alp 0.4 mg qn + GBE 1 tab bid + Vit E 0.1/d	TD was not relieved by switching Que to Ola and combining it with GBE and Vit E
October 12, 2020	Readmission	Ola 10 mg/d + PTZ 25 mg bid + THP 2 mg bid	TD was not relieved by a combination of PTZ and THP during hospitalization
October 21, 2020-June 08, 2022		Que 0.2 g/d + PTZ 25 mg bid + Vit E 0.1/d	TD was not relieved by switching to Que and combining it with PTZ and Vit E
June 09-11, 2022	Readmission	Que 0.1 bid + DTB 6 mg bid + Vit E 0.1/d + PTZ 50 mg tid + Alp 0.4 mg qn	TD was slightly ameliorated when administered in combination with DTB after admission; however, her tongue could not be retracted into the mouth. Video 1 (June 10, 2022). Baseline: AIMS 31, PANSS 56, CGI 7. D3: AIMS 29, PANSS 56, CGI 6
June 12-15, 2022		Clo 25 mg/d + DTB 6 mg bid + Vit E 0.1/d + PTZ 25 mg tid + Lor 1 mg qn	TD was relieved remarkably after switching Que to Clo, and her tongue could now be retracted into the mouth. Video 2 (June 14. 2022) D7: AIMS 23, PANSS 52, CGI 4
July 16-19, 2021		Clo 25 mg bid + DTB 6 mg bid + Vit E 0.1/d + PTZ 25 mg qn + Lor 1 mg qn + MECT for the first session	TD was ameliorated after combining MECT, and the tremor in her lower jaw was reduced. D10: AIMS 22, PANSS 48, CGI 3
July 20-22, 2021		Clo 25 mg bid + DTB 6 mg bid + Vit E 0.1/d + MECT for the second session	TD did not worsen after stopping Lor and PTZ
July 23, 2021	Discharge		D14: AIMS 20, PANSS 48, CGI 3
July 24, 2021-now		Clo 25 mg bid + DTB 6 mg bid	TD did not worsen after stopping Vit E, and she could take a semi-fluid diet. Video 3 (December 26, 2022). D182: AIMS 20, PANSS 46, CGI 3

AIMS: Abnormal involuntary movement scale; Alp: Alprazolam; Clo: Clozapine; DTB: Deutetrabenazine; GBE: Ginkgo biloba extract; Lor: Lorazepam; MECT: Modified electroconvulsive therapy; Ola: Olanzapine; PANSS: Positive and Negative Syndrome Scale; PTZ: Promethazine; Que: Quetiapine; ROS: Risperidone oral solution; TD: Tardive dyskinesia; THP: Trihexyphenidyl; Vit E: Vitamin E.

Personal and family history
The patient denied any personal or family history of other diseases.

Physical examination
The physical examination was not remarkable except for TD symptoms (Video 1). Mental examination showed clear consciousness, passive contact, poor thinking with delusion of reference, and depressive mood because of involuntary movements. Her insight was poor. She was not found to be experiencing hallucinations.

Laboratory examinations
After admission, many related examinations were conducted, but no abnormalities were found.

Imaging examinations
A head computed tomography scan revealed no abnormality.

FINAL DIAGNOSIS
The patient was diagnosed with schizophrenia, TD, and hypertension.

TREATMENT
After admission, the patient was given deutetrabenazine 6 mg bid. Her buccal tremor was slightly resolved 3 d later, but her tongue was still protruded and could not be retracted back. Quetiapine was switched to clozapine on day 4; consequently, the buccal tremor remarkably resolved, and the tongue could be retracted into the mouth from day 6

onward (Video 2). She was encouraged to undergo additional MECT. After obtaining written informed consent, she was given three sessions of MECT, and the buccal tremor resolved further. On day 14, she was discharged with the prescription of clozapine (25 mg bid) and deutetrabenazine (6 mg bid) (Table 1).

OUTCOME AND FOLLOW-UP

After discharge, the patient could take a semifluid diet with clozapine (25 mg bid) and deutetrabenazine (6 mg bid), and her quality of life improved remarkably during 6 mo of follow-up (Video 3, Table 1).

DISCUSSION

TD is mainly caused by FGAs and managed by lowering the FGA dose or switching to SGAs, or it can be treated with deutetrabenazine and valbenazine. In this case, TD was induced by taking 4 mg risperidone daily for 6 mo, and TD did not completely resolve after switching to other SGAs like quetiapine and olanzapine. This was a case of late-onset schizophrenia with possible hypersensitivity to risperidone. In this case, the underlying mechanism of TD could be that the plasma concentration of risperidone was high because of reduced metabolic function in older patients. It could also possibly be explained by reduced number of dopamine receptors, leading to increased sensitivity to SGAs[9,10]. This case suggests that SGA use is also associated with a high risk of developing TD in patients with late-onset schizophrenia, which should be monitored with instruments like AIMS.

The patient responded poorly to medications like GBE, vitamin E, benzodiazepines, and promethazine. Her TD symptoms resolved partially with deutetrabenazine, a selective vesicular monoamine transporter 2 inhibitor[11], but resolved remarkably with clozapine. Clozapine is associated with a low risk of TD, which may be due to its low affinity to and rapid dissociation with dopamine D_2 receptors[12], suggesting that TD can be aggravated by long-term binding of dopamine D_2 receptors.

TD symptoms and mental symptoms of the patient resolved markedly after three sessions of MECT. Although MECT is not a first-line recommendation for treating TD[13], it poses no risk of precipitating, aggravating, or perpetuating TD and may be an important alternative choice for TD treatment.

CONCLUSION

In summary, TD is a serious condition caused by long-term use of antipsychotic medications. The underlying mechanism of TD is complex and remains unknown. The best treatment strategy for TD is prevention and monitoring during using antipsychotics. When it comes to treatment, multiple measures like switching to clozapine or combining it with deutetrabenazine or MECT could lead to a better prognosis than a single treatment.

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FOOTNOTES

Co-first authors: Liang Lv and Ping Guo.

Author contributions: Lv L, Guo P, Wang SK, and Chen HX conceived, designed, and refined the study protocol; Lv L, Fang Y, and Feng M were involved in data collection; Lv L and Fang Y analyzed the data; Guo P drafted the manuscript; Wang SK and Chen HX revised the manuscript; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Lv L and Guo P contributed equally to this work as co-first authors. The reasons for designating Lv L and Guo P as co-first authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-first authors 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, Lv L and Guo P contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Lv L and Guo P as co-first authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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CASE REPORT

Lung ultrasound for the early diagnosis of acute lung injury: A case report

Xin Zheng, Na Liu

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Abstract

BACKGROUND

The extensive availability of ultrasound (US) technology has increased its use for point-of-care applications in many health care settings. During anaesthesia and surgery, acute respiratory failure or pulmonary oedema are common life-threatening events that, if not recognized and treated appropriately, result in a high mortality rate.

CASE SUMMARY

We report a patient under anaesthesia whose lung US examination showed multiple vertical artefacts (B-lines) in the lung tissue, indicating pulmonary oedema. The respiratory state improved with the resolution of the pulmonary oedema after our treatment.

CONCLUSION

We believe that US of the lungs may be a useful tool for dynamic respiratory monitoring at the bedside during anaesthesia.

Key Words: Lung ultrasound; Acute respiratory failure; Ultrasound; Lung; Case report

Core Tip: The extensive availability of ultrasound (US) technology has increased its use for points of care applications in many health care settings. During anesthesia and surgery, acute respiratory failure or pulmonary edema are common life-threatening events that, if not recognized and treated appropriately, result in a high mortality rate. We report on a patient under anesthesia whose lung US examination showed multiple vertical artifacts (B-lines) in the lung tissue, indicating pulmonary edema. The respiratory state was improved with the resolution of pulmonary edema after our treatment. We believe that US of the lungs may be a useful tool for dynamic respiratory monitoring at the bedside during anesthesia.

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INTRODUCTION

Lung ultrasound (US) (LUS) is now a standard tool for the diagnosis of acute lung injury (ALI), which refers to a clinical syndrome characterized by bilateral lung injury, severe diffuse failure of the lung, and even hypoxemia[1]. Perioperative lung injury is the main cause of excess health care use, avoidable mortality, and postoperative morbidity[2]. If not recognized and treated appropriately, cases of mild pulmonary injury with nonspecific signs and symptoms would increase the morbidity and mortality rate[3]. Focused US (point-of-care US) is defined as an ultrasonic evaluation at the bedside, where an ultrasonic evaluation is conducted in real time[4]. These images are collected by the anaesthesiologist perioperatively, and they can immediately be integrated into the medical decision-making process. The reported case shows the importance of performing LUS to evaluate respiratory function in the operating room.

CASE PRESENTATION

Chief complaints

On arrival at the operating room, the patient presented with increased respiratory effort.

History of present illness

An 89-year-old man diagnosed with acute intestinal obstruction was scheduled to undergo laparoscopic exploration.

History of past illness

No basic past illness.

Personal and family history

His personal history shows no abnormalities.

Physical examination

His heart rate was 103 beats per minute, his blood pressure was 120/74 mmHg, and his respiratory rate was 22 breaths per minute.

Laboratory examinations

An arterial blood gas analysis was taken immediately, which showed a PH value of 7.25, partial oxygen pressure of 59 mmHg, partial carbon dioxide pressure of 48 mmHg.

Imaging examinations

His chest X-ray on the first day of admission showed no abnormal findings except for mild right pleural effusion (Figure 1). Bedside ultrasonography was performed and displayed the disappearance of lung sliding and the presence of multiple B-lines in both lungs (Figure 2).

FINAL DIAGNOSIS

We diagnosed pulmonary oedema using sonography.

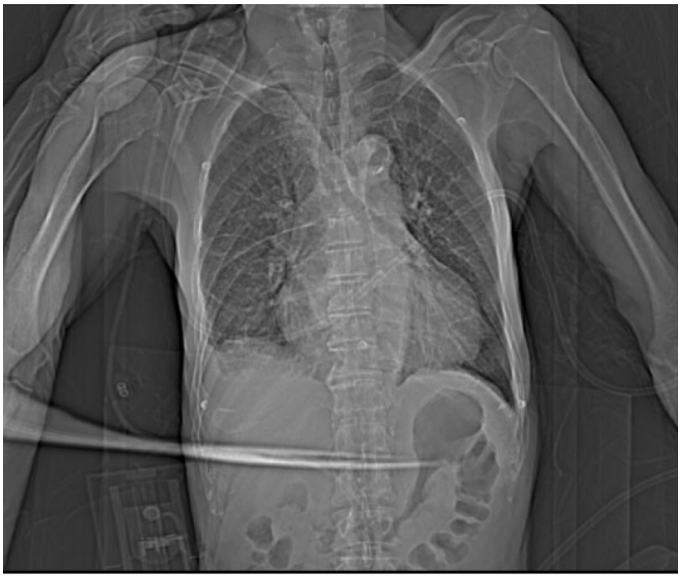

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Figure 1 Chest X-ray on the first day of admission.

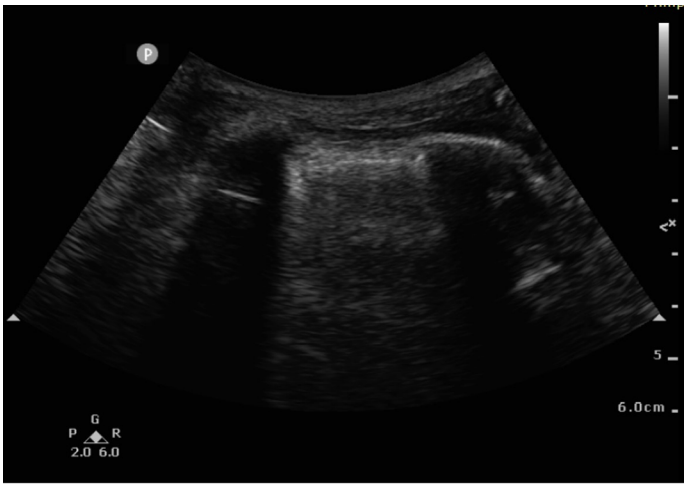

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Figure 2 Ultrasonography shows the presence of B lines.

TREATMENT

Intubation and ventilation were initiated immediately. Controlled ventilation was chosen using FiO_2 100% oxygen and 10-15 cm H_2O positive end-expiratory pressure (PEEP). While the patient was undergoing the lung recruitment manoeuvre with US, we observed that the area of collapsed alveoli reaerated as the PEEP reached 15 cm H_2O. Dobutamine and epinephrine were given after the valve preload, and his haemodynamics gradually stabilized.

OUTCOME AND FOLLOW-UP

After surgery, the patient was sent to the intensive care unit. His respiratory symptoms resolved on the second day (Figure 3), and 100% oxygen was gradually removed. The patient was successfully extubated and discharged after 12 d of hospitalization.

DISCUSSION

The current observational case showed that LUS is an important tool to monitor lung involvement in many different

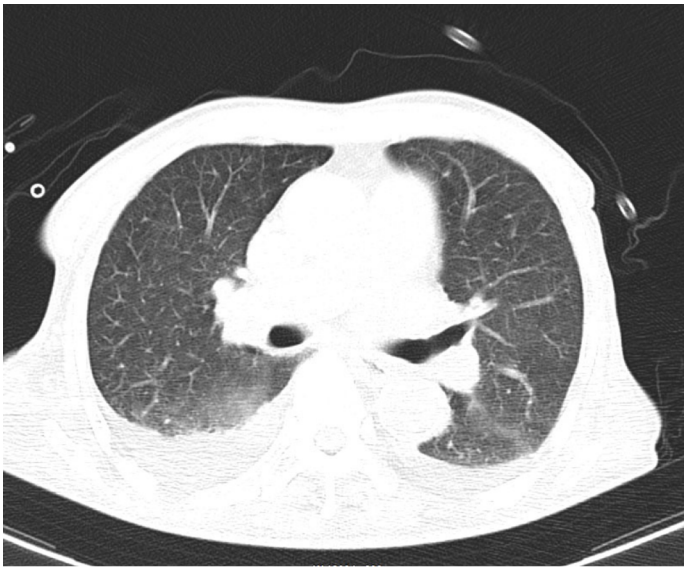

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Figure 3 A chest computed tomography scan shows the minimal presence of pulmonary oedema on the second day of intensive care unit admission.

situations. Perioperative lung injury complicates postoperative recovery for many patients. The rate of postoperative pulmonary complications is between 11% and 59%, which has led to a significant increase in mortality and morbidity and an increase in the use of hospital resources[5].Perioperative lung injury includes respiratory insufficiency, gas exchange disorders and pneumonia. Mild lung injury is generally not a threat to life; however, a delayed diagnosis may be harmful because it is associated with compromised circulation and respiration in unstable patients[6].

LUS can be performed at the bedside by an anaesthesiologist in the operating room and can provide accurate images of the lung state with diagnostic and therapeutic relevance[7]. A high sensitivity and specificity of LUS were shown in the diagnosis of pneumothorax and interstitial syndrome[4,8]. Although chest computed tomography (CT) is the gold standard to assess lung involvement[9], it necessitates the transfer of a ventilated patient out of the operating room. CT cannot always be performed promptly. Any delay in the provision of radiological evidence may be deleterious in some instances. LUS examination may be a valid alternative to CT scans[10]. It is not intrusive and is easily repeatable at the bedside, enabling the assessment of lung recruitment following PEEP or any other manoeuvres requiring direct visualization of the lungs.

Lung ultrasonography is useful for the diagnosis and estimation of lung recruitment by PEEP[11]. Several randomised controlled trials reported that patients undergoing laparoscopic surgery receiving 5 cm of H_2O PEEP experienced significantly better oxygenation and less postoperative atelectasis than patients with zero PEEP[2]. Tsubo *et al*[12] used transoesophageal ultrasonography to evaluate the reaeration induced by PEEP of a hyperdense left lower lobe. Researchers noticed that the ultrasonic densities "disappeared" using 15 cm H_2O PEEP for ALI patients. LUS examinations can be used to monitor the responsiveness of each 3- to 4-cm H_2O increase in PEEP until moderate or severe aeration loss becomes normal.

CONCLUSION

As shown by this case report, lung ultrasonography may be a valuable tool to evaluate lung recruitment in real time at the bedside. Intraoperative point-of-care US performed by the anaesthesiologist provides the possibility of assessing lung reaeration in surgical patients. LUS may be an important alternative to chest CT scans in the perioperative setting.

FOOTNOTES

Author contributions: Zheng X performed the data collection and drafted the article; Liu N revised the article.

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CASE REPORT

New treatment for gastric duplication cyst: Endoscopic ultrasonography-guided fine-needle aspiration combined with lauromacrogol sclerotherapy: A case report

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Abstract

BACKGROUND

Gastric duplication cysts are very rare disease that are mainly diagnosed by endoscopic ultrasonographic fine-needle aspiration biopsy. In the past, this disease was usually treated with traditional surgery and rarely with minimally invasive endoscopic surgery. However, minimally invasive endoscopic therapy has many advantages, such as no skin wound, organ preservation, postoperative pain reduction, early food intake, fewer postoperative complications, and shorter post-procedure hospitalization.

CASE SUMMARY

We report a case of endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) combined with lauromacrogol sclerotherapy for pyloric obstruction due to gastric duplication cysts.

CONCLUSION

EUS-FNA combined with lauromacrogol sclerotherapy provides a new option for the treatment of gastrointestinal duplication cysts.

Key Words: Gastric duplication cysts; Endoscopic ultrasonography; Fine-needle aspiration; Lauromacrogol sclerotherapy; Case report

Core Tip: Endoscopic ultrasonography-guided ablation, as a minimally invasive treatment, has received increasing attention in the past few years. This case report introduces the treatment experience of a 29-year-old male patient. For this patient, we successfully treated a gastric duplication cyst with endoscopic ultrasonography-guided fine-needle aspiration combined with lauromacrogol sclerotherapy for the first time. The patient's symptoms were relieved with minimal trauma, and there were no complications during the 3-year follow-up.

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INTRODUCTION

Gastric duplication cysts are rare congenital abnormalities of the gastrointestinal tract and are extremely rare, accounting for only 2%-9% of all gastrointestinal duplication cysts[1]. They mainly occur in children and rarely in adults. According to the relevant literature reports[2,3], the main treatment method for gastric duplication cysts is surgical treatment, including laparotomy and laparoscopic surgery. Cases of endoscopic treatment are very rare. Only a few cases have reported endoscopic submucosal dissection surgery or endoscopic submucosal tunnelling techniques to resect gastric duplication cysts[4,5]. Currently, endoscopic ultrasonographic fine-needle aspiration biopsy is recognized as the first-line diagnostic method for gastric duplication cysts[6]. To the best of our knowledge, there is no previous literature report on the treatment of gastric duplication cysts by endoscopic ultrasonography-guided fine-needle aspiration (EUS) (EUS-FNA) combined with lauromacrogol ablation. In this paper, we report a case of gastric duplication cysts treated by EUS-FNA combined with lauromacrogol sclerotherapy.

CASE PRESENTATION

Chief complaints

A 29-year-old man came to our hospital for treatment because of abdominal dis-tension and abdominal pain for three months and vomiting for two days.

History of present illness

Three months before the visit, the patient developed intermittent abdominal distension and pain without obvious causes, especially in the upper abdomen, occasionally accompanied by belching and acid reflex. The patient's symptoms could not be relieved after rest, and the above symptoms were aggravated by eating. During the period, the patient's weight was reduced by 10 kg compared with the previous period, but the patient still did not pay attention to it. The patient developed vomiting 2 d before the visit, and the vomit was of the stomach contents.

History of past illness

The patient was previously healthy.

Personal and family history

No relevant disorders were identified.

Physical examination

Upon admission, the patient's vital signs were stable. Abdominal physical examination: the abdomen was flat and soft, no gastrointestinal peristalsis wave was observed, slight tenderness in the upper abdomen, no obvious rebound pain and muscle tension, and obvious succussion splash could be heard.

Laboratory examinations

His preoperative laboratory findings were normal.

Imaging examinations

The patient underwent endoscopic gastroscopy in the outpatient department of our hospital, which revealed submucosal masses in the antrum and incomplete pyloric obstruction (Figure 1A). The enhanced computed tomography (CT) scan revealed a cystic density shadow within the initial cavity of the duodenum, measuring approximately 6.78 × 4.7578 × 6.94 centimeter in size, exhibiting smooth edges and a slightly thickened cyst wall. Furthermore, the enhanced CT scan demonstrated enhancement of the cyst wall. No enlarged lymph nodes were detected within the abdominal cavity or

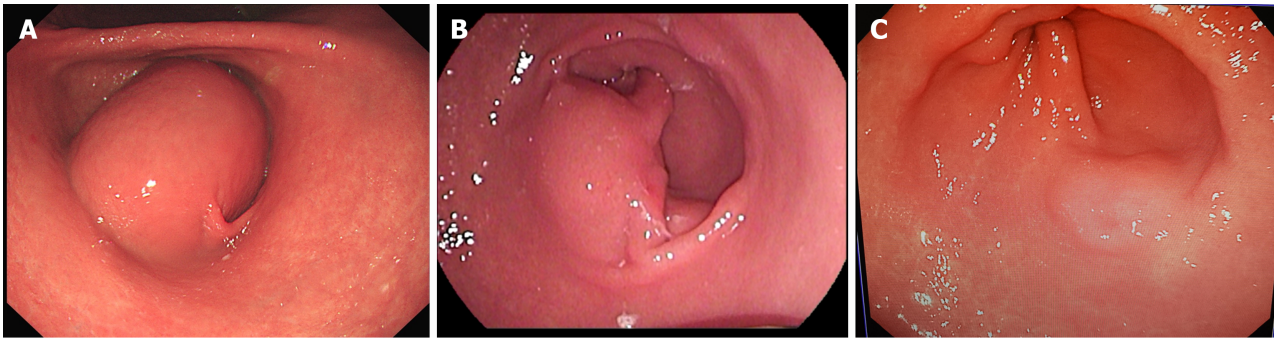

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Figure 1 Electronic gastroscopy. A: Preoperative; B: Six months after the operation; C: Nineteen months after the operation.

retroperitoneum (Figure 2A). For further diagnosis and treatment, the patient underwent (EUS). Ultrasound doppler showed that there was an anechoic homogeneous oval lesion (69.7 × 44.9 millimeter) originating from the submucosa in the gastric antrum (Figure 3A). The cyst wall was smooth, and there was no obvious blood flow signal in the cyst wall. The results of imaging examinations provided an important basis for the final diagnosis.

FINAL DIAGNOSIS

According to the initial gastroscopy imaging findings of the patient, we considered the localization and qualitative aspects. In terms of localization, we were relatively clear, considering it as the source of gastric tissue. Qualitatively, we considered that benign or low-grade malignant lesions were more likely. In clinical work, we often encounter gastric space occupying lesions, we pay more attention to gastric cancer and other malignant lesions, the diagnosis is relatively easy. However, the knowledge of diagnosis and differential diagnosis of benign lesions is relatively lacking. We considered the following diseases: gastric stromal tumor, gastric leiomyoma, gastric lymphoma, and gastric duplication cysts. For further diagnosis and treatment, the patient underwent enhanced abdominal CT and EUS, and we found a cystic mass. Combined with the patient's clinical manifestations and imaging examination, the final diagnosis was gastric duplication cysts with incomplete pyloric obstruction after surgery and cytological examination.

TREATMENT

The patient's diagnosis, age, surgical risk assessment, potential complications, and postoperative quality of life were comprehensively evaluated. Following a multidisciplinary treatment meeting in our hospital, it was decided that the treatment scheme of this patient was surgical laparoscopic distal subtotal gastrectomy or minimally invasive treatment under endoscopic ultrasound. Subsequently, we explained in detail the condition and the pros and cons of the two treatment methods to the patient. Laparoscopic surgery has rich treatment experience, clear surgical vision, and may be more thorough in treatment. However, the trauma is relatively large, there are many postoperative complications, and the postoperative recovery of gastrointestinal function in postoperative patients with slow effect of comprehensive rehabilitation. It may lead to serious decline in patients' quality of life after surgery. Endoscopic minimally invasive treatment has the advantages of less trauma, fewer postoperative complications, quicker recovery and remaining the organ and the function. But the treatment technology is not yet mature and may be at risk of additional surgical procedures. After careful consideration, the patient finally chose the latter.

The patient was instructed to refrain from eating and drinking water upon admission, but considering the potential presence of gastric juice and residual food in the stomach cavity, general anesthesia may increase the risk of aspiration pneumonia. Therefore, we finally choose local anesthesia. Following oral administration of dyclonine hydrochloride mucilage for laryngeal anesthesia and lubrication, the patient underwent EUS-guided sclerotherapy with polylauryl alcohol. The COOK19G (ultrasound biopsy needle) puncture needle was used to puncture the cyst, avoiding the blood vessel, and approximately 60 mL of light yellow transparent liquid was extracted. We performed cytological examination on the extracted cystic fluid, and the results showed only foam cells. The cystic cavity was rinsed repeatedly with physiological saline until the cyst fluid became clear. Subsequently, the cystic cavity was rinsed repeatedly with approximately 15 mL of lauromacrogol, and finally, approximately 1/3 (5 mL) of lauromacrogol was retained in the cavity. The operation process was smooth. The operation procedure is shown in the Video.

OUTCOME AND FOLLOW-UP

After treatment, the patient's obstruction symptoms disappeared. The patient received acid suppression and intravenous

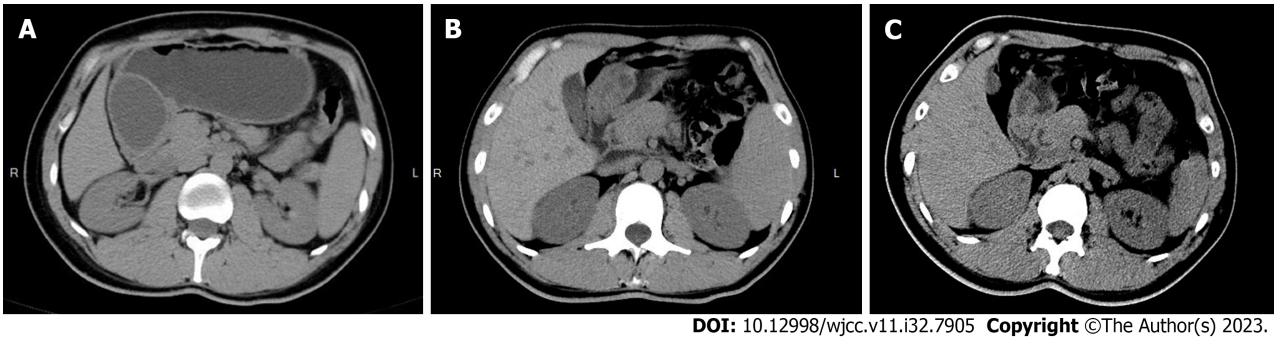

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Figure 2 Computed tomography. A: Preoperative; B: Six months after the operation; C: Nine-teen months after the operation.

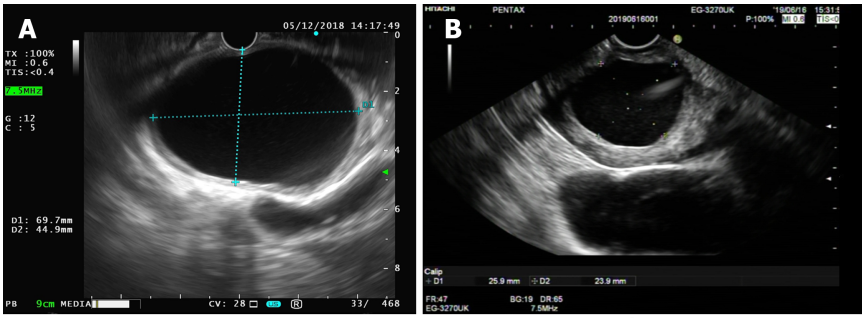

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Figure 3 Endoscopic ultrasonography. A: Preoperative; B: Six months after the operation.

nutritional support during hospitalization. On the third postoperative day, the patient exhibited satisfactory recovery and was discharged from the hospital. Additionally, a gradual transition from a liquid diet to a regular diet was recommended. Six months after the operation, the patient's endoscopic gastroscopy and abdominal CT showed that the cyst was significantly reduced and had developed a thick wall (Figures 1B and 2B). Re-examination by the ultrasonic gastroscope showed a cyst in the gastric antrum, with a thick wall and a diameter of approximately 25.9 × 23.9 millimeter (Figure 3B). At 19 mo after the operation, the patient refused ultrasonography. The endoscopic gastroscopy showed that the mucosa of the greater curvature of the gastric antrum was slightly higher than the mucosal surface, and the mucosa was smooth and intact (Figure 1C). Abdominal CT showed that there was a thick-walled cyst of approximately 1.5 centimeter in the gastric antrum with only a small amount of cyst fluid (Figure 2C). At present, the patient has been followed up for 3 years, and there has been no recurrence or any complication. Compared with before the onset of the disease, the quality of life of the patients after operation has not changed significantly. To closely monitor alterations in condition, we still recommend that patients undergo gastroscopy and CT examinations every 2-3 years.

DISCUSSION

In 1934, WE Ladd took the lead in introducing the concept of gastrointestinal duplication cysts[7]. Gastrointestinal duplication cysts were often described as spherical or tubular. Spherical cysts, which account for 80% of gastrointestinal duplication cysts, are the most common form and they usually do not communicate with the intestinal lumen. Tubular cysts are common in the small intestine and colon and they communicate with the intestinal lumen[1]. Gastrointestinal duplication cyst is a very rare congenital disease in adults, with a higher incidence in women than in men[8]. It can occur anywhere in the digestive tract, most commonly in the ileum, and gastric involvement is the rarest form. There are also some adults with gastrointestinal duplication cysts that are asymptomatic. Therefore, gastrointestinal duplication cysts are extremely rare in adults.

Gastric duplication cysts are most common in the greater curvature of the stomach[9]. The involvement of the gastric antrum and symptoms of obstruction are rarely reported. The clinical symptoms of gastric duplication cysts mainly depend on the age of the patient and the location and size of the lesion. In adults, gastric duplication cysts are mostly asymptomatic and are usually found incidentally by radiology or endoscopy. However, symptoms related to complications may occur, such as pain, obstruction, weight loss, ulcers and bleeding[10]. We reported that this patient was found to have a duplication cyst of the gastric antrum, mainly with obstructive symptoms.

Multiple imaging modalities, such as abdominal ultrasound, EUS, CT and magnetic resonance imaging (MRI), are used for gastrointestinal duplication cysts. Abdominal CT and MRI can identify gastrointestinal duplication cysts. However, due to the complex composition of the cyst fluid, it is difficult to distinguish some cystic fluid images with a high protein content from solid masses, which are easily misdiagnosed as conditions such as gastrointestinal-stromal-tumours[11].

EUS is essential for the diagnosis of submucosal masses. It can accurately distinguish the relationship between the cyst wall and adjacent gastrointestinal structures, thus helping to distinguish solid from cystic lesions. EUS-FNA can obtain histopathology, which is important for a differential diagnosis from other solid lesions and the exclusion of malignant transformation of cysts[6]. Therefore, EUS, especially EUS-FNA, has become a first-line diagnostic method for gastrointestinal duplication cysts.

Currently, there is no accepted treatment for gastrointestinal duplication cysts. Close follow-up is recommended for small or asymptomatic gastric duplication cysts. For symptomatic or giant cysts, surgical resection (including laparoscopic minimally invasive surgery) is usually preferred to remove the cyst and relieve the symptoms[2,3]. However, the functionality injury of normal organs caused by the surgery, as well as a variety of postoperative complications, make many flinch from the treatment of gastric duplication cysts.

Lauromacrogol was first synthesized in 1936. The main component of lauromacrogol is lauryl polyoxyethylene ether, mixed with ethanol and sterilized water. Lauromacrogol can close cysts by destroying the cells in the cyst wall, preventing cyst fluid secretion, adhesion, and fibrosis. Lauromacrogol does not cause any pain, either during tissue or intravenous injection, because it also has an effect of anaesthesia. It can provide the broadest range of safe treatment without exosmosis leading to necrosis. Lauromacrogol is easier and safer to use than anhydrous alcohol, another hardener. Therefore, since the 1860s, lauromacrogol has been used as a sclerotherapy agent in clinical treatment and has been widely used for the treatment of renal cysts, liver cysts and pancreatic cysts[12-16]. Referring to the treatment experience of lauromacrogol in other cystic lesions, we consider the use of lauromacrogol for sclerotherapy of gastric duplication cysts to be safe. In this case report, we successfully treated a gastric duplication cyst with EUS-FNA combined with lauromacrogol for the first time. As a new treatment method, EUS-FNA-guided lauromacrogol sclerotherapy has its own advantages in various aspects, including less trauma, a short hospital stay, less pain, a lower cost, and a reduced risk of postoperative adverse events, and it can be applied in cases of recurrence or new lesions.

Cases of malignant transformation[17,18] caused by gastric duplication cysts have been reported in the past. In our treatment, whether the damaged cyst wall after lauromacrogol sclerotherapy still has a risk of carcinogenesis and the best indication for treatment still require long-term follow-up and research. We also recommend annual CT and endoscopy and close follow-up for patients after sclerotherapy.

CONCLUSION

As a new treatment method, EUS-FNA guided lauromacrogol sclerotherapy has its own advantages in various aspects, including less trauma, a short hospital stay, less pain, a lower cost, and a reduced risk of postoperative adverse events, and it can be applied in cases of recurrence or new lesions. EUS-FNA combined with lauromacrogol sclerotherapy provides a new option for the treatment of gastrointestinal duplication cysts.

FOOTNOTES

Author contributions: Bu YW, Han RQ and Er LM designed the paper and wrote and edited the manuscript; Bu YW, Han RQ, Ma WQ, and Wang GN performed the literature review, collected all the data related to the case report; Bu YW, Ma WQ, Wang GN and Er LM recorded/edited the video; Bu YW, Han RQ, Ma WQ, Wang GN and Er LM reviewed original draft; all authors have read and agreed to the published version of the manuscript.

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CASE REPORT

Immunotherapy in SMARCB1 (INI-1)-deficient sinonasal carcinoma: Two case reports

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Abstract

BACKGROUND

SMARCB1/INI-1 deficient sinonasal carcinoma (SDSC) is a rare subset of sinonasal undifferentiated carcinoma with a poor prognosis. Here, we present two case reports of SDSC patients. We also review the literature on this tumor. This is the first published report of SDSC treatment with immunotherapy.

CASE SUMMARY

Here we present two patient cases of SDSC in which initial consultation and diagnosis were complicated but SDSC was ultimately diagnosed. One patient received a traditional treatment of surgery and adjuvant chemoradiotherapy, while the other patient received additional immunotherapy; the prognoses of these two patients differed. We review previous diagnostic literature reports and SDSC treatments and provide a unique perspective on this rare type of tumor.

CONCLUSION

SDSC is a rare, diagnostically challenging carcinoma with a consistently poor prognosis, early distant metastases, and frequent recurrence. Timely diagnosis and intervention are critical for treatment, for which the standard of care is surgery followed by adjuvant chemoradiotherapy, though immunotherapy may be an effective new treatment for SDSC.

Key Words: SMARCB1; INI-1; Sinonasal carcinoma; Gene deficient; Immunotherapy;

Surgery; Case report

Core Tip: SMARCB1/INI-1 deficient sinonasal carcinoma (SDSC) is a rare carcinoma with a poor prognosis and no standard treatment guidelines. Currently, the most effective treatment option is surgery followed by adjuvant chemoradiotherapy. Here, we present two SDSC patients with complicated consultation experiences. The patients differed in treatments and prognoses, and there was no indications of local recurrence or distant metastases in patient with immunotherapy. We also review the literature on SDSC treatment. This first report on immunotherapy in SDSC provides a unique perspective on treatments for this rare tumor.

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INTRODUCTION

Approximately 3%–5% of all sinonasal carcinomas are deficient in nuclear expression of SMARCB1, a tumor-suppressor gene on chromosome 22q11.2 that encodes INI-1 protein[1]. These SMARCB1-deficient sinonasal carcinomas (SDSC) are highly aggressive and malignant with poor prognoses[2-4]. SDSC was first described in 2014 by Agaimy *et al*[3] and Bishop *et al*[5], though the tumor is rare and remains classified by the World Health Organization only as a variant pattern of sinonasal undifferentiated carcinoma (SNUC)[6]. Patients are typically diagnosed with high-mortality locally advanced disease, but no standard guidelines are approved for disease management, and treatment options remain controversial[7]. Therapeutic approaches must be found to cure this disease with minimal side effects.

Developments in cancer molecular biology and immunology have provided immunotherapy treatments for other head and neck tumors, and many locally advanced and metastatic malignancies respond well to immunotherapy[8]. SDSC tumor progression is driven by the downregulation of the major histocompatibility complex and a tumor microenvironment that promotes immune escape, meaning that immunotherapy may be an effective intervention, though there is currently limited evidence of efficacy in treating SDSC[9].

In this report, we describe two cases of treatment progression in patients with SDSC who received a traditional treatment with surgery and adjuvant chemoradiotherapy, with one patient also receiving immunotherapy and remaining disease-free upon follow-up. Unlike most previously reported retrospective diagnostic cases, these two cases were prospectively diagnosed. To our knowledge, this is the first literature report of an SDSC patient responding well to immunotherapy; such cases set an important precedent for the treatment of this rare tumor.

CASE PRESENTATION

Chief complaints

Case 1: A 34-year-old man with a 20-pack-year smoking history presented with an intermittent left nasal obstruction with headache and loss of smell for about 1 mo.

Case 2: A 50-year-old man with a 10-pack-year smoking history presented with a swollen left eye for 4 wk.

History of present illness

Case 1: This patient presented to another hospital with an intermittent left nasal obstruction with headache and loss of smell for about 1 mo. Magnetic resonance imaging (MRI) of the nasopharynx revealed a mass in the left nasal cavity with invasion of the left axillary sinus, bilateral ethmoid sinus, and sphenoid sinus. He underwent a lumpectomy and was diagnosed with a poorly differentiated sinonasal carcinoma that did not exclude SDSC.

Case 2: Symptoms began 4 wk prior and were associated with episodic left-sided epistaxis.

History of past illness

Neither patient had past disease.

Personal and family history

Neither patient exhibited past personal or family history.

Physical examination

Case 1: Physical examination indicated hyperemia nasal mucosa, with the nasal septum deviated to the right and the left nasal passage showing changes after surgery.

Case 2: Physical examination revealed a centered nasal septum with no neoplasms and purulent discharge in both nasal passages.

Laboratory examinations

Case 1: Laboratory studies revealed a squamous cell carcinoma antigen concentration of 1.13 ng/mL (normal range ≤ 2.50 ng/mL), a carcinoembryonic antigen concentration of 1.07 ng/mL (normal range ≤ 3.40 ng/mL), and a cytokeratin 19 fragment antigen concentration of 1.75 ng/mL (normal range ≤ 3.30 ng/mL).

Case 2: Laboratory studies revealed a squamous cell carcinoma antigen concentration of 2.22 ng/mL (normal range ≤ 2.50 ng/mL), a carcinoembryonic antigen concentration of 1.56 ng/mL (normal range ≤ 3.40 ng/mL), and a cytokeratin 19 fragment antigen concentration of 1.62 ng/mL (normal range ≤ 3.30 ng/mL).

Imaging examinations

Case 1: This patient presented to our hospital for a follow-up examination on September 21, 2021. An MRI of the nasopharynx showed a heterogeneously enhancing mass in the anterior part of the left maxillary sinus that was considered a residual tumor (Figure 1A-C).

Case 2: Post-contrast MRI was performed and showed a large mass in the left ethmoid sinus and sphenoid sinus measuring 4.2 cm × 2.7 cm × 1.6 cm, extending into both the left orbit and cranial cavity without lymphadenopathy (Figure 1D-F).

MULTIDISCIPLINARY EXPERT CONSULTATION

Case 1: The surgically resected tissue measured 3.5 cm × 2.4 cm × 1.2 cm and was grey-brown in color. Tumor cells were histologically nested (Figure 2A) with diffuse expression of creatine-kinase (CK); tumors were immunohistochemically negative for Vimentin, S-100, CD56, and thyroid transcription factor 1 (Figure 2B-E). Immunohistochemistry revealed a loss of INI-1 protein in the nuclei of the tumors and surrounding tissue. The Ki-67 proliferative index was approximately 70%.

Case 2: Pathological examination revealed diffuse expression of CK, CK8/18, and Nestin. Cells were partially positive for P40, P63, Syn, CD117, S-100, and epithelial membrane antigen, and were negative for CD56, leukocyte common antigen, CK7, H3K36M, and anti-smooth muscle antibody (Figure 3). The patient refused further pathological examination for INI-1 staining and was initially misdiagnosed with adenoid cystic carcinoma because of the glandular morphology (Figure 3B). Fortunately, an inter-institutional pathology consultation (Tongren Hospital, Beijing) demonstrated the loss of SMARCB1 (INI-1) expression in tumor nuclei.

FINAL DIAGNOSIS

These two patients were diagnosed with SDSC based on immunohistochemical staining and morphology. Tumors were diagnosed as pathological T4N0M0 stage IV using the tumor-node-metastasis staging system (American Joint Committee on Cancer, 8th edition).

TREATMENT

Case 1: The multidisciplinary care team proposed surgery followed by chemoradiotherapy. The patient underwent a complete excision of the tumor with resection of the bony wall of the ethmoid sinus, followed by adjuvant radiotherapy (60 Gy in 30 fractions, 5 d/wk for 6 wk) and chemotherapy (docetaxel plus cisplatin, administered in four cycles every 3 wk). The multidisciplinary team discussed this case again after surgery and chemoradiotherapy, and the patient and family decided to initiate immunotherapy with anti-PD1 (tislelizumab) that began in March 2022.

Case 2: This patient underwent complete resection of the tumor with frontal sinusotomy, total ethmoidectomy, and skull base reconstruction, and then finished subsequent radiotherapy (70.4 Gy in 32 fractions, 5 d/wk) and adjuvant chemotherapy (paclitaxel plus cisplatin, administered in four cycles every 3 wk).

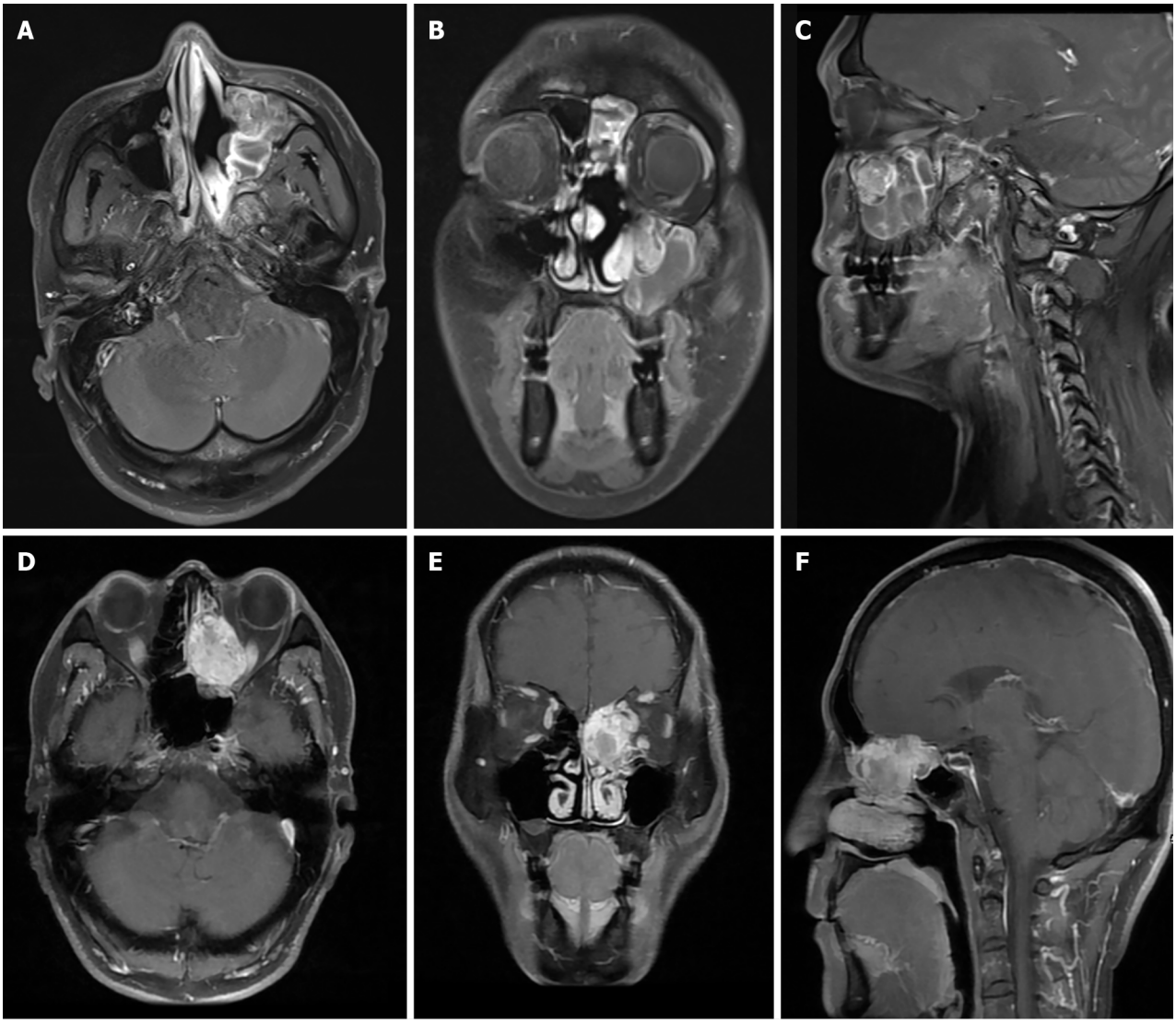

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Figure 1 Preoperative T1 post contrast magnetic resonance images of Case 1 and 2. A and D: Axial section; B and E: Coronal section; C and F: Sagittal section.

OUTCOME AND FOLLOW-UP

Case 1: After 2 years of follow-up, there were no serious adverse reactions, and laboratory/imaging tests indicated no local recurrence or distant metastasis. Figure 4 shows the timeline of this patient's clinical management and outcome.

Case 2: Through August 22, 2022, we observed no serious adverse reactions, regional recurrences, or distant metastases, though laboratory tests revealed elevated tumor markers that warrant a high degree of vigilance. The patient refused further image examinations. Figure 5 shows the timeline of this patient's clinical management.

DISCUSSION

SMARCB1/INI-1 is a tumor suppressor gene involved in epigenetic regulation of gene transcription[10]. The encoded INI-1 protein is a core subunit of the switch/sucrose nonfermenting (SWI/SNF) complex, which is ubiquitously expressed in healthy cell nuclei and participates in transcriptional regulation and many other cell functions (Figure 6)[11]. SDSC is a highly aggressive and rare subset of SNUC with poor prognosis that is characterized by loss of nuclear expression of SMARCB1. This tumor type has been well studied (Figure 7)[5,7], and the clinical manifestations, diagnosis, differential diagnosis, and treatment of SDSC have been systematically reviewed[12-16]. In this report, we describe two complex patient cases that were ultimately diagnosed correctly as SDSC. Below, we review the SDSC literature regarding clinical presentation, diagnosis, and treatment.

SDSC occurs mostly in middle-aged and elderly people (age range 19–89 years) and is slightly more common in males. Tumors are typically located in the nasal cavity and invade the adjacent paranasal sinus, fossa orbitalis, and cranial base

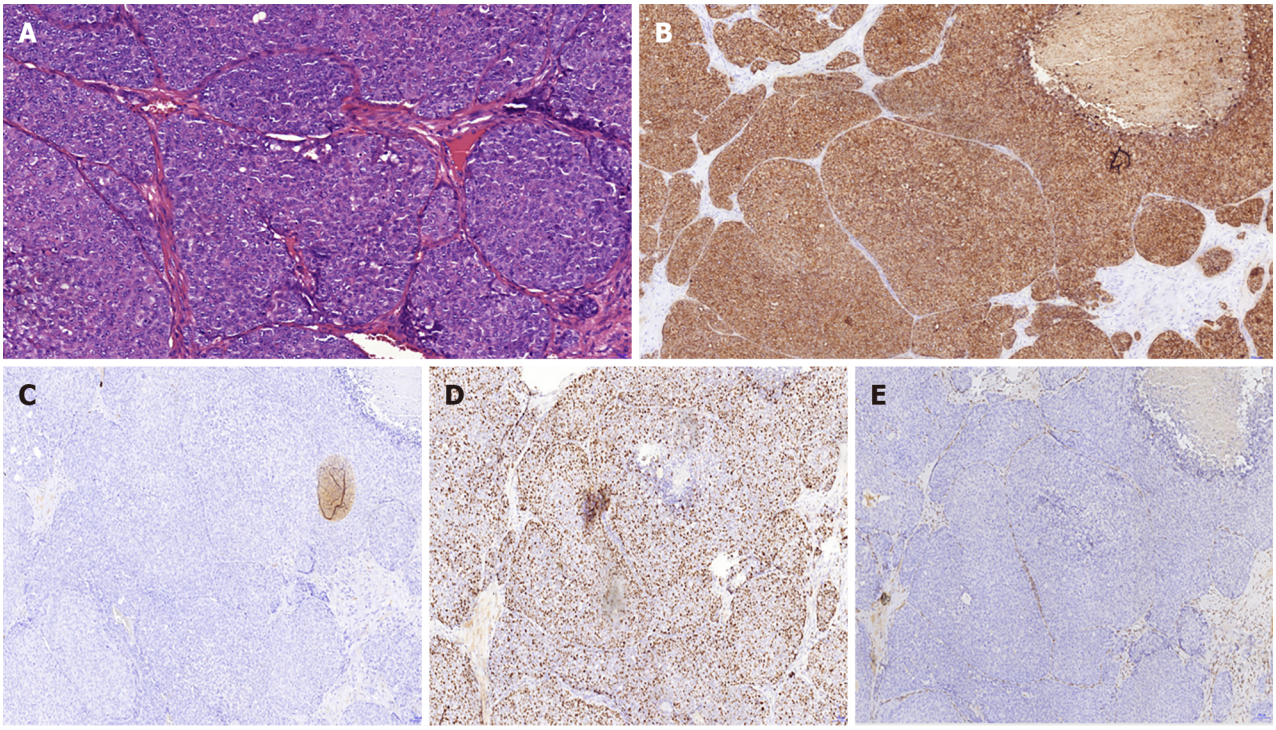

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Figure 2 Histopathological and immunohistochemical features of Case 1. A: Tumor cells grew as nested (hematoxylin and eosin staining, ×200); B and C: The tumor cells were positive for creatine-kinase (×100) and negative for S-100 (×100); D: The Ki-67 proliferative index was approximately 70% (×100); E: INI-1 expression was present in the nuclei of surrounding non-neoplastic cells but completely absent in the tumor cells (×100).

[17]. Patients mostly complained of different degrees of nasal obstruction, epistaxis, headache, or blurry vision[7,18]. SDSC patients generally present these nonspecific symptoms with massive and locally advanced tumors, with > 60% staged as T4 with lung metastases. Imaging often shows a mass with infiltrative growth and low or moderate MRI signal. Here, we report a 34-year-old man and a 50-year-old man who presented with a nasal obstruction and eye swelling, respectively; both were diagnosed with stage T4 tumors. MRI images are mentioned above.

Clinically, SDSC is a misunderstood malignancy[18,19]. A systematic review has showed that 72.5% of patients were first misdiagnosed initially[16]. SDSC should be differentiated from a variety of poorly differentiated or undifferentiated sinonasal tumors. Two studies have compared SDSC with INI-1-positive SNUC; SDSC has a lower recurrence rate (17%-53%) than other sinonasal malignancies (53%-60%), while SNUC patients experience disease-free survival for approximately four times longer than SDSC[14,20]. Thus, differentiating SDSC from SNUC is essential for selecting appropriate targeted therapies. SDSC has various morphologic features but no clear differentiation; Agaimy *et al*[7] found that most tumors display either a predominantly basaloid (61%) or plasmacytoid/rhabdoid (36%) morphology. In the latter, tumor cells have abundant eosinophilic cytoplasm with inclusion bodies, eccentric nuclei, and glandular differentiation. This glandular morphology was observed in case 2 (Figure 4B), which led to the initial misdiagnosis as adenoid cystic carcinoma. Using microscopic morphology alone, SDSC is difficult to diagnose, so undifferentiated tumors should be examined immunohistochemically for INI-1[3,5].

As a highly aggressive and rare malignancy, timely intervention is critical. No standard guidelines are currently approved for the management of this rare carcinoma[21]. The most effective treatment option for SDSC is a multimodal approach with surgery and subsequent adjuvant chemoradiotherapy, though few retrospective studies are available.

One retrospective study demonstrated that comprehensive surgical treatment can prolong recurrence-free survival (RFS), while non-surgical systemic therapy was an independent poor prognosis factor[16]. Moreover, surgery combined with chemoradiotherapy had a better overall-survival (OS) and RFS than surgery alone; surgical treatment alone often resulted in early relapse and metastatic disease. As Agaimy reported, over 77% of patients underwent surgical resection with adjuvant chemoradiation and currently remain tumor-free after follow-up[7]. Therefore, adjuvant radiation therapy or chemoradiotherapy is required to improve prognosis; neoadjuvant chemoradiation with cisplatin also reduced tumor volume and morbidity relative to surgical resection alone[18,22]. Wasserman *et al*[22] and Kakkar *et al*[18] found that tumor volume was dramatically reduced by pre-surgical neoadjuvant treatment, which facilitated complete surgical resection and improved patient OS. Therefore, neoadjuvant therapy may be a suitable treatment for large tumors prior to surgical excision.

Recurrence and mortality rates, however, are still typically high. A systematic review of 82 cases revealed that most SDSCs are diagnosed at an advanced stage, resulting in a poor prognosis (average mortality 45.3%), a median OS of 22 mo, and a high frequency of distant metastases (49.3%)[15]. Immune escape is enabled by the downregulation of major histocompatibility complex molecules[9], but the upregulation of preferentially expressed antigens in melanoma and breast cancer type 1 (BRCA1) may pave the way for immunotherapy[23]. Immunotherapy may reduce relapse and

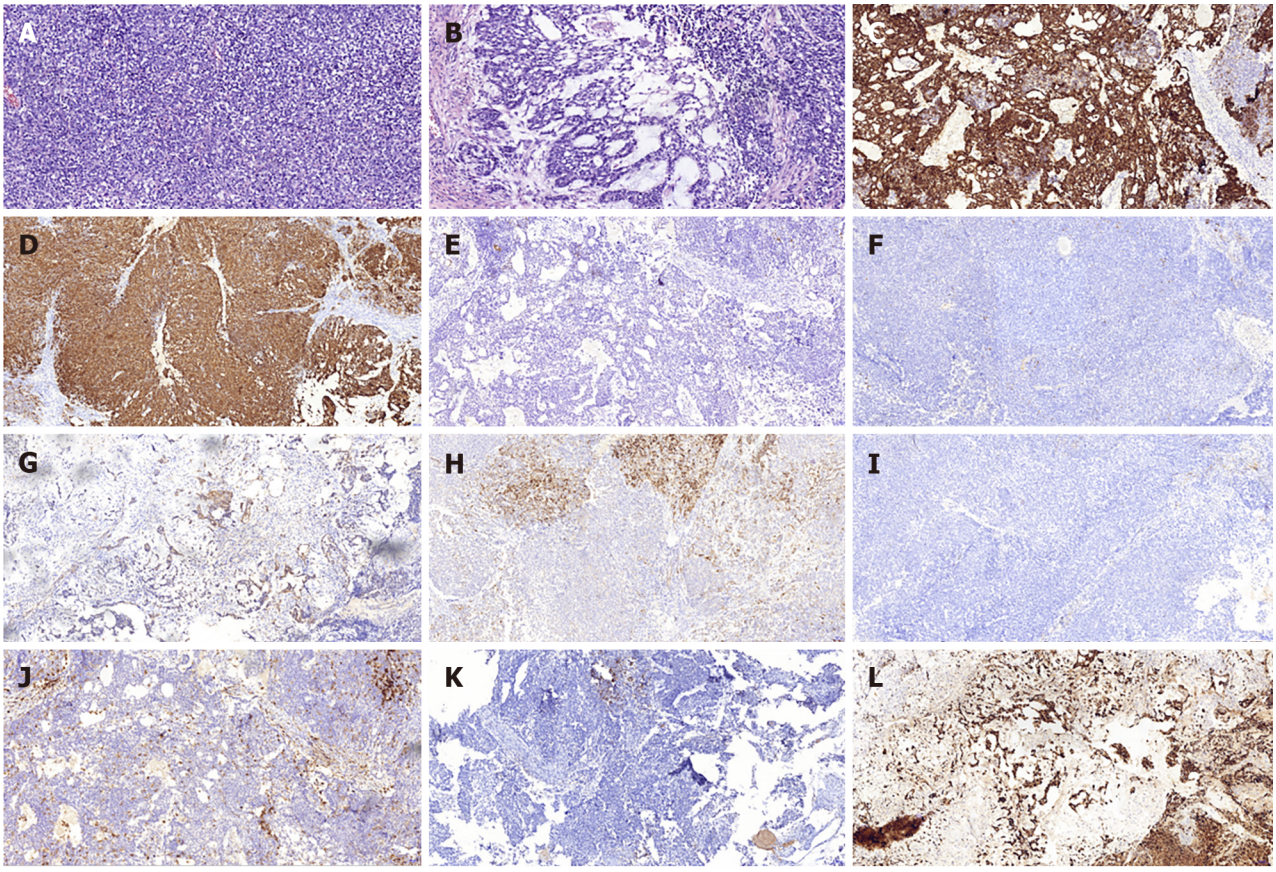

Figure 3 Histopathological and immunohistochemical features of Case 2. A and B: Tumor cells had no clear differentiation, glandular morphology and mucoid interstitial substance could be observed in some areas. (Hematoxylin and eosin staining, ×200); C-J: The tumor cells were diffuse positivity for CK(x100), CK8/18 (×100), partial positivity for P40 (×100), P63 (×100), S-100 (×100), Syn (×100), and negativity for CK7 (×100), LCA (×100); K: Tumors had a PD-L1 combined positive score of one (×100); L: The Ki-67 proliferative index was approximately 70% (×100).

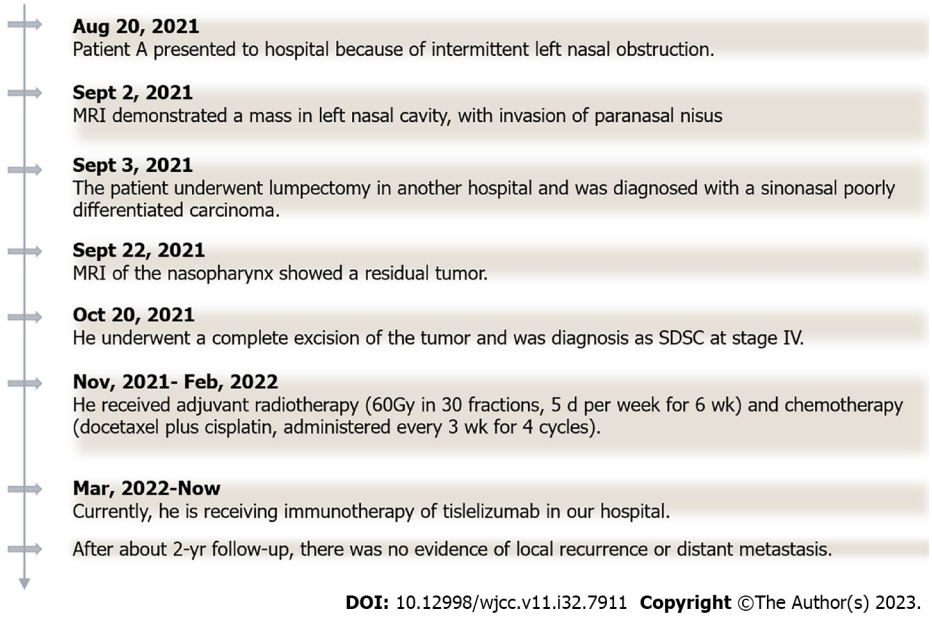

Figure 4 Timeline of Case 1's clinical management and outcome. MRI: Magnetic resonance imaging; SDSC: SMARCB1-deficient sinonasal carcinomas.

Aug 1, 2021
Patient B presented in our hospital with 4-week swollen left-side eye and episodic left-sided epistaxis.

Aug 4, 2021
Post contrast MRI showed a large mass in the left ethmoid sinus and sphenoid, extending into both left orbit and cranial cavity without lymphadenopathy

Aug 6, 2021
He underwent complete resection of the tumor with frontal sinusotomy, total ethmoidectomy and skull base reconstruction.

Aug 15, 2021
This patient was diagnosed as T4NOMO SDSC at stage 4 finally.

Aug, 2021- Dec 2021
Then he finished subsequent radiotherapy at a prescribed dose of 70.4Gy in 32 fractions given on 5 d per week and adjuvant chemotherapy with paclitaxel plus cisplatin per 3 wk for 4 cycles.

Aug 9, 2022- Dec 26, 2022
Laboratory tests reveal elevated tumor markers.

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Figure 5 Timeline of Case 2's clinical management and outcome. SDSC: SMARCB1-deficient sinonasal carcinomas.

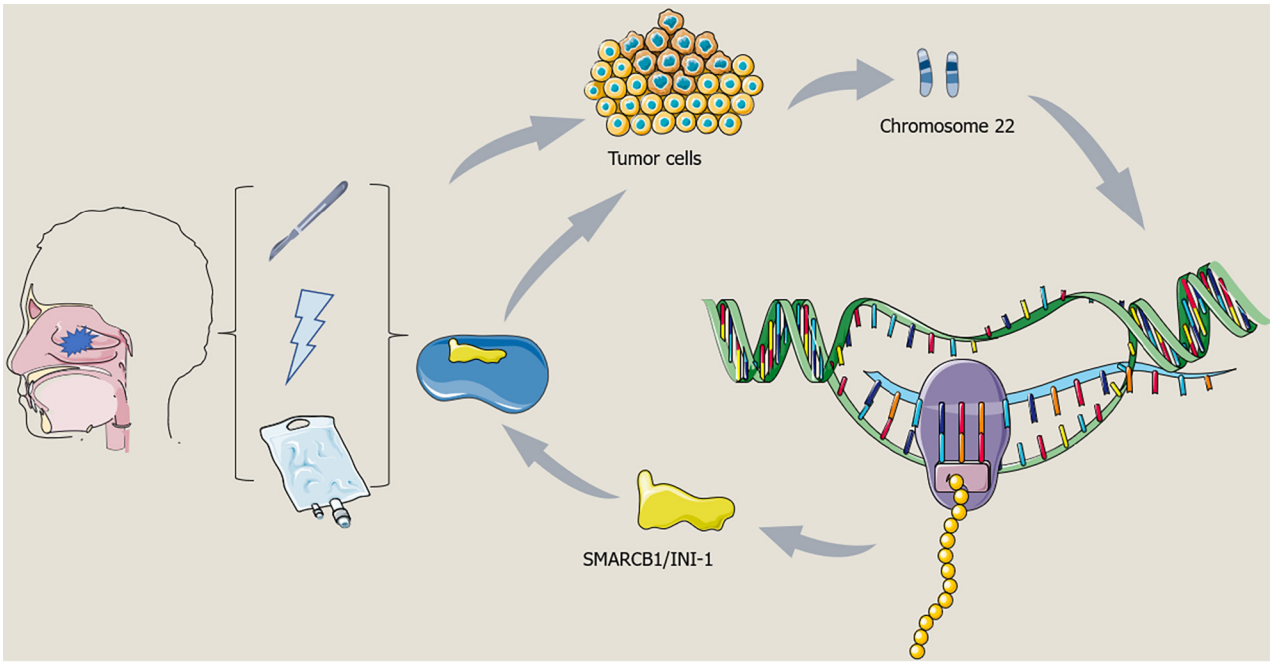

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Figure 6 SMARCB1 is a tumor suppressor gene located at chromosome 22q11.2. The protein encoded by this gene is a core subunit of the switch/sucrose nonfermenting complex, which can be ubiquitously expressed in the nucleus of all normal cells and can participate in regulating transcription and many other functions of cells.

mortality in the treatment of SDSC.

Clinical data on SDSC immunotherapy are lacking; fewer than five cases of sinonasal cancer treatment with immunotherapy have been reported[24,25]. In one reported SNUC case, a young man received triple modality treatment (chemotherapy, surgery, and radiation) and showed a long-lasting response to immunotherapy[25]. SDSC may also respond well to this treatment. In this report, we compared two SDSC patients with or without immunotherapy, thus providing the first published report of SDSC treatment using immunotherapy. Immunotherapy produced a long-lasting progress-free survival that sets a new precedent for immunotherapy in SDSC. However, several limitations exist for using immunotherapy with SDSC patients, and more clinical evidence and mechanistic studies are required.

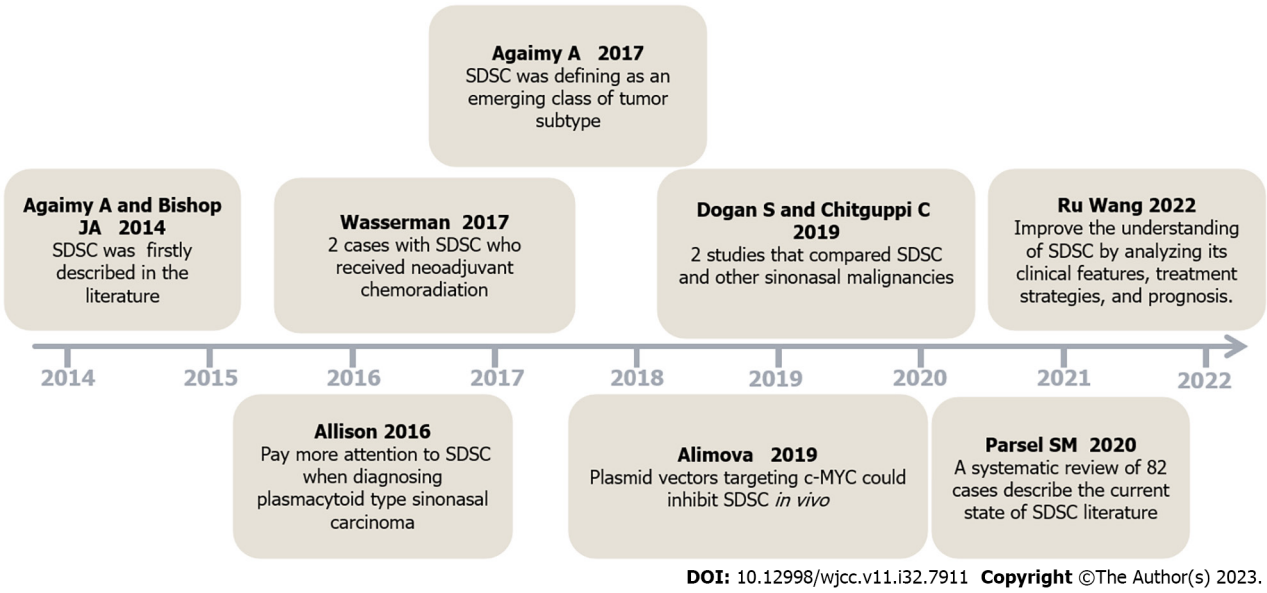

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Figure 7 Selected publications further studied SMARCB1-deficient sinonasal carcinoma. SDSC: SMARCB1-deficient sinonasal carcinomas.

CONCLUSION

In this report, we describe two SDSC patients with different prognoses. SDSC is a rare carcinoma with early distant metastases and a poor prognosis. The patient who underwent traditional treatment showed elevated tumor markers at the 1-year follow-up, while the patient who received immunotherapy experienced a long-lasting progress-free survival. This is the first report of immunotherapy treatment in SDSC patients and provides a valuable reference for the clinical treatment of this rare tumor.

FOOTNOTES

Author contributions: Zhang L contributed to manuscript writing and editing; Gao AX and He YL contributed to data collection; Xu MJ contributed to data analysis; Lu HJ contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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CASE REPORT

Interstitial pneumonia combined with nocardia cyriacigeorgica infection: A case report

Dao-Da Qi, Yi Zhuang, Yang Chen, Jing-Jing Guo, Ze Zhang, Yan Gu

Specialty type: Respiratory system

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
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Grade C (Good): 0
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Abstract

BACKGROUND

Nocardia infection is a relatively uncommon disease, with no reports among patients with interstitial pneumonia. Due to its atypical clinical symptoms and chest computed tomography (CT) findings and the frequent yielding of negative results by conventional cultures, it poses challenges for timely diagnosis and treatment.

CASE SUMMARY

A 63-year-old female patient presented to our hospital in July 2022 with a 3-mo history of intermittent cough and poor appetite, accompanied by a 2-wk long duration of headaches. She had a previous medical history of interstitial pneumonia and was on oral prednisone and cyclosporine. Chest CT revealed the presence of newly developed round nodules. The diagnosis of *Nocardia cyriacigeorgica* infection was confirmed through metagenomic next-generation sequencing (mNGS) performed on bronchoalveolar lavage fluid. Targeted anti-infection therapy was initiated, resulting in symptom improvement and radiological resolution, further validating the mNGS results.

CONCLUSION

Nocardia cyriacigeorgica infection is a clinically rare condition that is primarily observed in immunocompromised patients. Its clinical and radiological manifestations lack specificity, but mNGS can aid in rapidly obtaining pathogenic information. Early initiation of targeted antimicrobial therapy based on mNGS results can improve patient prognosis.

Key Words: Interstitial pneumonia; Nocardia cyriacigeorgica infection; Literature review;

Case report

Core Tip: In patients with interstitial pneumonia receiving oral steroids and immunosuppressants, the presence of new nodules, masses, or cavitary lesions should raise suspicion of concurrent Nocardia infection. In addition to routine examinations and tests, metagenomic next-generation sequencing can provide rapid pathogen identification, facilitating early targeted antimicrobial therapy and ultimately improving patient outcomes.

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INTRODUCTION

Nocardia is an opportunistic pathogen commonly found in immunocompromised patients[1]. Currently, over fifty species of Nocardia have been identified[2], including *Nocardia asteroides*, *Nocardia brasiliensis*, *Nocardia farcinica*, and *Nocardia otitidiscaviarum*. These species constitute the main causative agents of human diseases. Given that inhalation is the primary route of exposure, clinical infections often manifest as pulmonary nocardiosis. *Nocardia cyriacigeorgica* is a relatively uncommon pathogen[3] and is observed in organ transplant recipients, individuals on prolonged corticosteroid therapy, and patients with various chronic lung diseases[4,5]. However, cases of *Nocardia cyriacigeorgica* infection combined with interstitial pneumonia have not yet been documented. In this study, we report a case of a patient diagnosed with interstitial pneumonia and concurrent pulmonary *Nocardia cyriacigeorgica* infection at the Second Hospital of Nanjing, China. By reviewing the relevant literature, we aim to enhance the understanding of interstitial pneumonia concomitant with pulmonary Nocardia infection.

CASE PRESENTATION

Chief complaints

A 63-year-old female patient was admitted in July 2022 with intermittent cough and poor appetite for three months, accompanied by two weeks of headache.

History of present illness

The patient had experienced paroxysmal cough without significant sputum production since April 2022, and the cough initially went unnoticed. Subsequently, the aforementioned symptoms recurred intermittently. In early June 2022, the patient sought outpatient care at a tertiary hospital in Nanjing, where chest computed tomography (CT) indicated interstitial pneumonia, and rheumatologic autoantibody testing yielded positive results for anti-Sjogren's syndrome A. A diagnosis of interstitial pneumonia associated with Sjögren's syndrome was made, and treatment with prednisone (30 mg qd) and cyclosporine (75 mg, bid) was initiated. The patient's cough improved gradually following treatment. A follow-up CT on July 8, 2022 showed marked absorption of interstitial pneumonia, with a newly developed circular nodule in the right upper lobe measuring approximately 22 mm × 21 mm. However, a week later, the patient developed a fever, with a peak temperature of 39.2 °C, prompting her visit to our hospital.

History of past illness

The patient had no significant past medical history.

Personal and family history

The patient had no significant personal history, reproductive history, or family history.

Physical examination

On admission, the patient's vital signs were as follows: temperature 36.5 °C, pulse rate 105 beats/min, respiratory rate 18 breaths/min, blood pressure 120/83 mmHg, and SpO_2 94% (without oxygen supplementation). The patient was alert, breathing normally, without cyanosis of the lips, and the patient had no superficial lymph node enlargement. Decreased breath sounds were auscultated in the right upper lung, while no crackles or wheezes were detected in either lung. No abnormalities were observed on cardiac auscultation or abdominal palpation, and there was an absence of lower extremity oedema and pathological reflexes.

Laboratory examinations

The highly C-reactive protein (CRP) level was > 10.00 mg/L. Routine blood tests were as follows: white blood cell count 6.00 × 10^9/L, neutrophil percentage (N%) 80.6%, absolute lymphocyte count 0.83 × 10^9/L, lymphocyte percentage (L%) 13.8%, haemoglobin 133 g/L, and platelet count 143 × 10^9/L. Biochemical parameters included total bilirubin 22.7 μmol/L, direct bilirubin 12.5 μmol/L, alanine aminotransferase 46.9 U/L, albumin 29.4 g/L, and globulin 29.9 g/L. The lymphocyte subset counts were as follows: $CD4^+$ T cells 83 cells/μL and $CD8^+$ T cells 601 cells/μL. Rheumatologic autoantibody tests yielded positive results for antinuclear antibodies. In addition, tumour marker tests, sputum fungal and bacterial cultures, acid-fast bacilli smears, galactomannan (GM) tests, beta-glucan (G) tests, cryptococcal antigen qualitative assays, tuberculosis infection T-cell assays, and respiratory pathogen IgM screening all yielded negative results.

Imaging examinations

Lesion changes occurred on chest CT at different periods (Figure 1).

FINAL DIAGNOSIS

The patient was diagnosed as an interstitial pneumonia combined with Nocardia cyriacigeorgica infection.

TREATMENT

The patient was initiated on treatment with prednisone 15 mg/d orally for Sjögren's syndrome and moxifloxacin 0.4 g/d intravenously for empirical broad-spectrum antibacterial therapy. Voriconazole was added (initial dose 360 mg bid, maintenance dose 240 mg bid) for empirical antifungal prophylaxis. Considering nutritional risk (NRS2002 score of 3, MNA-SF score of 5), oral nutritional supplementation was administered as oral nutrition supplements. The patient also received symptomatic treatments such as nebulization, hepatoprotection, and gastric protection.

Despite the initial treatment, the patient continued to experience fever. A follow-up CT on July 15, 2022 indicated a block-shaped high-density shadow with cavitation formation in the anterior segment of the right upper lobe. The lesion (48 mm × 47 mm) had significantly progressed compared to July 8th, with interstitial inflammation observed in both lungs. Given the patient's low $CD4^+$ T-cell count and the history of long-term oral corticosteroid and immunosuppressant use, as well as chest CT showing shadow, compound sulfamethoxazole (SMZ) tablets (2 tablets/1.6 g SMZ bid) and carpofungin (50 mg/d) were used for pneumocystis pneumonia prevention. Meanwhile, percutaneous lung puncture was recommended to identify the pathogen, but the patient declined. Consequently, fibreoptic bronchoscopy examination and BAL were performed. The regular bronchoalveolar lavage fluid (BALF) test results (fungal and bacterial cultures, acid-fast staining for tuberculosis, G/GM test, and tumour cell exfoliation) were all negative. Metagenomic next-generation sequencing (mNGS) of the BAL fluid indicated the presence of *Nocardia cyriacigeorgica*, with a sequence count of 286487 and a relative abundance of 28.20%. Consequently, targeted antimicrobial therapy was promptly initiated. Moxifloxacin and carbapenems were discontinued, and compound sulfamethoxazole tablets were escalated to 3 tablets/2.4 g SMZ tid, complemented by the addition of third-generation cephalosporins for enhanced antimicrobial coverage.

OUTCOME AND FOLLOW-UP

After 14 d of hospitalization, the patient's cough, headache, and fever had disappeared, and her diet had returned to normal. Follow-up blood tests showed highly sensitive CRP < 10.00 mg/L, white blood cell count 5.17 × 10^9/L, neutrophil percentage 45.5%, absolute lymphocyte count 2.5 × 10^9/L, and lymphocyte percentage 48.3%. The lymphocyte subset counts were as follows: $CD4^+$ T cells 158 cells/μL and $CD8^+$ T cells 2134 cells/μL. CT scans indicated a reduction in the size of the right upper lung lesion compared to previous images. Subsequently, the patient was discharged and continued oral administration of complex sulfamethoxazole tablets and prednisone. Regular outpatient follow-up was recommended.

DISCUSSION

Nocardia is a filamentous bacterium characterized by its aerobic, gram-positive, and weakly acid-fast staining properties, and it belongs to a genus within the Actinobacteria phylum. It is widely distributed in natural environments, particularly in soil and humus, frequently causing opportunistic infections in immunocompromised patients. However, approximately one-third of Nocardia infections can also occur in immunocompetent individuals[1].

Patients with pulmonary nocardiosis typically lack specific symptoms, leading to diagnostic challenges. Definitive diagnosis often relies on histopathological examinations and/or culturing. Identification through mass spectrometry following bacterial cultivation serves as the "gold standard" for distinguishing different subtypes of Nocardia[6]. Sputum is the most commonly used respiratory sample for Nocardia isolation, and BALF or percutaneous needle aspiration

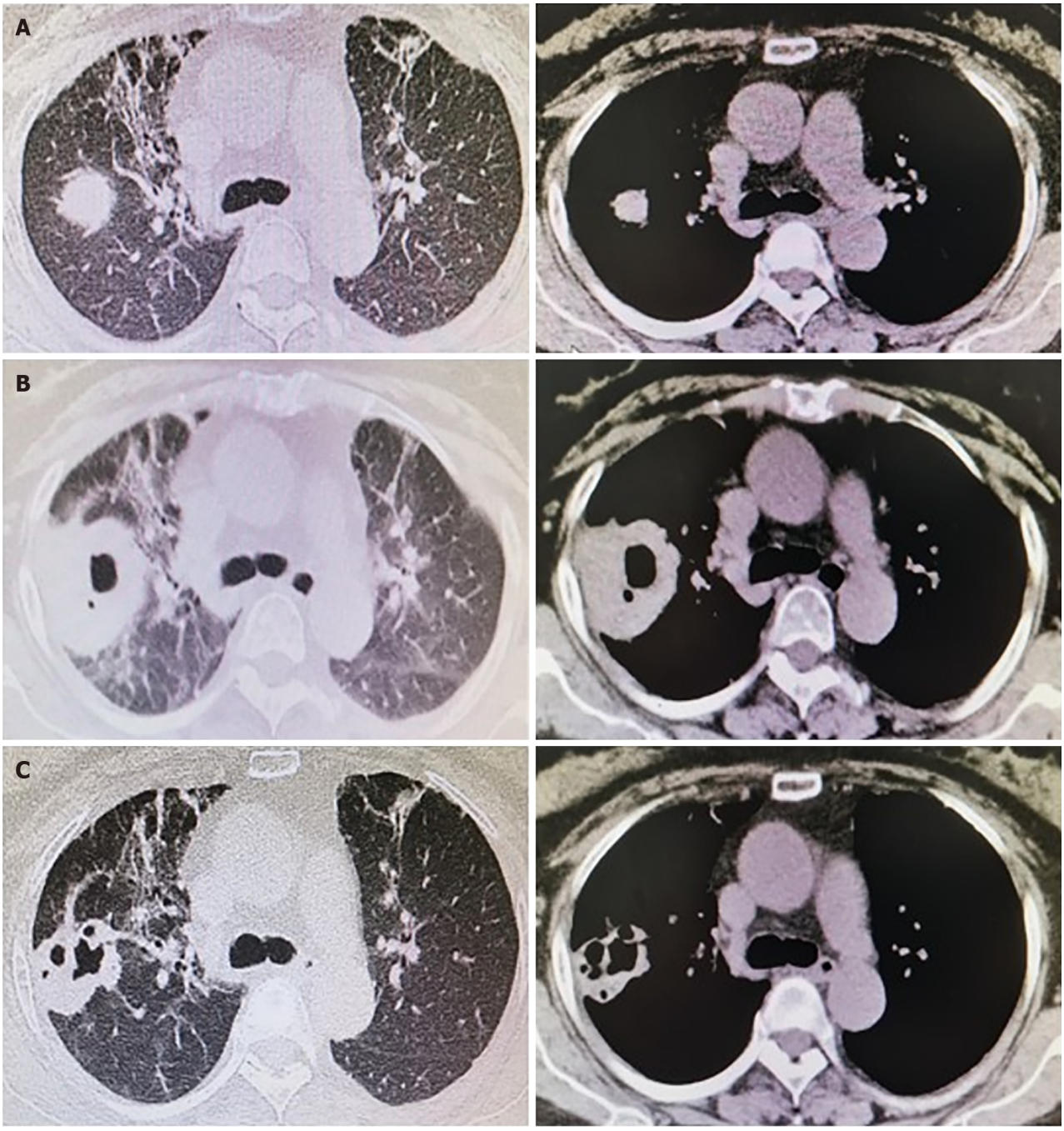

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Figure 1 Changes in chest computed tomography. A: Chest computed tomography (CT) on July 8, 2022. A right upper lobe pulmonary mass measuring 2.2 cm × 2.2 cm, with relatively smooth margins; B: Chest CT on July 15, 2022. A right upper lobe pulmonary mass measuring 4.8 cm × 4.7 cm, with internally regular cavities; C: Chest CT on July 28, 2022. A right upper lobe pulmonary mass measuring 2.7 cm × 3.3 cm, with multiple small cavities within.

biopsy is also used as an invasive method for obtaining samples[7]. BALF offers advantages such as simplicity of operation, minimal specimen contamination, and relatively reliable results. In contrast, percutaneous lung puncture biopsy carries the risk of pneumothorax or bleeding. In this case, the patient was more willing to undergo less invasive bronchoalveolar lavage through fibreoptic bronchoscopy.

However, Nocardia species are slow-growing and difficult to isolate, requiring extended incubation periods of up to 14 d. Conventional cultures often yield false-negative results, leading to a delayed diagnosis and a delay in the initiation of targeted treatment, and subsequently contribute to disease spread and increased morbidity and mortality rates[8,9]. mNGS is a highly sensitive, high-throughput detection method that identifies present microorganisms and their proportions by aligning all nucleic acids in the sample to a reference genome[10,11]. Compared to traditional culture methods, mNGS has a shorter detection period and higher sensitivity, especially for traditionally culture-negative samples[12,13]. By sequencing deoxyribonucleic acid or RNA fragments, theoretically all infectious pathogens present in clinical specimens can be identified, particularly for rare and atypical complex infectious diseases[14]. Moreover, the detection rate is not compromised by prior antibiotic treatment[15]. In this case, traditional pathogen testing failed to

identify a definitive pathogen. However, BALF mNGS quickly detected *Nocardia cyriacigeorgica*, leading to timely adjustments in the patient's antimicrobial regimen and significant clinical improvement, as evidenced by radiographic absorption.

Nocardia infection is a relatively rare cause of pneumonia, primarily occurring in immunodeficient patients, particularly those with cellular immune defects. In this case, the use of cyclosporine prior to infection is one of the risk factors, as cyclosporine specifically suppresses T-cell function and increases susceptibility to Nocardia infection. The use of glucocorticoids also contributed to the susceptibility in this patient, which was also observed in chronic obstructive pulmonary disease patients[1]. Beyond chronic obstructive pulmonary disease, patients with structural lung diseases such as bronchiectasis, allergic bronchopulmonary aspergillosis, and nontuberculous mycobacterial lung disease can also develop concurrent Nocardia infections[5,16,17]. However, Nocardia infections that occur in patients with interstitial pneumonia are relatively uncommon. Odashima *et al*[18] analysed pathogens in 46 patients with idiopathic pulmonary fibrosis complicated with chronic lung infection and detected Nocardia infection in only one patient. Farina *et al*[19] collected data from 30 Nocardia infection cases, and only one patient had lung fibrosis among them.

Pulmonary Nocardia infection mainly exhibits a subacute or chronic course, while cases with an acute presentation, similar to the one in this instance, are rare. Clinical symptoms are nonspecific and include fever, cough, chest pain, night sweats, and weight loss. Common CT findings of pulmonary Nocardia infection include consolidation, nodules, and masses, with a predilection for the upper lobes. Cavitary lesions may develop in approximately 33% of patients, and a minority may experience chest wall involvement. Enlargement of the mediastinal and hilar lymph nodes is not a typical feature of pulmonary nocardiosis[20]. The combination of these findings with nonspecific clinical symptoms often leads to misdiagnoses such as tuberculosis infection, fungal infection, vasculitis, or malignancy[21-23]. In this case, the patient's rapidly progressing nodular opacities and cavities posed a diagnostic challenge, as they were difficult to distinguish from pulmonary aspergillosis. The diagnosis was eventually achieved through BALF mNGS examination, leading to targeted antimicrobial therapy and significant clinical improvement, with radiographic evidence of absorption, further validating the mNGS results.

Sulphonamides are the first-line treatment choice for Nocardia infections. Amikacin, imipenem, and linezolid are also alternative options. Carbapenems and linezolid have been found to be effective against all pathogenic Nocardia species. Immunodeficient or critically ill patients often require combination therapy. The duration of Nocardia infection treatment is generally more than 6 mo, depending on disease severity, immunodeficiency, and clinical course. Patients with central nervous system involvement may require extended treatment[1]. Some cases involving lung abscesses and empyema may require surgical interventions such as drainage and debridement[23]. Compound SMZ, a combination of sulfamethoxazole and trimethoprim (TMP), is the most commonly employed oral sulphonamide. TMP acts as an enhancer of sulfamethoxazole, amplifying its therapeutic effects while concurrently mitigating potential adverse reactions. In fact, in this particular case, the patient experienced relief in body temperature and symptoms upon receiving prophylactic treatment with compound SMZ against *Pneumocystis pneumonia*, thus substantiating the accuracy and timeliness of both the diagnosis and treatment.

CONCLUSION

In summary, in patients with interstitial pneumonia receiving oral steroids and immunosuppressants, the presence of new nodules, masses, or cavitary lesions should raise suspicion of concurrent Nocardia infection. In addition to routine examinations and tests, mNGS can provide rapid pathogen identification, facilitating early targeted antimicrobial therapy and ultimately improving patient outcomes.

FOOTNOTES

Author contributions: All authors examined the patient; Zhuang Y and Gu Y participated in the discussion for the treatment and gave important suggestions; Qi DD and Chen Y drafted the manuscript; All authors critically revised the paper for important intellectual content, and all authors approved the final version of the manuscript.

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CASE REPORT

Intracranial infection accompanied sweet's syndrome in a patient with anti-interferon-γ autoantibodies: A case report

Jun-Hui Zheng, Dan Wu, Xiao-Yun Guo

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Abstract

BACKGROUND

Several reports of adult-onset immunodeficiency syndrome have been associated with anti-interferon-gamma (IFN-γ) autoantibodies (AIGAs). However, it is rare to find AIGAs with intracranial infections.

CASE SUMMARY

In this case study, we report a case of an AIGAs with intracranial infection and hand rashes considered Sweet's syndrome. The patient presented to our hospital with a persistent cough, a fever that had been going on for 6 mo, and a rash that had been going on for a week. The patient started losing consciousness gradually on the fourth day after admission, with neck stiffness and weakened limb muscles. The upper lobe of the left lung had a high-density mass with no atypia and a few inflammatory cells in the interstitium. Brain magnetic resonance imaging and cerebrospinal fluid suggest intracranial infection. The pathology of the skin damage on the right upper extremity revealed an infectious lesion that was susceptible to Sweet's disease. It has an anti-IFN-γ autoantibody titer of 1:2500. She was given empirical anti-non-tuberculous mycobacterial and anti-fungal treatments. The patient had no fever, obvious cough, headache, or rash on the hand. She got out of bed and took care of herself following hospitalization and discharge with medicine.

CONCLUSION

Adults with severe and recurrent infections of several organs should be considered for AIGAs if no other known risk factors exist. AIGAs are susceptible to subsequent intracranial infections and Sweet's syndrome.

Key Words: Adult-onset immunodeficiency syndrome; Anti-interferon-gamma auto-

antibodies; Intracranial infection; Sweet disease; Case report

Core Tip: Anti-interferon-gamma (IFN-γ) autoantibodies (AIGAs) have been associated with adult-onset immunodeficiency syndrome. Most patients have multiple organ involvement upon presentation; lymph nodes are the most frequently affected organ, followed by the skin, lungs, bones, and joints. We describe a patient with AIGAs who also had an intracranial infection and hand rashes as Sweet's syndrome. Anti-IFN-γ was increased despite the lack of a confirmed non-tuberculous mycobacterial (NTM) infection, and the empirical anti-NTM treatment in this patient was successful. Without recognized risk factors, AIGAs should be considered in patients with severe and recurrent infections of multiple organs. In AIGAs, subsequent intracranial infection and Sweet's syndrome are possible.

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INTRODUCTION

Adult-onset immunodeficiency syndrome associated with anti-interferon-gamma (IFN-γ) autoantibodies (AIGAs) has been discovered in Southeast Asia, including Thailand, Vietnamese, Japan, the Hong Kong Special Administrative Region of China, and Taiwan, since it was first reported in the Philippines in 2004[1-7].

The strong correlation between high-titer neutralizing antibodies to IFN-γ and this adult-onset immunodeficiency syndrome supports the critical function of IFN-γ in controlling many pathogens. Autoantibodies against IFN-γ have been linked to opportunistic infections, most frequently non-tuberculous mycobacterial (NTM) infections, and others, and can lead to immunodeficiency[1,8,9]. Thus, AIGAs may be viewed as a new form of late-onset immunodeficiency that confers a predisposition to some bacterial and fungal infections and severe mycobacterial illnesses.

Most patients have multiple organ involvement upon presentation; lymph nodes are the most often affected organ, followed by the skin, lungs, bones, blood, and joints[10]. The non-specific symptoms and rarity of this syndrome make it challenging to identify in the early stages of the disease. According to reports, 49%-57% of AIGAs had skin manifestations [11,12]. The skin manifestation of adult-onset immunodeficiency syndrome, known as Sweet's syndrome, is frequently associated with AIGAs[13]. Acute febrile neutrophilic dermatosis, another name for Sweet's syndrome, is a rare inflammatory condition. Its symptoms are acute onset dermal neutrophilic lesions, leukocytosis, and pyrexia. Sweet's syndrome frequently appears as erythematous plaques and nodules and is most commonly seen in reactive dermatitis. We have reported a patient with intracranial infection accompanied by hand rashes who also had IFN-γ autoantibodies, a condition known as Sweet's syndrome.

CASE PRESENTATION

Chief complaints

A 51-year-old female came to our hospital for treatment and presented with a persistent cough, fever for 6 mo, and rash for a week.

History of present illness

Symptoms started 6 mo back with recurrent cough and fever. Additionally, the lymph nodes in her right neck were swollen. A cervical lymph node biopsy revealed lymph node tuberculosis from the outer hospital. The cough subsided, and the lymph nodes shrank after anti-tuberculosis therapy. However, the cough persisted and recurred. Although chest computed tomography (CT) enhancement showed exudation and proliferation of tuberculous lesions in the upper lobe of the left lung, neoplastic lesions were not ruled out. Several inflammatory cell infiltration and necrosis, which are changes brought on by infection, were observed in the pathological findings. According to the thoracoscopic (left pleural) view, the vessels and lymphatic vessels were hyperplastic and dilated in the fibrous tissue. A significant amount of lymphocytes, plasma cells, and neutrophils were infiltrated. There was mild hyperplasia of mesenchymal cells on the surface, demonstrating inflammatory alterations, and hyperplasia of local tissue cells, some of which were papillary and crystal in appearance. The cough improved after receiving anti-infection and anti-tuberculosis treatment. However, the cough persisted to some degree. A week prior, the fever returned, and a rash with partial blisters and ulceration, together with pus flow and blackness, emerged on the right upper limb (Figure 1). The body had multiple nodules, partial ulceration, and a slight exudation. A paroxysmal headache followed it. On the fourth day after being admitted, the patient started to gradually lose consciousness and experience neck stiffness and weakened limb muscles. The patient

Table 1 Changes in carbohydrate antigen 125, immunoglobulins G and inhibitory lymphocytes

	Before therapy (2021/5/9)	After treatment (2021/7/8)
CA125 (≤ 35 U/mL)	46	12.7
IgG (8-16 g/L)	23.85	17.91
Th (19%-48%)	9.3	18.7

After treatment, the values of CA125, IgG, and Th returned to the normal counts. CA125: Carbohydrate antigen 125, IgG: Immunoglobulins G; Th: Inhibitory lymphocytes.

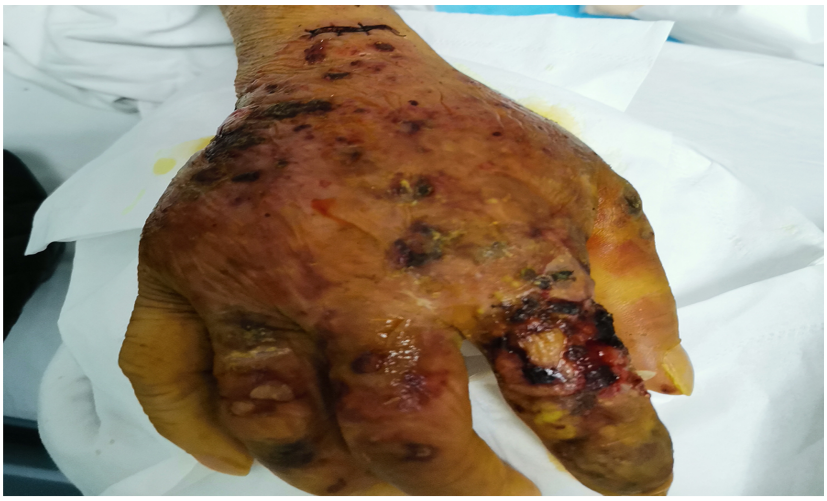

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Figure 1 Skin lesions on the patient's right hand. The rash appeared on the right upper limb, with partial blisters and ulceration, accompanied by pus flow and blackness.

slowly developed lethargy.

History of past illness

The patient denied having ever had an infection, such as tuberculosis.

Personal and family history

The patient denied having a history of tumors or similar diseases in her family.

Physical examination

The vital signs were as follows upon physical examination: body temperature, 36.4 °C; blood pressure, 119/86 mmHg; heart rate, 109 beats per min; and respiratory rate, 20 breaths per min. A rash with partial blisters, ulceration, pus flow, and blackness appeared on the right upper limb. Many nodules and partial ulcerations were seen throughout the body, along with slight exudation. Four days after being admitted, the patient gradually showed signs of lethargy, neck resistance, grade IV muscle strength in both upper limbs, grade II muscle strength in both lower limbs, and a positive Babinski sign on both sides.

Laboratory examinations

The peripheral white blood cell count was 16.9 × 10^9/L (3.69-16 × 10^9/L), ranging from 14.18 × 10^9/L neutrophils (2-7.7 × 10^9/L), 0.58 × 10^9/L eosinophilic (0.05-0.5 × 10^9/L), 1.48 × 10^9/L lymphocytes (0.8-4 × 10^9/L), and 405 × 10^9 /L (100-300 × 10^9/L) platelets (Figure 2) at the time of admission. Serum C-reactive protein concentration of 173.98 mg/L (0-3 mg/L) and erythrocyte sedimentation rate of 84.8 mm/h (0-20) were significant indicators of the inflammatory syndrome (Figure 3). The tumor marker had a carbohydrate antigen 125 level of 46 U/mL (≤ 35 U/mL). Humoral immunity was normal except for a slight increase in immunoglobulins G: 23.85 g/L (8-16 g/L). The number of inhibitory lymphocytes decreased by 9.3% (19%-48%) (Table 1). Antibodies to the human immunodeficiency virus are negative. Antibodies against tuberculobacter are positive. A bone marrow puncture was done due to increased levels of white blood cells and platelets. The results of the bone marrow aspiration showed reactive hyperplasia, no aberrant hyperplasia of juvenile cells, and no lymphoma.

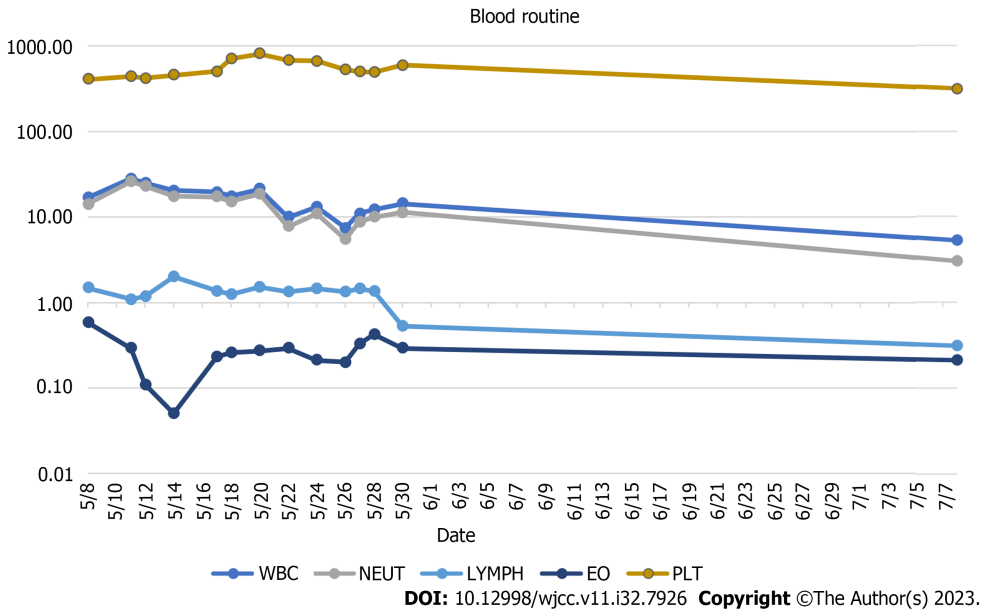

Figure 2 The changes in the blood routine indexes of the patient. The patient's white blood cells and neutrophils were significantly elevated at the time of admission and they gradually decreased to normal after treatment. Eosinophils and lymphocytes had only a little effect during the treatment course, while the platelets were first elevated and then decreased to the normal counts. WBC: White blood cells; NEUT: Neutrophils; LYMPH: Lymphocyte; EO: Eosinophil; PLT: Platelet.

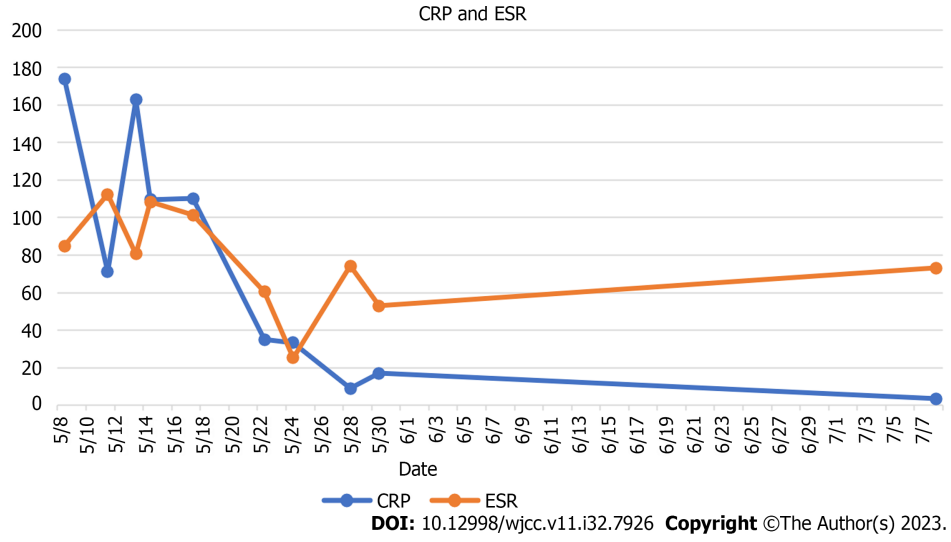

Figure 3 C-reactive protein and erythrocyte sedimentation rate of the patients. After treatment, the levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) decreased significantly when compared to that at the time of admission (CRP normal range 0-3 mg/L, ESR normal range 0-20 mm/h). CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

Imaging examinations

Chest CT improvement showed a 7.7 cm × 7.2 cm × 5.9 cm high-density mass in the left upper lobe of the left (Figure 4). There was no atypia and a small number of inflammatory cells in the interstitium, according to the pathological results of the left upper lobe of the lung. In alveolar lavage fluid, no malignant tumor cells were found. Yeast-like fungal spores were discovered in the pulmonary branch brush. The results of the second-generation sequencing of the lung tissue suggested *Propionibacterium acnes*.

Multiple ischemia lesions were found in the right basal ganglia, bilateral frontal lobes, periventricular, radiative crown, and hemioval center on a brain magnetic resonance imaging (MRI) scan plus enhancement (Figure 5). The results of the CT angiography revealed no definitive stenosis, occlusion, dilation, or aberrant vascular signs in bilateral anterior, middle, and posterior cerebral arteries and bilateral internal carotid, basilar, and vertebral arteries. The patient had a lumbar puncture, and the cerebrospinal fluid (CSF) was examined. CSF was clear and colorless. The Pandy test was weakly positive. The total number of white blood cells in CSF was 166 × 10^6/L, with neutral lobule accounting for 76.1%, lymphocytes accounting for 23.6%, and acid cells accounting for 0.3%. The protein content of CSF was 0.56g/L, and the chlorine level in CSF was 118 mmol/L (Table 2). CSF-based section showed more neutrophils and no malignant tumor

Table 2 Cerebrospinal fluid analysis

CSF parameter	Normal	Before therapy (2021/5/11)	After treatment (2021/5/17)
CSF pressure (mmH_2O)	80-180	230	160
Appearance	Clear	Clear	Clear
Pandy test	Negative	Weak positive	Weak positive
CSF WBC (10^6/L)	0-5	166	15
CSF N (%)		76.1	17.9
CSF L (%)		23.6	72
CSF E (%)		0.3	0.1
CSF protein (g/L)	0.08-0.45	0.56	0.72
CSFchloride ion (mmol/L)	120-130	118	113
CSF glucose (mmol/L)	2.5-4.4	2.66	2.48

Upon admission, the patient showed a high cerebrospinal fluid white blood cell (CSF WBC) count and a high CSF pressure. After treatment, the intracranial infection was controlled, which mainly indicated that the CSF pressure had restored and the CSF WBC count had decreased. CSF: Cerebrospinal fluid; CSF WBC: Cerebrospinal fluid white blood cell; CSF N: Cerebrospinal fluid neutrophils; CSF L: Cerebrospinal fluid lymphocytes; CSF E: Cerebrospinal fluid eosinophilic.

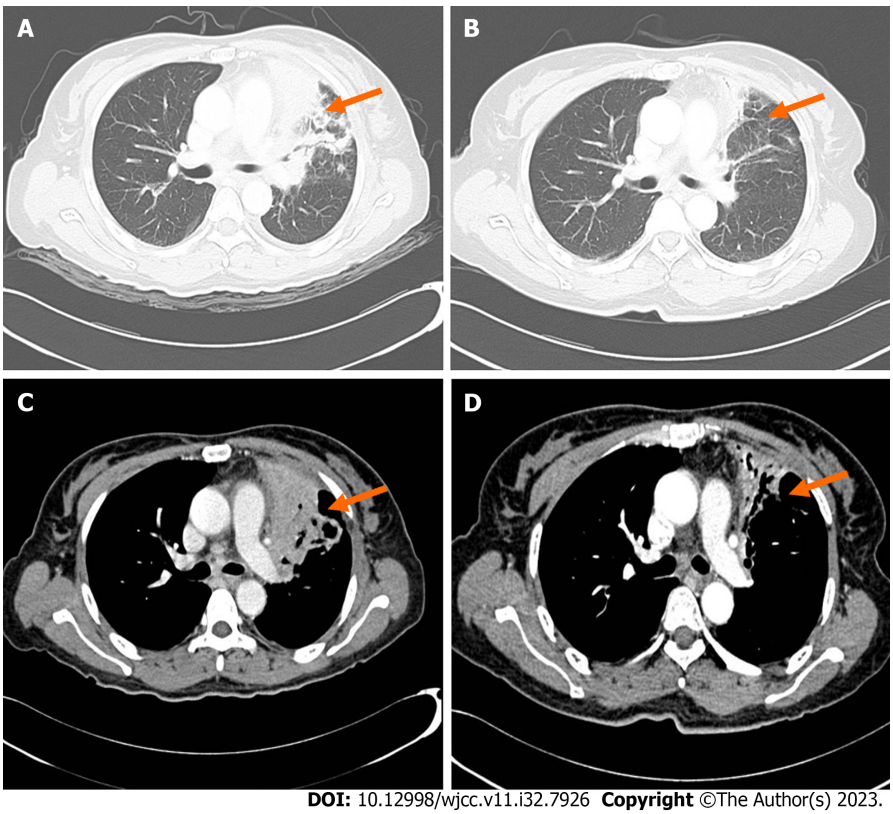

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Figure 4 Chest computed tomography enhancement. A: Lung window of 2021-05-10 (orange arrow); B: Lung window of 2021-07-12 (orange arrow); C: Mediastinal fenestra of 2021-05-10 (orange arrow); D: Mediastinal fenestra of 2021-07-12 2021-05-10 chest computed tomography (CT) revealed a high-density mass of size 7.7 cm × 7.2 cm × 5.9 cm in the upper lobe of the left lung in the lung window and lymph node enlargement in the mediastinal window. 2021-07-12 chest CT indicates improvement in the pulmonary lesion after treatment (orange arrow).

cells.

Fungi, tuberculosis, and bacteria were not discovered in the wound secretion of the right upper limb through several smears and cultures. According to the pathology of the damaged skin on the right upper extremity, Sweet disease-predisposed neutrophilic dermatitis was an infectious lesion (Figure 6). The antacid did not affect the specific discoloration. With no signs of lymphoma or tuberculosis, periodic acid-Schiff stains revealed eosinophilic bodies in the cytoplasm of histiocytes, which required differentiation from fungi. Skin sequencing from the second generation revealed

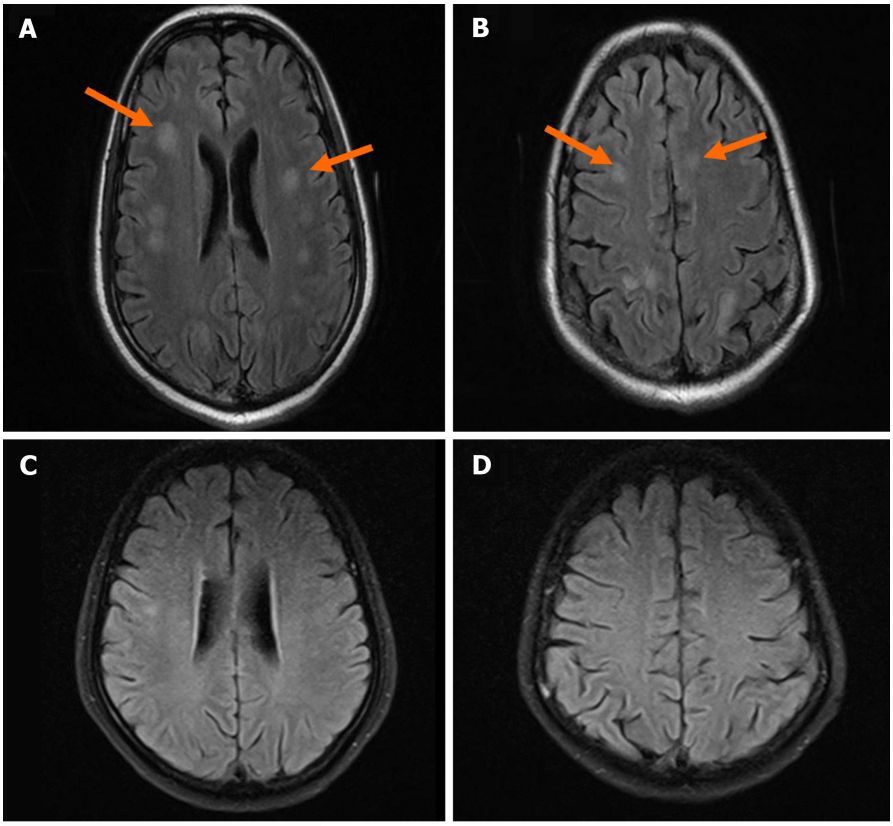

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Figure 5 Brain magnetic resonance imaging. A and B: Brain magnetic resonance imaging (MRI) of 2021-05-11 (orange arrows); C and D: Brain MRI of 2021-07-09 2021-05-11 brain MRI scan plus: T2 flair enhancement revealed multiple ischemic lesions in the right basal ganglia, bilateral frontal lobes, peri-ventricular, radiative crown, and hemioval center. 2021-07-09 brain MRI indicates improvement in the brain after treatment.

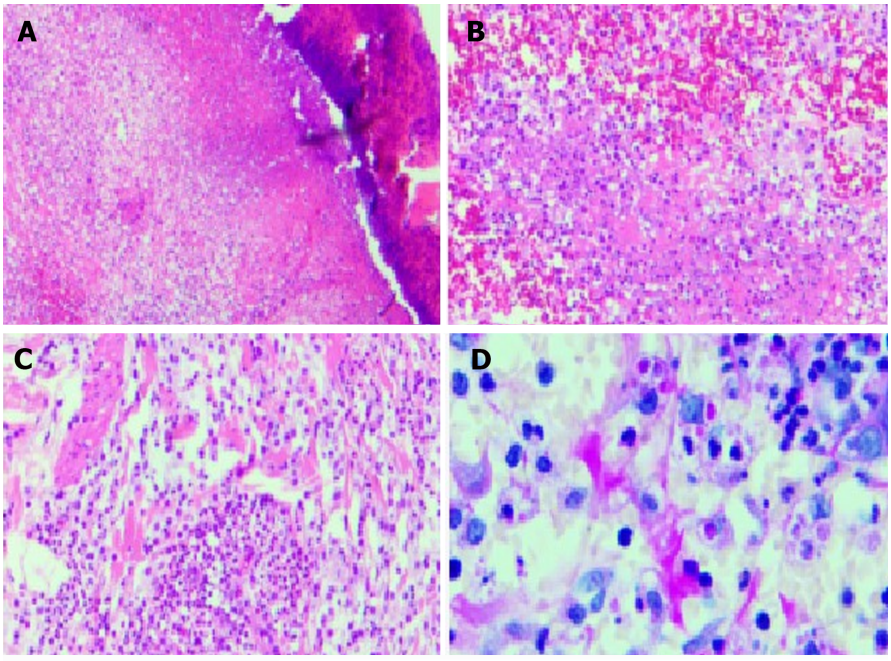

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Figure 6 Hepatic encephalopathy staining of the right-hand lesion skin. A: × 5; B: × 10; C: × 20; D: × 40. Epidermal erosion was observed by microscopy. Multiple focal necrosis were observed in the dermis, accompanied by further infiltration of lymphocytes and neutrophils. No epithelioid cells and caseous necrosis were observed. The observation was consistent with that of skin infection.

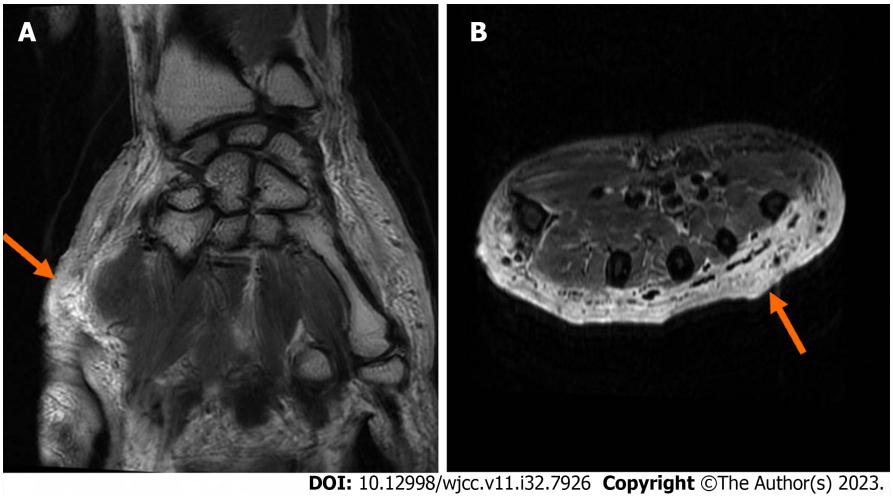

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Figure 7 Right-hand magnetic resonance imaging. A: Coronal position of the right hand magnetic resonance imaging (MRI) of 2021-5-15 (orange arrow); B: Axial position of the right hand MRI of 2021-5-15 2021-05-15 right-hand MRI indicates a slight swelling of the right hand; the subcutaneous fat space of the right palm was slightly blurred, implying the possibility of inflammatory changes (orange arrow).

Malassezia and *Malassezia globoides*. The MRI results of the right hand showed a slight swelling of the right hand, and the subcutaneous fat space of the right palm had a slight blurring, which was considered a sign of inflammatory changes (Figure 7).

We tested the patient's plasma for AIGAs due to the presence of the skin, lung, and intracranial multi-system lesions. Its titer was higher. The optical density (OD) value was still > 0.5 after a 2500-time dilution (OD normal range < 0.5).

FINAL DIAGNOSIS

AIGAs with intracranial infection and Sweet's syndrome was the final diagnosis.

TREATMENT

Ceftriaxone (1000 mg bid), amikacin (600 mg qd), azithromycin (500 mg b.i.d.), rifampicin (600 mg q.d.), ethambutol (1000 mg q.d.), and fluconazole (200 mg qd).

OUTCOME AND FOLLOW-UP

The patient had no fever, no obvious cough, no rash on the hand, and no headache after spending 20 d in the hospital before being discharged with medicine. The patient could get out of bed and care for herself because she was conscious. When she was seen again at the hospital two months later, all the signs were better than they had been. The patient continued receiving anti-mycobacterium therapy during future outpatient visits.

DISCUSSION

When a patient has multiple organ infections, typically from opportunistic infections without known immunosuppression, the diagnosis of adult-onset immunodeficiency syndrome associated with AIGAs should be considered. Since tests for established immunodeficiencies like human immunodeficiency virus are negative and antibodies to IFN-γ are strongly positive in this case, we gave the diagnosis of AIGAs some thought. Opportunistic infections, most frequently NTM infections and others, are linked to AIGAs[1-7]. Adult-onset immunodeficiency and NTM infection also showed a favorable additive interaction trend. We emphasize that even when culture results are negative, clinicians should be on the lookout for NTM infection in patients with AIGAs. Anti-IFN-γ was increased despite the lack of a confirmed NTM infection, and empirical anti-NTM treatment was successful in this case.

AIGAs damage multiple organs[10]. The lymphadenopathy, lungs, skin, and brain are the primary organs affected by this situation. CSF and brain MRI findings in this case led to the hypothesis of intracranial infection. Breakdown of the blood-brain barrier (BBB) is a common feature of many diseases of the central nervous system (CNS), including encephalitis. When the BBB is compromised in CNS diseases, there is a reduction in the transport of nutrients/oxygen, a quick influx of immune cells, and brain swelling that can exacerbate brain damage. According to a report, IFN-γ causes BBB

leakage. In brain endothelial cells exposed to disease tissue lysate, IFN-γ is a barrier disruptor[14]. Through Rho kinase-mediated cytoskeletal contractions, IFN-γ reduces barrier properties in cultured brain endothelial cells, leading to junctional instability and cell-cell separations. We decided to use a medication that may penetrate the BBB to treat the intracranial infection present in this case.

In this instance, there was also skin damage. Skin pathologic or dermatologic examination findings supported the existence of Sweet's syndrome. Neutrophilic dermatoses with negative microbial cultures were found by histopathology. Sweet's syndrome is associated with adult-onset immunodeficiency, which includes lymphadenopathy, pustular lesions, and leukocytosis[15]. Clinicians should be aware of the possibility of an underlying adult-onset immunodeficiency since patients with Sweet's syndrome have a specific clinical presentation that includes lymphadenopathy, pustular lesions, and leukocytosis.

CONCLUSION

In adults with severe and recurrent infections of multiple organs without other recognized risk factors, AIGAs should be considered. In AIGAs syndrome, the BBB may break down, leading to an intracranial infection. Sweet's syndrome usually coexists with this syndrome.

FOOTNOTES

Co-first authors: Jun-Hui Zheng and Dan Wu.

Author contributions: Zheng JH and Wu D substantial contribution to the conception and design of the work; Zheng JH, Wu D and Guo XY contribution to the acquisition, analysis, interpretation of data for the work; Zheng JH contribution to article writing and revising; Guo XY agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; all authors have read and approve the final manuscript. Zheng JH and Wu D contributed equally to this work, they are substantial contribution to the conception and design of the work.

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LETTER TO THE EDITOR

Potential and limitations of ChatGPT and generative artificial intelligence in medical safety education

Xin Wang, Xin-Qiao Liu

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Abstract

The primary objectives of medical safety education are to provide the public with essential knowledge about medications and to foster a scientific approach to drug usage. The era of using artificial intelligence to revolutionize medical safety education has already dawned, and ChatGPT and other generative artificial intelligence models have immense potential in this domain. Notably, they offer a wealth of knowledge, anonymity, continuous availability, and personalized services. However, the practical implementation of generative artificial intelligence models such as ChatGPT in medical safety education still faces several challenges, including concerns about the accuracy of information, legal responsibilities, and ethical obligations. Moving forward, it is crucial to intelligently upgrade ChatGPT by leveraging the strengths of existing medical practices. This task involves further integrating the model with real-life scenarios and proactively addressing ethical and security issues with the ultimate goal of providing the public with comprehensive, convenient, efficient, and personalized medical services.

Key Words: Medical safety education; ChatGPT; Generative artificial intelligence; Potential; Limitation

Core Tip: Generative artificial intelligence, represented by ChatGPT, has been experiencing rapid development. We believe that the era of leveraging artificial intelligence for medical safety education has arrived. To make the most of ChatGPT and generative artificial intelligence, it is essential to acknowledge both their strengths and limitations. By remaining vigilant and capitalizing on their advantages while addressing their shortcomings, we can strive to optimize and enhance the performance of ChatGPT and generative artificial intelligence. This ongoing exploration of the seamless integration of medical safety education with artificial intelligence is crucial in providing better medical services to the public.

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TO THE EDITOR

We have read the article by Liu *et al*[1] on medication safety. The findings of that research indicate that age and working status have positive and significant impacts on knowledge scores related to medication risk. Additionally, there is a significant positive correlation between working status and medication behavior scores. Moreover, the scores for knowledge, cultural beliefs, and medication behavior are significantly influenced by individuals' education levels, with higher levels of education leading to higher scores in these areas. This discoveries reported by this study contribute to the literature and provide valuable evidence related to medication safety among Chinese residents. Simultaneously, in combination with other related research, this study highlights the increasingly significant role of education in improving medication safety. Considering patient characteristics, a comprehensive approach that combines online and offline approaches to medical safety education will be a necessary path in the future to reduce medication risk among residents.

The main purpose of medical safety education is to help the public understand fundamental knowledge concerning medications, develop a scientific approach to drug usage, and enhance awareness and acceptance of diseases and medication treatments. These goals, in turn, help individuals avoid the dangerous consequences of such misconceptions in their daily lives. Effective health guidance plays a vital role in changing patients' lifestyles, improving their self-efficacy, and enhancing their overall physical and mental well-being[2]. Traditional methods of providing medication education to residents include one-on-one face-to-face explanations, group lectures, telephone guidance, electronic campaigns, books, magazines, and personalized online consultations[3-5]. Due to the swift development of information technology and the rapid rise of artificial intelligence, AI-based large-scale screening and digital intervention methods have gradually emerged and been applied in practice[6-10]. The global coronavirus disease 2019 pandemic has further accelerated the rapid adoption and widespread use of telehealth based on electronic information and telecommunication technologies[11]. The internet has become an essential source of health information and a medium for empowering patients[12]. Moreover, since the end of 2022, significant breakthroughs have been achieved by large language models, exemplified by ChatGPT[13]. Therefore, in the digital era, exploring generative artificial intelligence technologies such as ChatGPT offers significant opportunities in the field of medical safety education.

The potential of ChatGPT and generative artificial intelligence

ChatGPT, as a typical representative of generative artificial intelligence technologies, is a chatbot developed by OpenAI that utilizes a pretrained transformer language model known as GPT to comprehend and respond to natural language inputs[14]. Its purpose is to provide answers to various questions across different domains[15]. As a technological advancement in the 5.0 era[16], ChatGPT has been applied in numerous fields[17-20], and the health care sector is no exception[21-25].

The advantages of ChatGPT or generative AI (hereinafter referred to as ChatGPT) in the context of medical safety education can be summarized in terms of the following four aspects. First, ChatGPT possesses basic health care knowledge and the potential to conduct medical safety education. Research has shown that without any specialized training or reinforcement, ChatGPT achieved an accuracy rate of approximately 60% in all three subjects of the United States Medical Licensing Examination[26]. In the field of liver transplantation, ChatGPT can provide high-quality answers to relevant questions, making it a valuable resource for patient education[27].

Second, the anonymity offered by ChatGPT allows for better access to authentic patient information[28]. Due to the fear of stigmatization[29], patients may be reluctant to honestly disclose sensitive personal information related to their conditions[30], even resisting participation in medical safety education. By using ChatGPT as a medium for medical safety education, users' concerns with stigmatization can be minimized, encouraging them to honestly disclose crucial information related to their illnesses and thereby enhancing the effectiveness of medical safety education.

Third, ChatGPT can overcome the limitations of time, space, and language, thereby providing the public with more convenient and efficient pharmaceutical and health care services while maximizing resource utilization. ChatGPT can operate efficiently 24/7[31], significantly saving manpower, resources, and time. Users can easily access ChatGPT with just a few clicks, allowing them to receive medical consultations and answers without leaving their homes.

Finally, ChatGPT has great potential with regard to personalized medication education. It can analyze specific patient data to generate tailored treatment recommendations[32] and offer more personalized medical and health care services

and more effective problem-solving approaches. Compared to general health education for the entire public, the use of ChatGPT as a medium for medical safety education based on individuals' medical history, genetic information, and existing knowledge levels is more targeted and can assist users in improving their medical safety knowledge and practical skills more effectively.

The limitations of ChatGPT and generative artificial intelligence

It is worth noting that while generative AI, as represented by ChatGPT, has tremendous potential with regard to conducting medical safety education, its practical application still faces several limitations. First, medical and health care education, as a crucial aspect of the nation's well-being, must possess a high degree of scientific rigor, authority, and accuracy to effectively improve the public's medical knowledge and ensure residents' safety with respect to medication. While ChatGPT has the potential to serve as an information source and can respond actively to users' inquiries, the accuracy and reliability of these responses remain questionable[15,33]. False or erroneous information could have severe negative impacts on public health, even posing threats to people's lives and safety.

Second, ethical considerations pertaining to the use of ChatGPT must be taken seriously[34,35]. In the medical field, health care professionals have legal responsibilities and are bound by professional ethics to ensure the physical and mental well-being of patients. However, with regard to virtual robots such as ChatGPT, such legal responsibilities and moral obligations have yet to be clearly defined. How can the humanistic care of medicine be adequately reflected in their interactions? How can patients' personal information be properly protected? If accidents occur, how should responsibility for safety be assigned? These questions are all important and require thoughtful consideration.

Finally, the inappropriate use of ChatGPT may pose health risks. As ChatGPT operates through the internet and is accessed *via* electronic devices such as smartphones and computers, improper usage may not only fail to achieve the goals of medical and health care education but may even backfire. Prolonged screen time or internet addiction may impede individuals' normal physical activities and sleep, causing harm to their psychological and cognitive development[36].

Directions for future research

Given the potential issues pertaining to accuracy, ethical considerations, and health implications in medical safety education, it is essential to implement more robust measures to intelligently upgrade ChatGPT in the future. On the one hand, ChatGPT must be further integrated with real-life scenarios, making full use of electronic aids such as sensors and cameras to engage in real-time interactions with users. By accurately recognizing users' environments and usage patterns, it can provide a more immersive and authentic educational experience, thereby enhancing the accuracy and relevance of medical safety education.

In addition, all stakeholders should work together to establish relevant usage guidelines, industry standards, and regulatory frameworks to further regulate the application of ChatGPT in the medical field. Additionally, a clear delineation of safety and responsibility risks should be provided. This collective effort can contribute substantially to effectively addressing ethical and safety concerns.

The wave of generative artificial intelligence technologies represented by ChatGPT is approaching with great force and seems to be unstoppable. We firmly believe that only by recognizing the strengths and limitations of ChatGPT in medical safety education and by remaining vigilant and striving to optimize its performance can we fully explore the organic integration of education and artificial intelligence. In so doing, we can harness the potential of ChatGPT to empower medical safety education through technology and provide the public with more comprehensive, convenient, efficient, and personalized medical services.

FOOTNOTES

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