ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

Thrice Monthly Volume 13 Number 19 July 6, 2025

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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RESPONSIBLE EDITORS FOR THIS ISSUE

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng, Salim Surani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
July 6, 2025

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PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
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ONLINE SUBMISSION
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World Journal of Clinical Cases

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World J Clin Cases 2025 July 6; 13(19): 98095

DOI: 10.12998/wjcc.v13.i19.98095

ISSN 2307-8960 (online)

EDITORIAL

Potential role of large language models and personalized medicine to innovate cardiac rehabilitation

Rishith Mishra, Hersh Patel, Aleena Jamal, Som Singh

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C, Grade D

Novelty: Grade B, Grade C

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade C, Grade C

P-Reviewer: Maslova ZN; Passoni Lopes LC

Received: June 18, 2024

Revised: November 20, 2024

Accepted: February 20, 2025

Published online: July 6, 2025

Processing time: 274 Days and 5.4 Hours

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Abstract

Cardiac rehabilitation is a crucial multidisciplinary approach to improve patient outcomes. There is a growing body of evidence that suggests that these programs contribute towards reducing cardiovascular mortality and recurrence. Despite this, cardiac rehabilitation is underutilized and adherence to these programs has been a demonstrated barrier in achieving these outcomes. As a result, there is a growing focus on innovating these programs, especially from the standpoint of digital health and personalized medicine. This editorial discusses the possible roles of large language models, such as their role in ChatGPT, in further personalizing cardiac rehabilitation programs through simplifying medical jargon and employing motivational interviewing techniques, thus boosting patient engagement and adherence. However, these possibilities must be further investigated in the clinical literature. Likewise, the integration of large language models in cardiac rehabilitation will be challenging in its nascent stages to ensure accurate and ethical information delivery.

Key Words: Cardiac rehabilitation; Large language models; Patient education; Motivational interviewing; Artificial intelligence

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Core Tip: Large language models may help innovate cardiac rehabilitation programs on a larger scale, but there is a large paucity in evidence to support its utility and evaluating the validity of these innovative proposals. Likewise, this new innovation may be able to assist in developing more personalized medicine for patients and clinical research.

Citation: Mishra R, Patel H, Jamal A, Singh S. Potential role of large language models and personalized medicine to innovate cardiac rehabilitation. *World J Clin Cases* 2025; 13(19): 98095
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/98095.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.98095

INTRODUCTION

Cardiac rehabilitation is a multidisciplinary approach aimed to improve cardiovascular outcomes *via* emphasizing a patient's functional capacity and quality of life. Major components of cardiac rehabilitation include prescriptive exercise-based therapy, behavioral modifications, psychosocial counseling, and medical risk factor stratification[1-3]. While pharmacologic therapy is the initial choice of treatment for current cardiovascular morbidities, cardiac rehabilitation is somewhat of an underutilized tool that can serve as an adjunct to enhance patient outcomes, with current literature showing participation in exercise-based cardiac rehabilitation reducing cardiovascular mortality, recurrent cardiac events, and improving overall quality of life[4]. As cardiac rehabilitation is a rapidly growing field of interest that has shown evidence-based benefits, the current literature has been expanding on the potential implications given that only about 25% of individuals with eligible cardiovascular events will participate in cardiac rehabilitation[2,5] with some literature showing attendance rates at less than 20% over the past two decades[6,7]. Although cardiac rehabilitation can be valuable, adherence can be difficult for even the most motivated patients due to extraneous factors like health literacy, socioeconomic status, and personal obligations. This editorial aims to expand upon a recent publication by Kourek *et al* [6], which describes the latest updates on cardiac rehabilitation, including its indications, program structure, clinical outcomes, and potential limitations, while initiating a discussion regarding the likely innovations in the field of cardiac rehabilitation with patient adherence at its forefront. In particular, this editorial aims to build upon advancing cardiac rehabilitation by highlighting the possible incorporation of a large language model (LLM) as an educational tool to personalize further a patient's experience undergoing cardiac rehabilitation[6,7].

LLMS

LLMs are an expanding area of research interest as they have the capability to leverage deep learning to train and learn responses. These models are employed *via* chatbots (*i.e.*, ChatGPT). From a health literacy standpoint, LLMs may have the technological capabilities to directly impact health literacy by improving the readability of standard patient education methods, including pamphlets, action plans, and after-visit summaries[8,9]. However, there is currently a paucity of literature to support this claim. Let alone, studies have shown the potential benefits of artificial intelligence (AI) implementation on patient adherence with direct conversational influence on behavioral modification, particularly in vaccination adherence and weight-management in the overweight and obese patient population[10-13]. Although these findings are not directly in the field of cardiac rehabilitation, similar techniques can be offered to this patient population. For example, LLMs could be employed to learn and implement motivational interviewing concepts to initiate and maintain patient adherence to cardiac rehabilitation. An additional hypothetical situation where LLMs could aid the patients in cardiac rehabilitation could be in the ability to generate a personalized summary of the cardiac rehabilitation program for a patient. This personalized summary could adapt to the healthy literacy level for each patient, generating text at a grade reading level that provides the highest degree of comprehension for the patient. However, there is still a growing development of literature that demonstrates this specific situation in the field of rehabilitation[14]. Another role for LLMs could be in translating cardiac rehabilitation instructions to patients into their language of choice[15]. This can help facilitate the delivery of more equitable healthcare among those faced with language barriers.

While conversational methods in AI have been shown to improve patient adherence in preventative care in terms of improving health literacy, another potential avenue to explore is the impact of medical jargon on patient commitment to therapy. To expand, patients can find it difficult to follow medical jargon, which affects their awareness of their medical condition, its temporality, and treatment plans, creating a communication barrier between the patient and physician. A systematic review by Nickel *et al*[16] found that medical jargon resulted in an increased perception of disease severity, patient anxiety, and a desire for invasive management for their condition, highlighting that increased complexity of medical terms can influence the pattern of patient adherence. LLMs are a potential route that can assist how a physician communicates with a patient to advance health literacy by helping to translate medical jargon into a level that patients can understand. However, it is imperative for physicians and cardiac rehabilitation specialists to maintain a high degree of oversight with using these tools as minimizing medical jargon may blur the true meaning or severity of a condition[17, 18].

CONCLUSION

While this editorial described the possible utility of LLMs in assisting in motivational conversation techniques and simplification of terminology for patients, there remain major limitations to this technology. From an evidence standpoint, the possible utilities of LLMs must continue to be investigated at a larger scale. The current direction of literature has largely

utilized few LLMs, including ChatGPT, Copilot, and Gemini[19,20]. There may be an avenue for the development of LLMs which primarily learn from neural networks dedicated to using peer-reviewed, evidence-based resources, which may perform differently from these current models[21]. Secondly, there must be an ever-present need to develop further ethical and regulatory infrastructure on the use of LLMs in medicine overall. Currently, there remains a need for profound oversight by physicians and researchers to develop these models in order to effectively reduce and remove "hallucination" or the generation of inaccuracy and fabricated responses by LLMs based on the training of the model[22-24]. Additionally, it must be communicated to patients that LLMs are not medical sources of knowledge or healthcare providers but rather a communication tool to help deliver more equitable healthcare to individuals. This delivery can be in the form of personalizing the grade-reading level of the cardiac rehabilitation materials provided to patients or possibly transplanting these tools into different languages. Overall, these promising models will continue to develop given the great degree of resource allocation on advancing these promising tools[25].

FOOTNOTES

Author contributions: Mishra R administered the delegation of the report; Mishra R and Patel H wrote the initial draft; Jamal A provided a critical review and data collection of articles; Singh S designed the overall concept and outline of the manuscript.

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

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S-Editor: Fan M
L-Editor: A
P-Editor: Zhang XD

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World Journal of Clinical Cases

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World J Clin Cases 2025 July 6; 13(19): 101196

DOI: 10.12998/wjcc.v13.i19.101196

ISSN 2307-8960 (online)

EDITORIAL

Treatment of immunoglobulin A nephropathy: Current perspective and future prospects

Yusuf Ziya Şener, Seher Şener

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade D, Grade E

Novelty: Grade B, Grade C, Grade C

Creativity or Innovation: Grade B, Grade B, Grade C

Scientific Significance: Grade A, Grade B, Grade D

P-Reviewer: Al-Karawi AS; Bacharaki D; Zhou ZL

Received: September 6, 2024

Revised: February 9, 2025

Accepted: February 17, 2025

Published online: July 6, 2025

Processing time: 193 Days and 8 Hours

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Abstract

Immunoglobulin (Ig) A nephropathy is the most common type of primary glomerulonephritis globally. It typically manifests with microscopic hematuria and a spectrum of proteinuria, although rapidly progressive glomerulonephritis may occur in rare instances. Deposition of IgA in the mesangium seems to be the underlying disease mechanism. Despite current treatment, IgA nephropathy may progress into end-stage renal disease, indicating the necessity for the development of new therapeutic agents. Lifestyle modifications and anti-proteinuric treatment are recommended, and steroids have shown to be beneficial to high risk groups. Nevertheless, other conventional immunosuppressive agents, such as cyclophosphamide and mycophenolate mofetil, may be considered, despite the lack of sufficient evidence to support their efficacy. A considerable proportion of cases remain unresponsive to these treatments, underscoring the need for novel therapeutic approaches. There are several promising immunosuppressive drugs, such as B-cell lineage depleting agents or complement system inhibitors, that are currently undergoing clinical trials. These therapies may be considered for use in selected cases.

Key Words: Immunoglobulin A nephropathy; Telitacicept; Complement inhibitors; B-cell lineage depletion; Anti-proteinuric treatment

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Core Tip: Immunoglobulin A nephropathy represents the most prevalent form of primary glomerulonephritis, with the potential for progression to end-stage renal disease. Lifestyle modifications, dietary alterations and anti-proteinuric pharmacological agents have been demonstrated to induce clinical remission in most cases. However, some cases do not respond to supportive therapy. Short term use of corticosteroids should be considered in unresponsive cases. However, novel therapeutic strategies are required for patients with steroid-refractory disease. B-cell lineage depletion therapies and complement system inhibitors represent promising avenues for future research and may be considered in cases of persistent disease despite guideline-directed medical treatment.

Citation: Şener YZ, Şener S. Treatment of immunoglobulin A nephropathy: Current perspective and future prospects. *World J Clin Cases* 2025; 13(19): 101196
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/101196.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.101196

INTRODUCTION

The clinical presentation of immunoglobulin (Ig) A nephropathy was initially delineated by Berger and Hinglais[1] in 1968 in a patient exhibiting inter-capillary IgA deposition. It is regarded as the most common type of primary glomerulonephritis worldwide. Although it is usually considered a benign disease, a significant proportion of cases may progress to end-stage kidney disease[2]. Here, we provide a brief summary of the clinical presentation and pathophysiology followed by a literature review focusing on novel treatment approaches.

CLINICAL PRESENTATION AND PROGNOSIS

The clinical presentation may vary considerably, from incidental microscopic hematuria to nephrotic syndrome or rapidly progressive glomerulonephritis. However, in almost all cases, there is a history of a triggering infection, the majority of which are upper respiratory tract infections. The highest incidence of IgA nephropathy (IgAN) is observed in the Asia-Pacific region, while the lowest prevalence is seen in Africa and India[2]. The clinical presentation and prognosis of IgAN significantly varies across age groups and ethnicities. It is predominantly diagnosed between the second and fourth decades of life. In younger patients, the predominant findings are gross hematuria accompanied by urine sediment abnormalities. In contrast, elderly cases commonly present with acute kidney injury, reduced glomerular filtration, hypertension, and prominent proteinuria[3,4].

Previously, IgAN was regarded as a relatively benign disease. However, longitudinal studies have demonstrated that 25%-50% of patients ultimately progress to end-stage renal disease (ESRD) over time. Additionally, IgAN has been linked to an elevated mortality risk and a reduced life expectancy of approximately six years[5,6]. A number of defined predictors of worse outcomes in IgAN have been identified, including: (1) Heavy proteinuria; (2) Male gender; (3) Lower serum albumin level; (4) Diastolic hypertension; (5) Age below 30 years; and (6) Presence of renal dysfunction at the time of diagnosis and active urinary sediment[7]. Therefore, IgAN should not be considered as a benign course, and preventive measures should be implemented as early as possible to avoid disease progression.

PATHOPHYSIOLOGY

The deposition of immune complexes in the mesangium represents the primary mechanism underlying IgAN. It is well established that the level of galactose-deficient IgA1 (Gd-IgA1) is increased in patients with IgAN. Furthermore, Gd-IgA1 is proposed as a marker for diagnosis and assessment of the treatment response. IgG autoantibodies recognize gd-IgA1 antibodies and form circulating immune complexes that subsequently deposit in the mesangium. The deposition of immune complexes in the mesangium induces mesangial cell proliferation and extracellular matrix protein production, which is mediated by increased levels of cytokines and growth factors. This in turn results in impaired podocyte and filtration barrier functions, leading to proteinuria and hematuria[8]. Gut dysbiosis is also shown to contribute to the pathogenesis of IgAN by stimulating the production of Gd-IGA1[9].

TREATMENT

The management of IgAN should be determined based on the clinical presentation, the presence of renal dysfunction and the amount of proteinuria. The treatment of IgAN comprises lifestyle modifications, anti-proteinuric therapy and immunosuppressive treatment. Novel agents targeting B-cell lineage and the complement system have yielded promising results in early phase trials[3,10]. However, there is a paucity of consensus regarding the efficacy of tonsillectomy, with

current evidence suggesting its potential benefit in the Japanese population. The treatment approach for IgAN, including novel therapies, is illustrated in Figure 1.

Lifestyle modifications

It is recommended that the general recommendations for reducing cardiovascular risk be applied to patients with IgAN. The following measures are advised: (1) Smoking cessation; (2) Regular exercise; and (3) Maintaining weight within normal ranges. In addition, sodium intake should be restricted to below 2 g per day, as this is the only dietary recommendation that has been associated with outcomes[10,11]. Furthermore, blood pressure should be controlled, with the target systolic blood pressure set at below 120 mmHg. While some studies have indicated beneficial effects, there is nevertheless a paucity of consensus regarding the use of fish oil[10,11].

Anti-proteinuric treatment

Anti-proteinuric treatment comprises three main categories of pharmacological agents: (1) Renin-angiotensin-aldosterone system (RAAS) inhibitors; (2) Sodium-glucose cotransporter-2 (SGLT2) inhibitors; and (3) Endothelin receptor antagonists (ERAs). The RAAS inhibitors comprise angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB). RAAS inhibitors should be administered and the dose should be uptitrated to the maximally tolerated dose, particularly in patients with more than 500 mg/d proteinuria[11]. RAAS inhibitors are the only treatment that has demonstrated a clinical benefit among non-immunosuppressive therapies[12]. Combination of ACE inhibitors and ARBs results in a greater reduction in proteinuria levels. However, it is not recommended due to increased risk of adverse events including acute kidney injury and hyperkalemia[13].

SGLT2 inhibitors were initially developed as antidiabetic agents, and it was subsequently demonstrated that they exert beneficial effects on the treatment of heart failure and chronic kidney disease (CKD), irrespective of their anti-diabetic properties. "Dapagliflozin in patients with CKD" (DAPA-CKD) and "empagliflozin in patients with CKD" trials provided evidence that the addition of dapagliflozin or empagliflozin to standard care slowed CKD progression and resulted in a reduction in cardiovascular mortality in patients with or without diabetes[14,15]. A post-hoc subgroup analysis of IgAN patients enrolled in the DAPA-CKD trial revealed a significant benefit in this population[16]. Therefore, SGLT2 inhibitors should be considered in patients with persistent proteinuria despite maximally tolerated RAAS inhibition or as an adjunctive therapy on top of RAAS inhibition to improve outcomes. However, it should be noted that concomitant use of steroids and SGLT2 inhibitors might increase the risk of urinary tract infections[11].

Endothelin-1 plays a significant role in the pathophysiology of IgAN by inducing inflammation, vasoconstriction, podocyte injury and cell proliferation. The PROTECT study revealed a 41% greater reduction in proteinuria with sparsentan [a dual endothelin receptor A (ETA) and angiotensin receptor blocker] compared to irbesartan[17]. There are some concerns about ETAs in relation to salt and water intake, but there is growing evidence that the combined use of SGLT2 inhibitors and ETAs is an effective and safe treatment option[18]. Combined use of RAAS inhibitors, SGLT2 inhibitors and ERAs is proposed to be a standard supportive treatment of IgAN as similar to 4-pillar treatment of heart failure[19].

Conventional immunosuppressive therapy

Conventional immunosuppressive therapy comprises corticosteroids, cyclophosphamide, mycophenolate mofetil and azathioprine. The use of corticosteroids has been demonstrated to reduce proteinuria levels in patients with persistent proteinuria despite long-term anti-proteinuric therapy, as evidenced by the findings of the "supportive *vs* immunosuppressive therapy for the treatment of progressive IgAN" trial[20]. The "therapeutic effects of steroids in IgAN global" trial, in which 75% of participants are Chinese patients, also exhibited a notable reduction in proteinuria levels following corticosteroid treatment. However, the trial was terminated prematurely due to concerns regarding the potential for increased adverse effects associated with corticosteroid therapy[21]. The current guidelines recommend a short course of corticosteroid treatment (6 mo) for patients with persistent proteinuria despite maximal supportive care[10].

Although a small study demonstrated a beneficial impact of cyclophosphamide and azathioprine treatment on outcomes, subsequent studies failed to confirm those beneficial effects[11]. The impact of mycophenolate mofetil on IgAN also remains a topic of debate. Studies conducted in Chinese people suggest beneficial effects of mycophenolate mofetil, while studies reported from North America and European countries did not demonstrate such clear benefits[22-24]. Patients with persisting proteinuria (> 1 g/d) despite at least two rounds of steroids or conventional immunosuppressive therapy are defined as treatment refractory cases, and the novel therapeutic agents discussed below should be considered in those patients[25].

Targeting B–cell lineage

B lymphocytes and plasmocytes are responsible for the overproduction of Gd-IgA1. Thus, targeting B cells appears to be a reasonable approach for treating IgAN. The maturation of B cells is regulated by several factors, including B-cell-activating factor (BAFF) and a proliferation-induced ligand (APRIL), which are produced by macrophages and dendritic cells located in the lamina propria[26]. A variety of agents are used to deplete B cells, including anti-CD20 antibodies (such as Rituximab), anti-APRIL antibodies (such as Sibeprenlimab) and combined BAFF/APRIL inhibitors (such as Telitacicept and Atacicept). Rituximab proved ineffective in treating IgAN. However, sibeprenlimab and telitacicept demonstrated favorable outcomes in reducing proteinuria and inducing clinical remission in phase 2 trials. The results of the ongoing phase 3 trials, which include sibeprenlimab and telitacicept, are anticipated to yield promising results[3].

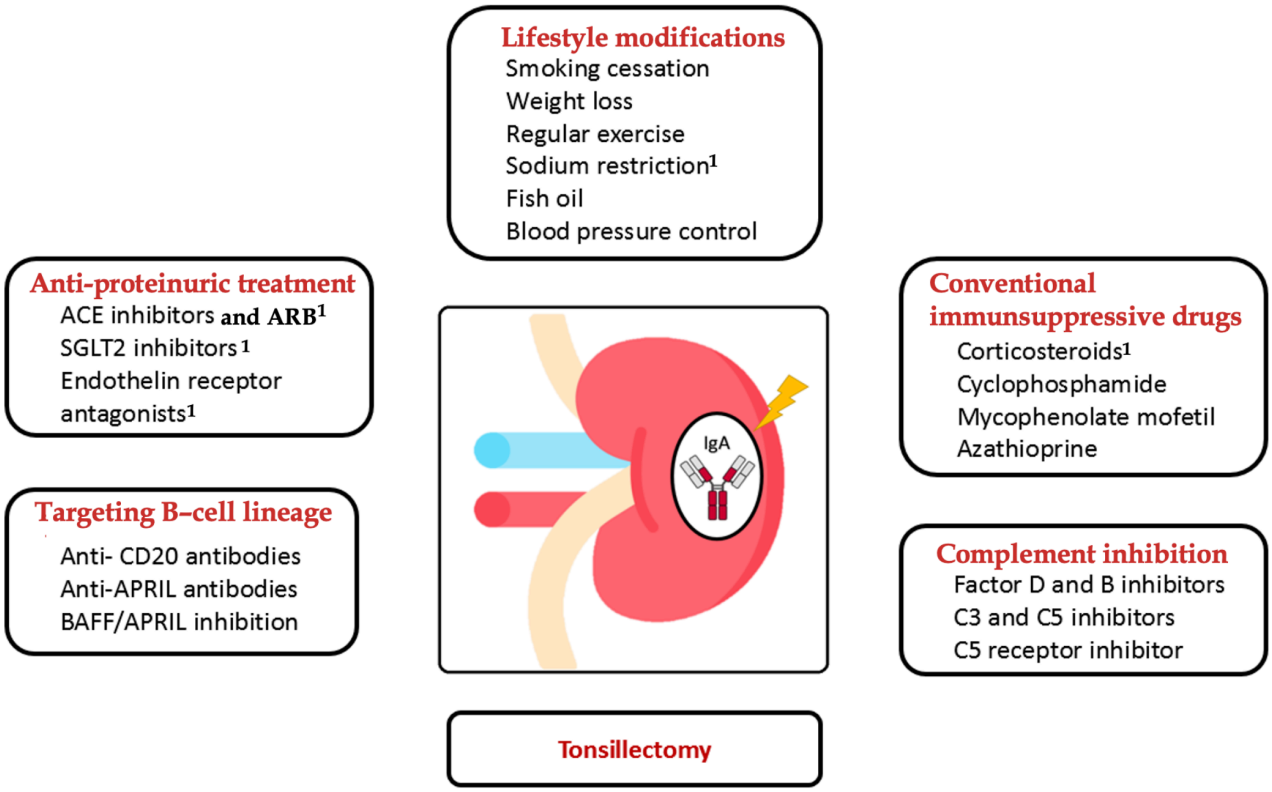

Figure 1 Treatment options in immunoglobulin A nephropathy. ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blockers; APRIL: A proliferation-induced ligand; BAFF: B-cell-activating factor; SGLT2: Sodium-glucose cotransporter-2. [1]Treatment options with proven certain clinical benefits by clinical trials.

Complement inhibition

The complement system plays a significant role in the pathogenesis of IgAN. Despite the deposition of IgG and IgM, the alternate pathway is activated instead of the classic pathway. There are several agents targeting numerous components of the complement pathway, and clinical trials are ongoing. The results of these trials will inform the role of complement inhibitors in IgAN[3].

Tonsillectomy

The benefits of tonsillectomy were only demonstrated in Japanese individuals. Tonsillectomy resulted in improved kidney survival and increased remission rates in Japanese patients. However, these findings have not been confirmed in other populations. Therefore, tonsillectomy is not routinely recommended in non-Japanese people[10].

CONCLUSION

IgAN is the most common primary glomerulonephritis worldwide, and in the absence of efficacious treatment, it progresses to ESRD. The fundamental aspect of the treatment plan is supportive care, which encompasses a combination of lifestyle modifications and anti-proteinuric therapy. While RAAS blockers were previously the sole available option, SGLT2 inhibitors and ERAs have recently been identified as efficacious alternative anti-proteinuric regimens. While clinical remission is achieved in most cases with supportive treatment, a considerable proportion of patients require additional intervention to control the disease. Given that the principal mechanism underlying the disease appears to be increased production of Gd-IgA1 by B cells, immunosuppressive treatment is employed in high-risk patients. The clinical benefit was only established with corticosteroids by clinical trials and with mycophenolate mofetil in Chinese patients. B-cell lineage depletion therapies (Telitacicept, *etc*) and complement system inhibiting agents are promising novel therapies, and their role in the treatment is likely to become more important depending on the results of ongoing trials. It should be noted that pathological findings regarding the severity of inflammation and fibrosis may guide the treatment approach. The impact of novel therapies should be evaluated in diverse ethnicities, as genetic background plays a pivotal role in IgAN.

FOOTNOTES

Author contributions: Şener YZ contributed to the design, concept and writing of the manuscript; Şener S contributed to the design, literature review and manuscript editing; all of the authors read and approved the final version of the manuscript to be published.

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

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S-Editor: Luo ML
L-Editor: Filipodia
P-Editor: Zhang XD

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World Journal of Clinical Cases

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World J Clin Cases 2025 July 6; 13(19): 104976

DOI: 10.12998/wjcc.v13.i19.104976

ISSN 2307-8960 (online)

EDITORIAL

Necessity of collaboration between pain physicians and orthotists in pain medicine

Jin-Bok Yi, Min Cheol Chang

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade D

Novelty: Grade C

Creativity or Innovation: Grade D

Scientific Significance: Grade C

P-Reviewer: Kaya B

Received: January 8, 2025

Revised: February 19, 2025

Accepted: February 27, 2025

Published online: July 6, 2025

Processing time: 70 Days and 21.3 Hours

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Abstract

In this editorial, we comment on the article by Nagamine *et al*, published in the *World Journal of Clinical Cases*. The authors suggest that virtual reality technology has potential in alleviating pain by enhancing brain network functionality. Alongside virtual reality, various treatment methods are used to effectively manage musculoskeletal pain. One such method is the use of orthoses, which are applied in clinical settings. We emphasize the need for collaboration between pain physicians and orthotists when applying orthoses for pain management. The efficacy of orthoses is maximized when customized to the physical characteristics of each patient, type of disease, and location of pain. Orthoses are designed to restore anatomical alignment and biomechanical function; however, their success depends on the expertise of trained orthotists, who should effectively communicate with physicians and understand the mechanical principles of musculoskeletal alignment. The professional knowledge of orthotists is critical in ensuring that orthoses are appropriately designed and applied to achieve therapeutic efficacy. Since no single treatment modality typically offers sufficient relief for musculoskeletal pain, effective collaboration between pain physicians and orthotists is crucial to optimize the use of orthoses in the management of pain.

Key Words: Pain; Physician; Orthotist; Pain medicine; Orthosis

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Core Tip: Effective management of musculoskeletal pain often requires a multidisciplinary approach, combining treatments, such as drug therapy, physiotherapy, and orthotic devices. Orthoses are usefully being applied in controlling pain by restoring anatomical alignment and preventing further injury. To maximize their efficacy, orthoses must be customized to the physical characteristics of each patient, type of disease, and location of pain. Collaboration between pain physicians and trained orthotists is essential for ensuring appropriate design and application of orthoses. It leads to improved patient outcomes in the management of pain.

Citation: Yi JB, Chang MC. Necessity of collaboration between pain physicians and orthotists in pain medicine. *World J Clin Cases* 2025; 13(19): 104976
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/104976.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.104976

INTRODUCTION

When treating musculoskeletal pain, various therapeutic modalities, including drug therapy, physiotherapy, injections, and psychotherapy, are necessary to improve treatment outcomes[1,2]. Orthoses can also effectively control musculoskeletal pain[3,4]. They prevent musculoskeletal tissue injury and facilitate the recovery of injured tissues by preventing excessive joint motion or inappropriate posture and movement[5]. The efficacy of an orthosis in treating pain is maximized when it is customized based on the physical characteristics, type of disease, and location of pain of each patient, requiring collaboration between pain physicians and orthotists.

ROLE OF ORTHOSES IN MUSCULOSKELETAL PAIN MANAGEMENT

Orthoses are exoskeleton-like devices designed to control mechanical aspects of the musculoskeletal system, assisting in the restoration of anatomical alignment and related biomechanical functions. Considering these characteristics, orthoses must be fabricated by trained orthotists with a sound understanding of musculoskeletal alignment and its mechanical relationships, the ability to effectively communicate with physicians regarding prescriptions, and the ability to apply appropriate technologies in the fabrication process.

EXAMPLES OF THE APPLICATION OF ORTHOSES IN SPECIFIC CONDITIONS

Applying an appropriate orthosis to patients with carpal tunnel syndrome requires the orthosis to immobilize the wrist while stably maintaining a neutral position when worn and be fitted well for comfort[3]. Additionally, the orthosis should not cause unnecessary tension in the surrounding tissues.

In patients with tenosynovitis or osteoarthritis, an orthosis can prevent excessive use of the musculoskeletal components associated with the pain and assist in stabilizing tendons and joints to prevent inflammation and injury[4]. For an orthosis to be correctly applied, it must be fabricated based on the physical characteristics and structures of each patient, requiring a sufficient understanding of the mechanics of the forces exerted between the orthosis and the patient.

An insole device, a type of orthosis, is often essential for treating foot pain[6]. Foot pain is often caused by malalignment of the foot, such as pes cavus or pes planus, or by excessive pressure applied to a particular part of the foot. An insole device can correct malalignment of the foot, while materials, such as Poron or Plastazote applied to the part of the foot under excessive pressure can assist in reducing pain. Custom-made insoles should be fabricated considering biomechanical aspects, including alignment of the leg and shifts in the center of gravity due to weight-bearing and changes in posture. To correct misalignment, the insole must fit the shape of the foot, reflect biomechanical changes due to weight bearing, and control the biomechanical conditions. Additionally, the possibility of foot pain worsening due to an altered mechanical pattern after applying the insole should be considered, and if the pain worsens, the insole should be modified for comfort.

CONCLUSION

The professional knowledge and skills of orthotists are crucial for correctly applying orthoses to patients with musculoskeletal conditions. A single treatment modality often does not offer sufficient therapeutic efficacy for musculoskeletal pain. An orthosis is an effective pain treatment tool that, when applied correctly, can significantly enhance therapeutic outcomes. Therefore, collaboration between pain physicians and orthotists is essential to maximize the therapeutic efficacy of orthoses for the treatment of musculoskeletal pain.

FOOTNOTES

Author contributions: Yi JB and Chang MC designed the research study; Yi JB and Chang MC drifted and revised the manuscript.

Conflict-of-interest statement: The author has no conflicts of interest.

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S-Editor: Qu XL
L-Editor: A
P-Editor: Wang WB

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World Journal of Clinical Cases

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World J Clin Cases 2025 July 6; 13(19): 101850

DOI: 10.12998/wjcc.v13.i19.101850

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Total adenosine deaminase cases as an inflammatory biomarker of pleural effusion syndrome

Bernardo Henrique Ferraz Maranhão, Cyro Teixeira da Silva Junior, Jorge Luiz Barillo, Joeber Bernardo Soares Souza, Patricia Siqueira Silva, Roberto Stirbulov

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade D, Grade D

Novelty: Grade C, Grade C

Creativity or Innovation: Grade C, Grade C

Scientific Significance: Grade C, Grade C

P-Reviewer: Mohsen Hammad DB; Ulasoglu C

Received: September 28, 2024

Revised: November 4, 2024

Accepted: March 4, 2025

Published online: July 6, 2025

Processing time: 171 Days and 16.7 Hours

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Abstract

BACKGROUND

Although inflammatory diseases commonly affect the pleura and pleural space, their mechanisms of action remain unclear. The presence of several mediators emphasizes the concept of pleural inflammation. Adenosine deaminase (ADA) is an inflammatory mediator detected at increased levels in the pleural fluid.

AIM

To determine the role of total pleural ADA (P-ADA) levels in the diagnosis of pleural inflammatory diseases.

METHODS

157 patients with inflammatory pleural effusion (exudates, n = 124, 79%) and non-inflammatory pleural effusion (transudates, n = 33, 21%) were included in this observational retrospective cohort study. The P-ADA assay was tested using a

kinetic technique. The performance of the model was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). The ideal cutoff value for P-ADA in pleural inflammation was determined using the Youden index in the ROC curve.

RESULTS

The transudates included congestive heart failure (n = 26), cirrhosis of the liver with ascites (n = 3), chronic renal failure (n = 3), and low total protein levels (n = 1). The exudate cases included tuberculosis (n = 44), adenocarcinoma (n = 37), simple parapneumonic effusions (n = 15), complicated parapneumonic effusions/empyema (n = 8), lymphoma (n = 7), and other diseases (n = 13). The optimal cutoff value of P-ADA was ≥ 9.00 U/L. The diagnostic parameters as sensitivity, specificity, positive and negative predictive values, positive and negative likelihood values, odds ratio, and accuracy were 77.69 (95%CI: 69.22-84.75); 68.75 (95%CI: 49.99-83.88); 90.38 and 44.90 (95%CI: 83.03-95.29; 30.67-59.77); 2.48 and 0.32 (95%CI: 2.21-11.2; 0.27-0.51); 7.65 (95%CI: 0.78-18.34), and 75.82 (95%CI: 68.24-82.37), respectively (χ^2 = 29.51, P = 0.00001). An AUC value of 0.8107 (95%CI: 0.7174-0.8754; P = 0.0000) was clinically useful. The Hosmer-Lemeshow test showed excellent discrimination.

CONCLUSION

P-ADA biomarker has high diagnostic performance for pleural inflammatory exudates.

Key Words: Pleural effusion; Biomarker; Adenosine deaminase; Inflammation; transudate; Exudate

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Core Tip: Non-specialists find it difficult to diagnose pleural effusions. Although diagnosing the syndrome through imaging is simple, determining the cause is more difficult. To treat pleural disease as soon as possible, it is crucial to determine whether it is inflammatory. To our knowledge, this study is the first in Brazil and the world to establish a reference value with strict statistical criteria to classify inflammatory pleural effusion syndrome.

Citation: Maranhão BHF, Junior CTDS, Barillo JL, Souza JBS, Silva PS, Stirbulov R. Total adenosine deaminase cases as an inflammatory biomarker of pleural effusion syndrome. *World J Clin Cases* 2025; 13(19): 101850
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/101850.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.101850

INTRODUCTION

Pleural effusion syndrome (PES) is an excess of pleural fluid (PF) between the layers of the pleura[1]. Patients with active pleural inflammation or pleurisy complain of acute pain, localized, increasing, or decreasing in intensity, with breathing or coughing. Pleuritic pain tends to subside when an effusion develops. However, the most important clinical effect of pleural effusion is shortness of breath, which can significantly reduce quality of life[1].

Identifying whether a PES is an exudate with inflammatory diseases or a transudate with noninflammatory diseases is the first step in determining its cause. This classification system has important diagnostic implications[1]. Transudative pleural effusion usually represents an outward sign of disease in another organ. Therefore, its main causes are renal, hepatic, and cardiac disorders[1]. Transudate occurs because of hydrostatic or oncotic pressure imbalance. Inflammation was not observed. Therefore, transudates have low cell counts and protein content. Usually, a surgical procedure for PF or tissue extraction is not necessary for causal diagnosis[1]. Exudates occur secondary to diseases that cause inflammation or infection in the pleural space and tissue with increased pleural vascular permeability. Vascular changes allow leukocyte diapedesis and transport of large molecules[2]. Usually, surgical procedures for the withdrawal of PF and/or tissue are necessary for diagnosis and treatment[1]. Inflammatory PF can lead to severe surgical complications, such as empyema and pleural thickening[1].

An inflammation arises from the interaction between immune cells and many mediators that protect an organism from damaging stimuli. Adenosine is an endogenous purine nucleoside that modulates several physiological processes. It is considered a key mediator of the immune response. Under physiological conditions, the extracellular concentrations of adenosine are maintained at low levels as a result of rapid metabolism. However, the highest levels were observed under conditions of increased metabolic demand, such as hypoxia, tissue injury, and inflammation. Under resting conditions, some adenosine triphosphate (ATP) is dephosphorylated to adenosine; however, dangerous stimuli can increase the intracellular conversion of ATP to adenosine. Once released into the extracellular space, adenosine can be deaminated to inosine by adenosine deaminase enzyme (ADA) or taken up directly by cells by specific nucleoside transporters and rephosphorylated to ATP[3-5].

ADA is an important biomarker in organic fluids of cellular and humoral immune responses and translates to monocyte and macrophage activation. It is also essential for the proliferation and differentiation of lymphoid cells, especially T cells, in inflammatory diseases[6]. ADA induces the production of inflammatory cytokines such as tumor

necrosis factor alpha, transforming growth factor beta, and interferon gamma. In humans, total ADA has two isoforms: ADA1 and ADA2. ADA1 is found in all human tissues. It is highly expressed by T and B cells and accounts for approximately 90% of total ADA activity. The primary role of ADA1 is to regulate the intracellular adenosine levels. ADA2 exhibits autocrine activity. It is involved in the maturation of monocytes in anti-inflammatory macrophages (M2), dendritic cells, B cells, neutrophils, and CD26-Tregs. There is indirect evidence of the possible role of ADA2 as an endothelial growth factor[5].

ATP, adenosine, and ADA modulate purinergic responses during inflammation. ADA levels increased in response to higher adenosine levels. As a result, the inflammatory response is amplified[7,8]. Specific studies have demonstrated a relationship between pleural ADA (P-ADA) levels and pleural inflammatory disease. Thus, P-ADA could be relevant in the management of PES. It can indicate the inflammatory nature of pleural effusions. Different studies in several countries conclude that higher levels of P-ADA indicate a greater likelihood of pleural tuberculosis[9,10]. However, elevated P-ADA levels are not exclusive to pleural tuberculosis. Very high levels (> 150 U/L) of P-ADA are unusual in pleural tuberculosis. Alternative diagnoses are bacterial empyema, lymphoma, leukemia, and multiple myeloma[10,11].

Although inflammatory and infectious diseases frequently involve the pleural space and pleura, the immunological and molecular mechanisms underlying pleural involvement remain unknown[7]. Some diseases are associated with the infiltration of different types of immune cells, such as neutrophils, eosinophils, and lymphocytes. In addition to infiltrating cells, mesothelial cells actively participate in pleural inflammation by releasing various mediators and proteins. Increased levels of several inflammatory mediators have been detected in PF, including lipid, cytokines, and proteins. The presence of these mediators emphasizes the concept of pleural inflammation. Moreover, certain inflammatory mediators appear to characterize a specific cause of PES[12]. This study aimed to determine the role of total pleural adenosine deaminase (P-ADA, U/L; adenosine amino hydrolase; enzyme code 3.5.4.4) level as a biomarker for the diagnosis of pleural inflammatory diseases.

MATERIALS AND METHODS

The STARD and STROBE recommendations were followed in the study design, findings, and reporting[13,14]. Our investigation was a traditional observational retrospective cohort analysis or chart review of a type series of cases performed at two hospitals in Rio de Janeiro, Brazil, between March 2015 and December 2019.

Inclusion and exclusion criteria

Clinical and imaging evaluations were performed to confirm the causative diagnosis of PES[1]. An initial thoracentesis procedure was performed, followed by video-assisted thoracoscopic surgery (VATS) and histopathological analysis if necessary[1]. The diagnosis of pleural transudate was confirmed using the Maranhão and Silva Junior criterion[15]. This was validated according to Light's criterion, but with dosages of total protein and total lactate dehydrogenase (LDH) only in the PF[16]. The exclusion criteria were absolute contraindications or refusal to undergo thoracentesis or VATS, hemolysis in PF, chronic renal failure, jaundice, PES of unknown cause, and use of immunosuppressive medications. This is because ADA levels may be modulated by antiretroviral therapy in HIV subjects[6].

ADA assay

Adequate collection, storage, and processing of PF were observed for accurate diagnosis. The PF used for the P-ADA test was non-hemolyzed[17]. The PF preserved at −20 °C were thawed, and several biomarkers in the samples were measured. The ADA was performed using a commercial kit with a kinetic approach. Briefly, the P-ADA assay is based on the enzymatic deamination of adenosine to inosine, which is then converted to hypoxanthine by purine nucleoside phosphorylase. Hypoxanthine is transformed to uric acid and hydrogen peroxide by xanthine oxidase. Hydrogen peroxide reacts with N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline and 4-aminoantipyrine in the presence of peroxidase to generate a quinone dye, which was measured in a kinetic manner. One unit of P-ADA was defined as the amount of ADA that generates one μmol of inosine from adenosine per minute at 37 °C. The assay was linear from 0-200 U/L ($r^2 > 0.99$). Ultracentrifugation did not affect the results. ADA was stable for one week at 4 °C. The reagents were stable for one year if stored at 2–8 °C in amber flasks. ADA activity in the serum of healthy humans has a reference value range of 0–15 U/L[18]. This ADA assay with automated kinetic methods was also validated for various organic fluids, and there were no differences in the diagnostic accuracy for pleural tuberculosis between the classic manual method of Giusti and this Diazyme ADA assay method[19,20].

Statistical approach

Descriptive and inferential statistics, with receiver operating characteristic (ROC) curve analysis, were analyzed using a combination of the statistical software including NCSS version 2022, GraphPad version 5.0, and MedCalc version 20.11. The Grubbs double-sided method, which examines the most extreme values on both sides of the data, was used to detect the outliers. The normality and variance homogeneity of the data were evaluated using the Shapiro-Wilk test (W). An unpaired *t*-test with standard deviation was used to compare the means of the two groups with a Gaussian distribution. The median and interquartile range were used to express non-normal distributions (IQR). When the sample was not normally distributed, the Wilcoxon-Mann-Whitney *U* test was used to compare data. The non-parametric Kruskal-Wallis (K-W) test (*H*-test) was used to check the hypothesis that several unpaired samples originated from the same population. A *post-hoc* test, according to Dunn's test, was performed when the K-W test had a *P* value less than the selected significance level. The χ^2 test was used to compare groups and proportions. The *P*-value for both sides was 0.05.

Sample size and sampling technique

The sample size calculation was based on the expected area under the ROC curve (AUC > 0.50), null value of the AUC (AUC = 0.50), and ratio of sample sizes between positive and negative cases (n = 2) according to the MedCalc software [21]. For an α-level of 0.05 and a β-level of 0.20 (statistical power = 80%), a sample of 19 cases was required in the positive group (exudates) and 38 in the negative group (transudates), giving a total of 57 cases. The sample size in this study consisted of 157 PF samples from 157 patients with proven transudative or non-inflammatory diseases used as controls (n = 33) and exudative pleural effusions with inflammatory diseases of several causes (n = 124). Bias was avoided because the data was recorded in a series of patients only with PES (cases and controls) with the purpose of management after a standard diagnostic protocol. In case series, information bias can occur but may be reduced by selecting an appropriate control group[14].

Optimal P-ADA threshold

The nonparametric technique of DeLong *et al*[22] was used to obtain the ROC curve to study the diagnostic parameters of P-ADA as an inflammatory biomarker. Youden index was used to determine the optimal P-ADA threshold (J). The J value is the highest sum of sensitivity and specificity[22,23].

Model performance, discrimination, and potential clinical usefulness

Model performance refers to how well a statistical model fits the data used to build it. It was evaluated using metrics such as AUC-ROC and diagnostic parameters with 95%CI[13,14]. Discrimination refers to the ability of a biomarker to distinguish between individuals with and without a disease or condition. Discrimination was classically evaluated using AUC-ROC (C-statistic) with 95%CI[24,25]. Hosmer and Lemeshow proposed the following classifications as general rules for the discrimination accuracy of a logistic regression model based on the AUC space[24]: Excellent discrimination (0.90-1.0), very good discrimination (0.80-0.90), good discrimination (0.70-0.80), sufficient discrimination (0.60-0.70), poor discrimination (0.50-0.60), and biomarker not useful (0.00–0.50). Clinical usefulness refers to whether a biomarker has practical utility in a clinical setting, such as in helping to diagnose a disease, predicting disease progression, or guiding treatment decisions. The potential clinical usefulness of P-ADA was evaluated using the AUC for diagnostic biomarkers in general, an AUC > 0.75 is clinically useful[26].

RESULTS

The 157 cases and causes of pleural exudates and transudates are represented with demographic information in Table 1. Exudates were more common than transudates [124 (79%) *vs* 33 (21%) patients, respectively]. Regarding the male sex, there was no significant difference in the proportion, as calculated by the χ^2 test, between exudates and transudates (P = 0.9415). The same was observed for the female sex in both groups (P = 0.9416). In the χ^2 test, only adenocarcinoma and lymphomas were significant (P = 0.0021 and P = 0.0003, respectively) for male sex.

Many quantitative studies on clinical biomarkers have demonstrated age-related changes in reference values. Early life, adolescence, old age, and after the menopause are important periods of life[27]. Regarding age, there was a significant difference in the medians (U = 895, P < 0.0001) between exudates (58.0; IQR: 41.5–73.5) and transudates (76.0; IQR: 63.0–86.25). However, it was not an objective of this study to evaluate a cutoff for P-ADA in relation to the range of ages for inflammatory diseases in PES.

The pattern of missing data was MAR or missing randomly. Only 3% of exudates (cases) and 6% of transudates (controls) had missing P-ADA values. For inflammatory diseases (exudates) in a patient with lymphoma, the Grubbs test yielded an outside value of 1121.1 U/L of P-ADA. There were no digitation errors, and this value was consistent with causal diagnosis. However, a median of 18.4 U/L was used (Table 2).

Table 3 shows that the median values of P-ADA were significantly different (U = 679.5; P < 0.0001) between inflammatory (18.4 U/L, IQR: 9.85–41.4) and non-inflammatory diseases (6.85 U/L, IQR: 2.67–11.26). The values of total protein and total LDH in the PF were in agreement with the Light and Maranhão and Silva Junior criteria[15,16].

Figure 1 shows the ROC curve obtained using the method described by DeLong *et al*[22]. For diagnostic purposes with inflammatory pleural effusions, according to the Youden index, the optimal cutoff value was ≥ 9.00 U/L of P-ADA. For discrimination of the model, there was an AUC of 0.8107, a 95%CI of 0.7174-0.8754. The standard error of the mean (SE) was 0.039. The Z-value to test was 7.837, with a two-sided P-value of 0.0000. The diagnostic parameters for P-ADA, with the best cutoff point selected for pleural inflammatory diseases, are listed in Table 4.

DISCUSSION

Retrospective studies sometimes reflect routine clinical practice better than prospective studies, although they may fail to identify all eligible patients and often result in lower quality data with more missing data. In this study, the author took care of the inclusion and exclusion criteria and the statistical treatment of missing data[13].

ADA modulates the immune system and plays an important role in several diseases, including rheumatoid arthritis with ADA modulating metabolic remodeling and joint destruction; chronic pulmonary diseases with ADA participating in modulating purinergic responses; inflammatory bowel diseases with ADA involved in modulating purinergic responses; sepsis with ADA playing a key role in modulating purinergic responses; and pleural tuberculosis with ADA

Table 1 Demographic characteristics and causes of inflammatory and noninflammatory diseases in 157 patients with pleural effusion syndrome in the State of Rio de Janeiro, Brazil, from March 2015 to December 2019, *n* (%)/median (25th-75th percentiles)

Cause	Patient (*n*)	Prevalence (%)	Age	Female	Male
Non-inflammatory[1]	33	21.0	76.0 (63.0-86.25)	17.0 (52.0)	16.0 (48.0)
Inflammatory	124	79.0	58.0 (41.5-73.5)	66.0 (53.0)	58.0 (47.0)
Tuberculosis	44	28.0	39.0 (29.7-58.2)	22.0 (50.0)	22.0 (50.0)
Adenoc.	37	24.0	61.0 (45.0-77.0)	25 (68.0)	12 (32.0)
Simple PPE	15	10.0	67.0 (56.0-85.0)	6 (40.0)	9 (60.0)
CPPE/Empiema	8	5.0	52.5 (33.5-78.75)	2 (25.0)	6 (75.0)
Lymphoma	7	4.0	53.0 (47.0-63.0)	0 (0.0)	7 (100.0).
Squamous cell	7	4.0	66.0 (55.0-66.0)	4 (57.0)	3 (43.0)
Other[2]	6	4.0	73.0 (53.0-79.0)	4 (67.0)	2 (33.0)
Total	157	100.0	58.0 (41.75-73.25)	80 (51.0)	77 (49.0)

[1]Transudates: Congestive heart failure (n = 26), chronic renal failure (n = 3), cirrhosis of liver with ascites (n = 3), and serum low total protein levels (n = 1).
[2]Other exudates: Pseudo-Meigs syndrome (n = 1), Dressler's syndrome (n = 3), chylothorax (n = 1), leukemia (n = 1).
CPPE: Complicated parapneumonic effusions.

Table 2 Levels of pleural adenosine deaminase evaluated in 157 cases of pleural effusion syndrome confirmed with reference standard diagnostic tests[1]

Cause	Pleural fluids–sample size (*n*)	P-ADA (medians) (U/L)	25th-75th percentile
Non-Inflammatory disease (control)			
Transudate	33	6.85	2.67-11.26
Inflammatory disease (case)	124	18.4	9.25-41.4
Tuberculosis	44	42.0	32.9-61.9
Adenocarcinoma	37	9.75	6.7-14.9
Simple parapneumonic effusion	15	9.38	5.68-9.97
CPPE and empyema	8	32.9	16.0-61.7
Lymphoma	7	401.2	11.2-990.5
Squamous cell carcinoma	7	13.11	11.0-28.2
Other	6	15.2	7.4-49.0

[1]Shapiro-Wilk test for pleural adenosine deaminase (W = 0.347, P < 0.0001). K-W test for pleural adenosine deaminase (H = 81.34, P < 0.0001) and Dunn's test with P < 0.05: Tuberculosis *vs* transudates, *vs* simple PPE, and *vs* adenocarcinoma, and P > 0.05: CPPE and empyemas, lymphomas, squamous cell carcinoma, and other exudates.
CPPE: Complicated parapneumonic effusions; P-ADA: Pleural adenosine deaminase.

deeply inducing the production of inflammatory cytokines in PF[4].

The pleura and the pleural space have fascinating pathophysiologies. Many pleural diseases are associated with local and systemic inflammations[7]. However, the underlying inflammatory mechanisms have not yet been elucidated. This study described the causes of various pleural inflammatory diseases. The role of adenosine deaminase as a diagnostic biomarker was evaluated using rigorous statistical methods.

As shown in Table 1, the sex proportion and median age were comparable to those reported in earlier studies[9-11]. The prevalence of tuberculosis and malignancy was similar to those reported in other studies[9-11]. Other authors have studied P-ADA in pleural inflammatory diseases from medical thoracoscopy, but tuberculosis was not in the group analyzed[28].

The P-ADA level was statistically significant in separating pleural transudates and inflammatory diseases, mainly tuberculosis, as shown in Table 2. In Brazil and other countries with an elevated incidence and prevalence of tuberculosis and other inflammatory diseases, P-ADA activity is also an accurate biomarker for tuberculous pleural effusion with false-positive results for complicated parapneumonic effusions, empyema, and lymphoma[10,29-31]. As shown in

Table 3 Laboratory analysis of adenosine deaminase, proteins, and lactate dehydrogenase in 157 cases of pleural fluids from inflammatory and non-inflammatory pleural effusion syndrome, median (25th-75th percentiles)/ mean ± SD[1]

Non-inflammatory pleural effusion (control)	Result
Total pleural ADA[a]	6.85 (2.67–11.26)
Total pleural protein[b]	2.64 ± 1.52
Total pleural LDH, median[c]	190.5 (100.5–278.8)
Inflammatory pleural effusion (case)	
Total pleural ADA[a]	18.4 (9.25–41.4)
Total pleural protein[b]	5.05 (4.47–5.60)
Total pleural LDH[c]	568.5 (400.3–822.5)

[1]The Shapiro–Wilk test (W) rejected the normal data from pleural total adenosine deaminase, and pleural total LDH in exudate cases ($P < 0.05$), but not pleural total protein in controls ($P = 0.0881$).
[a]$P < 0.0001$.
[b]$P < 0.0001$, after logarithmic transformation of data.
[c]$P < 0.0001$.
ADA: Adenosine deaminase; LDH: Lactate dehydrogenase; IQR: Interquartile range.

Table 4 Measures of diagnostic parameters of adenosine deaminase following selection of the best cutoff point for pleural inflammatory diseases according to the Youden index in the receiver operating characteristic curve

Diagnostic parameter	Result (%)[2]	95%CI
Best cutoff (U/L)	≥ 9.00	-
Sensitivity	77.69	69.22-84.75
Specificity	68.75	49.99-83.88
Positive predictive value or precision	90.38	83.03-95.29
Negative predictive value	44.90	30.67-59.77
Positive likelihood ratio[1]	2.48	2.21-11.2
Negative likelihood ratio[1]	0.32	0.27-0.51
Diagnostic odds radio	7.65	0.78-18.34
Diagnostic or predictive accuracy[1]	75.82	68.24-82.37
Disease prevalence[1]	50.48	44.78-56.17

[1]These values are dependent on disease prevalence.
[2]$\chi^2 = 29.5138$ (2-Sided P-value= 0.00001). Statnote: The Youden index at the receiver operating characteristic curve is the optimal cutoff value that provides the best tradeoff between sensitivity and specificity.

Table 2, the Kolmogorov-Smirnov test was significant for the P-ADA classification of inflammatory and non-inflammatory diseases (H = 81.34, $P < 0.0001$). Dunn's test was significant ($P < 0.05$) for pleural tuberculosis *vs* transudates, simple PPE, and adenocarcinoma. However, the difference was not significant ($P > 0.05$) for pleural tuberculosis vs. CPPE, empyemas, lymphomas, squamous cell carcinoma, and other exudates.

In adenocarcinoma, tumor cells induce immune suppression through the accumulation of regulatory T cells (Tregs) and many other mechanisms[32]. The increase in total P-ADA levels in pleural tuberculosis is largely caused by the ADA-2 isoenzyme present in monocytes and macrophages in response to pleural infection or inflammation caused by *Mycobacterium tuberculosis*[29]. Inflammatory processes in pneumonia occur in the peripheral alveolar spaces. Increased vascular permeability of local capillaries may lead to increased fluid accumulation in the lungs and pleural cavities. In addition, locally released inflammatory mediators may diffuse into the subpleural or pleural tissue, resulting in the local activation of constitutive cells such as mesothelial cells. Moreover, circulating inflammatory cells migrate into the pleural cavity. The predominance of an inflammatory white cell count within PF is of limited diagnostic value[1,30]. However, immunocytochemical analysis should be used to differentiate malignant cell types[1].

ADA-1 Levels play an important role in the differentiation of lymphoid cells, and ADA-2 in the maturation of monocytes into macrophages[4,29]. P-ADA activity in T-cell lymphomas is similar to that in B-cell lymphoma[31]. The median P-ADA level for the lymphoma patients was 401.2 U/L (Table 2). When total P-ADA levels are greater than 150

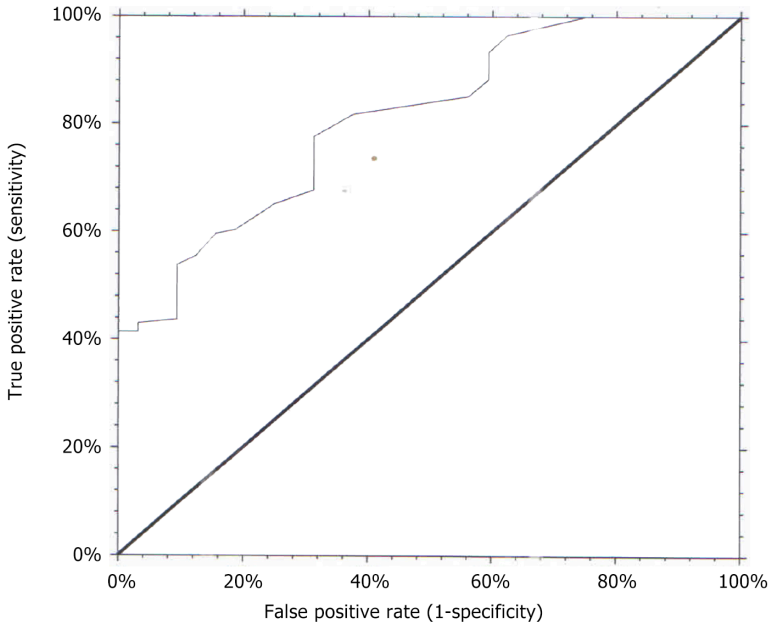

Figure 1 Nonparametric receiver operating characteristic curve of pleural adenosine deaminase for pleural inflammatory diseases. The selection criterion was the Youden index [J = 0.4644; distance to the receiver operating characteristic (ROC) curve corner = 0.3840]. The optimal cutoff value for ROC curve concavity was ≥ 9.00 U/L of pleural adenosine deaminase. Evaluation metric for checking the model's performance: Area under the curve (AUC), 0.8107; 95%CI: 0.7174-0.8754; SE: 0.039; *Z*-value to test (AUC ≠ 0.5), 7.837; 2-Sided *P*-value, 0.0000.

U/L, the differential diagnosis is CPPE, empyema, and lymphoid malignancies instead of tuberculous pleural effusion [31]. Therefore, in patients with cancer risk, high P-ADA levels should be interpreted with caution[33].

The median P-ADA levels were significantly lower in non-inflammatory diseases or transudates (6.85 U/L) than in inflammatory diseases or exudates (18.4 U/L) as shown in Table 3. The explanation for these findings is that a transudate, as opposed to an exudate, indicates that the pleural mesothelium is affected by systemic and/or pulmonary pressures. The barrier permeability characteristics were maintained. ADA has a low molecular radius of 29.10 angstroms and weight of 42 kDa. Therefore, transpleural transport from sera occurs *via* diffusion[2].

Depending on the objectives of biomarker dosage, several methods for selecting an optimal cutoff value have been proposed by expert authors[23,34]. The repercussions of receiving a false-positive diagnostic test result are serious. Therefore, it was crucial to choose an optimal cutoff value of P-ADA greater than or equal to 9.00 U/L for inflammatory diseases with high precision (90%) using the Youden index (Table 4). It is important to explain that there is no disagreement between the cutoff value greater than or equal to 9.0 U/L of P-ADA calculated by the ROC curve using the Youden criterion for pleural inflammatory diseases and the cut-off value found in the literature greater than or equal to 30.0 U/L. This last cutoff value of P-ADA was calculated using several criteria for the diagnosis of pleural tuberculosis [10]. Huan *et al*[35] established a P-ADA cutoff value of 29.6 U/L for tuberculosis pleural effusion (TPE). The authors concluded that optimizing the utility of P-ADA helps clinicians diagnose TPE when other initial laboratory workups are inconclusive. Masood *et al*[36] found a cutoff level for P-ADA of 30 U/L for tuberculosis PF with high sensitivity (71%) and specificity (82%).

The AUC indicates the potential of a biomarker. For clinical and practical purposes, we need to dichotomize the test results to classify the subjects as diseased or nondiseased. Therefore, the choice of an 'optimal' cutoff point for dichotomizing a continuous biomarker cannot be arbitrary. Youden's index is a better criterion because it selects biomarkers with larger values of both sensitivity and specificity[37]. The discrimination with an AUC of 0.8107 was very good according to the Hosmer–Lemeshow scale[24]. An AUC greater than 0.75 was clinically useful[26]. Another metric for evaluating the clinical usefulness of a biomarker is the clinical utility index, established by Åsberg *et al*[38]. There is some overlap between the evaluations of different aspects of the biomarker performance. Therefore, it is important to evaluate biomarkers using multiple metrics and consider the context in which they will be used[13,14]. In addition to the AUC, other values derived from the ROC curve are useful to define diagnostic characteristics of a biomarker. In contrast to diagnostic accuracy, predictive values provide more specific information of a biomarker. A high positive predictive value (PPV ≥ 80%) would be adequate to perform a diagnostic and initiate a treatment[39,40]. The PPV value found in this work for inflammatory PF was > 90%, as shown in Table 4. Yavuz *et al*[41] found a high sensitivity (91%) with a cutoff level de P-ADA greater or equal to 20.0 U/L for TPE. However, they observed a PPV of 67% and a specificity of 75%.

Despite its observational methodology, this study had limitations. Before adopting accurate models in clinical practice, additional studies using data from many hospitals are required for external validation[13,14]. Thus, a multicenter, worldwide study with accurately diagnosed cases with the highest number of subjects is necessary.

The future perspectives are positive. First, our diagnostic model is crucial in clinical practice and can be used to identify inflammatory pleural effusions with acceptable discrimination and predictive power. In addition, P-ADA levels also had high diagnostic performance for pleural tuberculosis worldwide (VPP > 80%) and rendered closed-needle

pleural biopsy unnecessary[9,10,20,33,35,42]. Second, purinergic signaling plays an important role in lung inflammation. The expression of adenosine receptors is altered in patients with airway inflammation. Adenosine receptor antagonists such as theophylline have therapeutic benefits in several inflammatory pulmonary diseases. Adenosine signaling has also been implicated in regulating the function of inflammatory cells such as macrophages and neutrophils[43]. Third, physiologically and acutely increased adenosine levels are associated with beneficial effects such as vasodilatation and a decrease in inflammation. In contrast, chronic overproduction of adenosine occurs under pathological conditions and is responsible for the adverse effects of adenosine associated with chronic lung and pleural inflammation, fibrosis, and tissue injury[44].

CONCLUSION

This study concluded that the P-ADA biomarker with the cutoff selected (≥ 9.0 U/L) using ROC curve analysis with the Youden index criterion had a high diagnostic performance for pleural inflammatory exudates.

ACKNOWLEDGEMENTS

The author, Cyro Teixeira da Silva Junior, is grateful to Professor Charles E. Metz (in memoriam) from the University of Chicago Medical Center for suggestions with ROC curve analysis that helped improve several papers in your academic career.

FOOTNOTES

Author contributions: Maranhão BHF and Stirbulov R executed the idea and planned, organized, and supervised the study; Souza JBS, Barillo JL, and Silva PS were responsible for data collection; da Silva Junior CT wrote the earlier and final drafts of the manuscript and was responsible for statistical analysis and interpretation of the results. All authors have read and approved the manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of the Faculty of Medicine, Federal Fluminense University (number 48946121.9.0000.5243).

Informed consent statement: Written informed consent was obtained from all participants before the study.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest regarding the content of this article. Funding The authors received no financial support for the research, authorship, or publication of this article.

Data sharing statement: sharing statement: The corresponding author can provide datasets that support the conclusions of this study upon request. The original datasets are not accessible to the general public because they contain data that may jeopardize the privacy of research participants.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement- checklist of items.

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Corresponding Author's Membership in Professional Societies: Sociedade Brasileira de Pneumologia.

S-Editor: Liu H
L-Editor: A
P-Editor: Zhang XD

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World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2025 July 6; 13(19): 101889

DOI: 10.12998/wjcc.v13.i19.101889

ISSN 2307-8960 (online)

SYSTEMATIC REVIEWS

Surgical management of patients with corneal lesions due to lid pathologies

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Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade D
Novelty: Grade C
Creativity or Innovation: Grade B
Scientific Significance: Grade C

P-Reviewer: Lin Y

Received: October 16, 2024
Revised: February 17, 2025
Accepted: February 27, 2025
Published online: July 6, 2025
Processing time: 154 Days and 1.6 Hours

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Abstract

BACKGROUND

The surgical management of corneal lesions resulting from eyelid pathologies requires a comprehensive approach to ensure optimal patient outcomes. Eyelid lesions, ranging from benign to malignant, can lead to corneal damage through mechanisms such as mechanical abrasion, secondary infection, or inflammatory responses.

AIM

To assess the surgical methodologies utilized in the treatment of corneal lesions resulting from eyelid disorders and evaluate their effects on patient outcomes, recurrence rates, and postoperative complications. The incorporation of advanced imaging techniques, including optical coherence tomography and ultrasound biomicroscopy, in conjunction with histopathological analysis, is addressed to improve surgical accuracy and patient outcomes.

METHODS
The authors searched online databases (PubMed and Cochrane) for publications on the surgical management of lid lesions. Records received from the two databases were checked for duplicates and relevance. Only records with full texts and in English language were included.

RESULTS
A total of 28 records were obtained following the screening for relevancy and duplication. The review underscores essential surgical approaches employed in the treatment of corneal lesions resulting from common eyelid diseases, focusing on operative efficacy, complication rates, and long-term results.

CONCLUSION
This systematic review emphasizes the significance of choosing suitable surgical techniques tailored to individual patient characteristics and stresses the need for interdisciplinary collaboration in ophthalmic care. The results indicate that sophisticated imaging techniques and careful preoperative preparation markedly improve surgical accuracy and long-term results.

Key Words: Lid diseases; Trichiasis; Distichiasis; Epiblepharon, Lagophthalmos; Corneal laceration; Ectropion

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Core Tip: Eyelid disorders can lead to significant corneal damage, necessitating precise surgical intervention. This systematic review evaluates surgical approaches for correcting entropion, ectropion, and other conditions affecting the ocular surface. The findings highlight the critical role of interdisciplinary collaboration, advanced preoperative imaging, and individualized surgical strategies in optimizing outcomes and minimizing recurrence.

Citation: Miotti G, Quaglia D, De Marco L, Parodi PC, D'Esposito F, Musa M, Tognetto D, Gagliano C, Zeppieri M. Surgical management of patients with corneal lesions due to lid pathologies. *World J Clin Cases* 2025; 13(19): 101889
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/101889.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.101889

INTRODUCTION

Corneal injuries are a prevalent reason for emergency room visits, constituting roughly 3 out of 100 cases, with corneal abrasions and foreign bodies as the most common manifestations. These injuries, varying in severity from minor to vision-threatening, can be classified as traumatic or exposure-related. Corneal abnormalities, including abrasion, laceration, or perforation, can occur through multiple processes. Mechanical damage, including contact lens edges, scratches from fingernails, or foreign objects in the eyelid or fornices, or in diseases such as distichiasis or trichiasis, are prevalent causes. Factors connected to exposure also play a part, mainly in neurotrophic disorders that hinder complete eyelid closure, such as seventh cranial nerve palsy or Bell's palsy. Additional factors encompass restricted eyelid disorders, proptosis or exophthalmos, diminished consciousness resulting from substance abuse or comatose states, and surgical interventions like unsuccessful blepharoplasty that can give lagophthalmos or exposure cornea during extended surgical interventions. Moreover, low tear production due to medications, ultraviolet burns, vitamin A deficiency, Sjögren's syndrome, deficiency of limbal stem cells, local topical anesthetic misuse, neurotrophic keratopathy resulting from infections or trigeminal nerve damage, and bacterial or microbial infiltration through the epithelium are all substantial factors leading to epithelial damage or ulceration.

Individuals with corneal injuries frequently have sensations of foreign bodies and agony, which may manifest several hours after the injury occurs. In instances of chemical burns, symptoms such as pain, tearing, and sight impairment manifest immediately. Identifying the source of the trauma is crucial, particularly when high-velocity instruments or caustic agents are implicated, to inform diagnostic and therapeutic approaches. The physical examination, enhanced by magnification and fluorescein staining, facilitates the visualization of corneal abnormalities and foreign substances. Perforating injuries present with altered iris morphology, a positive Seidel's test, and reduced anterior chambers that could be indicative of aqueous leaking[1].

This study seeks to thoroughly analyze the surgical procedures utilized in the management of corneal ulcers caused by eyelid traumatic and functional diseases (trichiasis, lagophthalmos, distichias, epiblepharon, entropion, lagophthamos and ectropion). Through the examination of published literature, we aim to assess procedure effectiveness, indications, complications, and long-term results, eventually offering a thorough resource for doctors managing these disorders.

MATERIALS AND METHODS

Using the PubMed database (https://pubmed.ncbi.nlm.nih.gov) and Cochrane databases (https://www.cochranelibrary.com), the authors created search strings with the keywords; eyelid disorder, corneal abrasion, corneal laceration, entropion, ectropion, epiblepharon, trichiasis, distichiasis, and lagophthalmos; returning 1635 records. Records older than 2008 were excluded from this review. Searches utilized a combination of terms such as 'eyelid problem,' 'corneal abrasion,' 'corneal laceration,' 'entropion,' 'ectropion,' 'epiblepharon,' 'trichiasis,' 'distichiasis,' and 'lagophthalmos' with appropriate Boolean operators (AND/OR) in order to enhance the outcomes, guaranteeing thorough inclusion of pertinent investigations. The search strategy is shown in the PRISMA diagram indicated in Figure 1 below.

In accordance with the methodology outlined by Tham *et al*[2], we performed a systematic review utilizing the PubMed and Cochrane databases. Search phrases were amalgamated using Boolean operators, and results were evaluated according to inclusion and exclusion criteria. Two separate evaluators (Quaglia D and Miotti G) appraised the relevance of the work, and any disagreements were reconciled by a third evaluator (De Marco L). Four hundred and eighty-five papers were discarded for not directly addressing the surgical therapy of corneal lesions resulting from eyelid diseases. These encompassed general ophthalmic evaluations, case reports, and studies devoid of surgical outcome data. Articles were eliminated by a systematic screening procedure involving title, abstract, and full-text assessment.

RESULTS

A total of 28 studies were incorporated into this evaluation following the application of eligibility criteria (Table 1). These studies assessed surgical procedures for corneal lesions associated with the eyelids, emphasizing operative effectiveness, complication rates, and long-term results. Research demonstrates that surgical methods using horizontal lid tightness have reduced recurrence rates. Preoperative imaging, including optical coherence tomography (OCT), has become an essential instrument in enhancing surgical planning. Moreover, interdisciplinary teamwork has demonstrated an improvement in overall patient outcomes. The review emphasizes the necessity of personalized surgical strategies adapted to the severity and cause of eyelid disorders. The research are categorized into three types: (1) Comparative assessments of surgical procedures; (2) Clinical outcomes and complication rates; and (3) Supplementary measures for enhanced prognosis.

The initial category encompasses research that evaluates the effectiveness of several surgical techniques, including lateral tarsal strip surgery, Quickert-Rathbun sutures, and full-thickness wedge resection, in treating entropion and ectropion. Research indicates that whereas all techniques enhance eyelid alignment, strategies that include horizontal lid tightness have reduced recurrence rates. The second category includes clinical trials that evaluate post-surgical success rates, complication profiles, and patient-reported outcomes after various procedures. Interventions using preoperative imaging, such as OCT, have demonstrated enhanced precision in surgical planning, hence decreasing postoperative problems. Finally, research in the third category underscores the significance of histological analysis and multidisciplinary cooperation in enhancing patient outcomes. These studies demonstrate that the integration of surgical procedures with conservative treatments, like lubricating eye drops and botulinum toxin injections, can improve both functional and cosmetic outcomes. These studies collectively offer a thorough overview of the changing landscape of surgical procedures for corneal diseases, emphasizing the necessity for customized methods based on unique patient presentations.

DISCUSSION

In this section we summarize evidence collected concerning the common conditions associated with corneal damage requiring surgical approach (trichiasis, lagophthalmos, distichias, epiblepharon, entropion, lagophthamos, ectropion). From a diagnostic and an outcome measurement perspective, advanced imaging modalities, including OCT and Ultrasound Biomicroscopy, have been beneficial in evaluating the anterior segment of the eye assessing corneal lesions resulting from eyelid diseases: OCT enables high-resolution cross-sectional imaging, allowing for precise preoperative evaluation of corneal integrity and stromal involvement. Ultrasound Biomicroscopy provides deeper tissue penetration, assisting in the assessment of posterior segment involvement and structural changes. These techniques assist in identifying surgical strategies and post-operative surveillance, enhancing patient outcomes.

Collaboration among ophthalmologists, plastic surgeons, and dermatologists is crucial for enhancing the surgical treatment of corneal lesions resulting from eyelid disorders. Ophthalmologists provide specialized knowledge in corneal health and the care of ocular surface diseases, whilst plastic surgeons provide sophisticated reconstructive methods to enhance eyelid functionality. Finally, dermatologists are essential in diagnosing systemic disorders that lead to cicatricial alterations potentially affecting the cornea. A multidisciplinary approach guarantees thorough care, minimizing complications, recurrence risk and improving patient safety.

Entropion

Entropion, characterized by the inward rotation of the eyelid, may impact both or one eye, with a greater prevalence in the lower lid. It is categorized in 4 primary types: Cicatricial, acute spastic, congenital, and age-related (involutional). The symptoms of this disorder include ocular redness and soreness, photophobia, sensitivity to wind, periorbital skin laxity, excessive lacrimation, and diminished vision, particularly in cases of corneal injury[3-6]. A retrospective investigation of

Table 1 Research publications regarding surgical management of patients with corneal lesions due to lid pathologies

Ref.	Year	Type of study	Results	Conclusions
Gu *et al*[3]	2009	Prospective cohort study with 14 patients	Acellular dermis was effective in reducing the palpebral aperture (P = 0.002), lagophthalmos (P = 0.016), and lengthening the upper eyelid height by reducing the upper margin-reflex distance (P = 0.008). There were 2 cases of recurrence because of the shrinkage of graft (70%) and 3 cases of conjunctival granulomas postoperatively	Acellular dermis grafting with insertion of therapeutic contact lenses is an effective and simple measure for rectifying severe cicatricial entropion both structurally and functionally
Swamy *et al*[4]	2008	Prospective with 147 eyelid operations	Ninety-four per cent of patients noted symptomatic improvement. The postoperative complications included excess keratin (29%), recurrence of cicatricial entropion (4.1%), punctuate epithelial erosion (2.7%), graft shrinkage (0.7%) and donor site bleeding (2.0%)	Cicatricial Entropion with hard palate mucous membrane grafting for both upper and lower eyelid surgery offers high symptomatic and anatomical cure rates
Hintschich [5]	2008	Review		
Marcet *et al*[6]	2015	Review		Understanding the demographics and factors linked to involutional entropion allows clinicians to better identify the condition and those most at risk. However, there is insufficient evidence to conclude that a short axial length is an independent risk factor for entropion. Recent advances in surgical techniques have fueled interest in minimally invasive procedures. It is crucial to address each patient's unique anatomical abnormalities with precision
Han *et al* [11]	2019	Retrospective interventional case series of 46 eyelids in 31 patients with involutional entropion and significant ocular irritation	During the mean follow-up period of 22.1 months (range, 12-34 months), 43 of the eyelids (93.5%) were successfully corrected. Two patients (3 eyelids) experienced recurrence: 1 had involutional entropion combined with a cicatricial component, and the other had blepharospasm and apraxia of eyelid opening related to Parkinsonism. No postoperative complications such as overcorrection, suture-knot exposure, or ocular irritation were observed	Mini-incisional entropion repair based on reinforcement of the lower eyelid retractors using transconjunctival buried sutures is quick, simple, and predictive for involutional entropion repair, and has a high success rate
Qurban and Kamil [12]	2022	Quasi-experiment study recruiting 50 patients with twenty-five patients in each group	Recurrence of the condition was observed in eight (32%) out of twenty-five patients in group A, who underwent the standard Weis surgical procedure, whereas only one (4%) out of the twenty- five patients of group B who underwent the modified surgical technique with external tamponade experienced recurrence	The modified surgical technique for entropion repair using an external tamponade has a favorable outcome with minimal recurrence and symptomatic relief
Cheung *et al*[14]	2018	Retrospective review of 52 eyelids of 46 patients who underwent pentagonal resection + inferior retractor plication for treatment of involutional entropion	A total of 52 eyelids of 46 patients received pentagonal resection + inferior retractor plication. None had recurrence of entropion, 1 (2.1%) had residual entropion, 2 eyelids (4.4%) had lower eyelid notching, 1 eyelid (2.2%) had infection and 1 eyelid (2.2%) had overcorrection. The overall success rate was 90.4%	Combined pentagonal resection + inferior retractor plication is an effective surgical procedure for primary involutional entropion with low recurrence rate; the authors report eye-lid notching as a complication
Koreen *et al*[17]	2009	Retrospective interventional case series (35 eyelids, 26 patients)	The success rate of primary repair was 77% (27 of 35 eyelids) with a mean follow-up time of 2.5 +/- 1.9 years. Four eyelids (11%) underwent repeat grafting for recurrent entropion secondary to graft shrinkage (3 eyelids) and graft dislocation (1 eyelid) for a cumulative success rate of 89%. The remaining 4 eyelids (11%) had recurrent entropion that was managed surgically with a technique other than repeat grafting	Anterior lamellar recession with buccal mucous membrane grafting is an effective surgical approach for the treatment of moderate to severe cicatricial entropion
Malhotra *et al*[18]	2012	Retrospective, 5-year, single-center, consecutive case series of patients with lower eyelid cicatricial margin entropion (21 eyelids, 19 patients)	The study included 21 eyelids from 19 patients (mean age 577 years) with cicatricial entropion: 38% of eyelids required a second procedure within a year, with 10% and 5% needing a third and fourth within three years. Common revisions were anterior lamellar repositioning, mucous membrane	Lower eyelid gray-line split, inferior retractor recession, lateral-horn lysis, and anterior lamella repositioning is of value as a lash-preserving procedure in moderate-to-severe cicatricial lower eyelid entropion, particularly where tarsoconjuctival contraction or eyelid margin distortion exists

			grafts, and everting sutures. Three patients had significant inferior fornix loss, and 90% of eyelids showed improvement after repeated surgeries, with mucosal grafts used in some cases. Lower eyelid elevation was 1 mm in 32% of patients, and lateral retraction improved in 47%	
Kadyan *et al*[19]	2010	Prospective interventional case series; 7 patients, 9 procedures	Residual lashes were noted in three patients. In two cases, the lashes were isolated and managed successfully by a single electrolysis treatment. One patient needed further anterior lamellar excision for residual remnant of trichiatic cilia at the lateral edge of the lid. All patients were satisfied with their post-operative appearance. None of the patients showed exacerbation of disease or needed additional immunosuppression as a consequence of the lid surgery	Anterior lamellar excision with spontaneous granulation is a straightforward and effective method for managing aberrant eyelashes. This technique minimized the risk of disease exacerbation, particularly in cases of ocular cicatricial pemphigoid, by limiting conjunctival manipulation. Additionally, it reduced post-operative lash-globe contact, enhancing patient outcomes
Wu *et al* [20]	2010	Retrospective consecutive case series of 26 eyelids with severe, recurrent, or segmental cicatricial entropion	The functional success rate was 90.5%, and the cosmetic success rate was 100%	The eyelash resection procedure is a safe, effective, and cosmetically acceptable procedure for treatment of severe, recurrent, or segmental cicatricial entropion
Chi *et al* [22]	2016	Consecutive series of 27 eyelids (15 upper and 12 lower eyelids) of 18 patients (9 men and 9 women)	The success rate was 81.8% (22 of 27 eyelids). Complications included eyelid margin notching (n = 1) and blepharoptosis secondary to avascular necrosis of the distal marginal fragment (n= 1), both were corrected by minor surgical intervention	Modified tarsotomy is effective for the correction of severe cicatricial entropion
Singh *et al* [25]	2021	Case series (Six eyelids of five patients)	Entropion resolved in all patients with restoration of eyelid margin and reduction in ocular discomfort. Trichiasis was present in all six eyelids (100%) preoperatively and resolved completely in all but one case (83% success rate) with three residual focal trichiatic lashes in the temporal area, which was successfully managed with radiofrequency ablation. There were no recurrences of trichiatic or distichiatic lashes at a median follow-up duration of 16 months (range, 12-18 months)	Labial mucosa can be effectively used to resolve recurrent cicatricial entropion by spacing the anterior lamella and reconstructing the lid margin and posterior lamella, leading to a low recurrence rate
Takahashi *et al*[26]	2014	Retrospective case series (3 patients with congenital entropion); authors also measured the diameters of the pre tarsal Orbicularis Oculi Muscle fibers in these patients and compared them with those measured in the previously reported 67 eyelids of 41 Japanese patients with congenital epiblepharon	Successful correction was achieved in all three patients without recurrence during 12-months of follow-up. No patient exhibited lower eyelid ectropion or lower eyelid retraction. The mean diameter of the pretarsal Orbicularis Oculi Muscle fibers was 21.9 μm (range, 20.5-23.7 μm), which was not significantly different from that of the congenital epiblepharon (25.3 μm; range, 18.1-34.7 μm; P = 0.272, Mann-Whitney U test)	Posterior layer advancement of the lower eyelid retractor is a useful surgical option for treatment of congenital entropion. No histological evidence of pretarsal Orbicularis Oculi Muscle hypertrophy was shown in congenital entropion, which demonstrated that debulking of the pretarsal Orbicularis Oculi Muscle may not be significant for correction of this entity
Huang *et al* [27]	2023	Comparison prospective study; ninety-six participants (180 eyes) with congenital lower eyelid entropion diagnosed between January 2019 and April 2021 were included in this study. The patients were divided into Group A (cutaneous orbicularis oculi excision treatment) and Group B (inferior eyelid margin fixation treatment)	No significant difference in age, sex, and eyes distribution in both groups. And higher efficiency rate was found in Group B (P < 0.05). And Group A had a higher recurrence rate in the follow-up after surgical treatment (P < 0.05)	The authors modified inferior eyelid margin fixation of the orbicularis eyelid muscle treatment is an ideal procedure with a high degree of efficacy and low recurrence rate in patients with congenital lower eyelid entropion
Khuu *et al* [28]	2023	Retrospective chart review. Twelve patients (19 eyelids). The mean patient age was 7.1 ± 6.1 years (range, 0.2-22 years)	The described entropion repair technique was successful and without recurrence in 17 eyelids (89%). There were no cases of ectropion, lid retraction, or other complications. There were two eyelids (11%) that had entropion recurrence after first procedure. Repeated repair resulted in success with no recurrence at last follow-up	Subciliary rotating sutures combined with a modified Hotz procedure effectively correct congenital lower eyelid entropion. Since this technique avoids manipulating the posterior layer of the lower eyelid retractors, it is beneficial when retractor reinsertion provides insufficient improvement. It also helps minimize the risk of eyelid retraction and overcorrection in specific cases

Burton *et al* [29]	2015	Review		No trials specifically evaluated whether interventions for trichiasis prevent blindness, but some showed modest vision improvement. Full-thickness incision of the tarsal plate with lash-bearing lid margin rotation was the most effective technique, preferably performed in the community. Both ophthalmologists and trained ophthalmic assistants can perform the surgery, and results were comparable using silk or absorbable sutures. Post-operative azithromycin improved outcomes, with low recurrence rates overall
Singh[30]	2022	Review		Treatment options for congenital and acquired distichiasis are similar, with no specific algorithms available. Managing acquired distichiasis in cicatrizing ocular surface diseases is challenging, with current treatments yielding success rates of 50%-60%. Procedures like electroepilation or direct cryotherapy are less effective compared to surgical excision of distichiatic lashes, which involves splitting the anterior and posterior lamella under direct visualization. Marginal tarsectomy, with or without a free tarsoconjunctival graft, has shown favorable results in both congenital and acquired cases. However, the exact differences in normal *vs* distichiatic lashes, including depth and growth patterns, remain unclear. Research into the depth of distichiatic eyelashes could improve the outcomes of procedures like cryotherapy or radiofrequency-assisted epilation, which are currently done without precise visualization
Woo and Kim[31]	2016	Review		While epiblepharon may improve as the face grows, surgical correction is necessary when significant corneal damage occurs due to lash contact. Surgical treatment should prioritize techniques that are both effective and low-risk, while avoiding the formation of a lower eyelid crease
Ma *et al* [33]	2020	Comparative study	In the surgical and nonsurgical groups, the baseline astigmatism magnitude was similar (2.22 ± 1.39 and 2.26 ± 1.46 D, P = 0.87). Complete resolution of keratopathy at 6 months was 71.4% and 11.5%. The astigmatism magnitude in the surgical group differed among baseline and 3 months (2.25 ± 1.23 D) and 6 months postoperatively (1.97 ± 1.28 D) (P = 0.001)	The surgical group exhibited greater improvement in keratopathy compared to the nonsurgical group, despite having more severe baseline pathology. A reduction in with-the-rule astigmatism was observed six months postoperatively, particularly in patients with higher initial astigmatism. However, the extent of this change was minimal, and the overall outcomes did not significantly differ from those of nonsurgical treatment
Sung and Lew[34]	2019	Retrospective was series study including 72 eyelids of 36 children with epiblepharon and epicanthal folds	Eyelid contour was normalized and the cilia touch was resolved after the epicanthal tension-releasing procedure	The epicanthal tension-releasing procedure combined with orbicularis oculi ring myotomy resulted in positive surgical outcomes. Clinical findings aligned with pathology and the success of the procedure suggest that medial epicanthal fibrosis is the primary cause of epiblepharon and epicanthal folds
Yan *et al* [35]	2016	Retrospective case control (67 patients-mean age, 5.7 ± 2.6 years- and 178 controls. All patients presented with epicanthus	All patients showed successful surgical outcomes according to improvement of symptoms and lack of cilia-cornea contact. There were no cases of recurrence or other complications	Obesity can exacerbate lower eyelid epiblepharon, which can be effectively treated using the rotating suture procedure and the L-plasty procedure. The L-plasty procedure is particularly recommended for patients who also have significant epicanthus
Lailaksiri *et al*[38]	2024	Retrospective cohort study; 30 patients (76% females; average age 608 ± 12 years) with facial palsy who underwent implantation of either the traditional pretarsal gold weight or a new supratarsal model	The new model group had significantly better eyelid contour, less weight prominence, less weight migration and less eyelid ptosis than the traditional model group. Improvement of lagophthalmos was not statistically significant between the two groups. The 24-month reoperative rate was 53.3% in the standard group *vs* 13.3% in the new model group	The author's newly designed supratarsal gold weight showed superior postoperative outcomes than the standard traditional model
Chung *et al* [39]	2020	Case report		Severe lagophthalmos successfully released with pentagonal wedge resection, fat redistribution, and full-thickness skin graft
Medina *et al*[40]	2022	Case report		Multiple contributing factors for severe ectropion of left lower eyelid treated with lateral tarsal strip procedure and full-thickness skin graft
Ghafouri *et al*[43]	2014	Retrospective review of case series (forty-one lower eyelids of 31 patients with involutional ectropion	Surgical success with anatomical correction of involutional ectropion was achieved in 39 of 41 eyelids (95.1%). There were no periop-erative or postoperative complications. Two	The combination of a lateral tarsal strip and internal retractor reattachment using full-thickness eyelid sutures effectively resolves horizontal eyelid laxity and tarsal instability, making it a successful technique for

		underwent surgical repair)	of 41 (4.9%) eyelids had recurrence of ectropion 7 and 18 months after the procedure	correcting involutional ectropion of the lower eyelid
Vahdani *et al*[44]	2021	Retrospective case-note review; twenty-four eyelids of 21 treated patients (17 males; 81%) with lower eyelid cicatricial ectropion	Comparing the outcomes of modified Bick's procedure + full-thickness skin grafting *vs* modified Bick's procedure + monopedicle myocutaneous flap there was no statically significant difference in terms of anatomical (P = 0.48) and functional (P = 1.0) success rates. No cases of failure or recurrence were noted during the follow-up period	Anterior lamellar deficit ectropion arises without visible scarring. It is essential to thoroughly address both the horizontal laxity and the anterior lamellar deficit linked to this condition to reduce the chances of early failure and recurrence. The combination of medialized buccal pad (modified Bick's procedure) with full-thickness skin graft or myocutaneous flap is a safe and effective treatment for this type of "cicatricial ectropion" and demonstrates a low rate of early recurrence
Korteweg *et al*[45]	2014	Cross-sectional outcome (30 cases of paralytic ectropion)	Lateral periosteal flap canthoplasty assessed through Ectropion Severity Score proved to be reliable and sensitive to the presence of ectropion. Significant improvement of the ectropion sequelae was measured after a mean follow-up period of 2 years. In 3 cases (13%), a revision procedure was necessary because of relapse of lower eyelid sagging after a mean time of 1.9 years	The periosteal flap canthoplasty is an effective technique that provides lasting results for patients with paralytic ectropion. This same periosteal flap can also be utilized in revision procedures

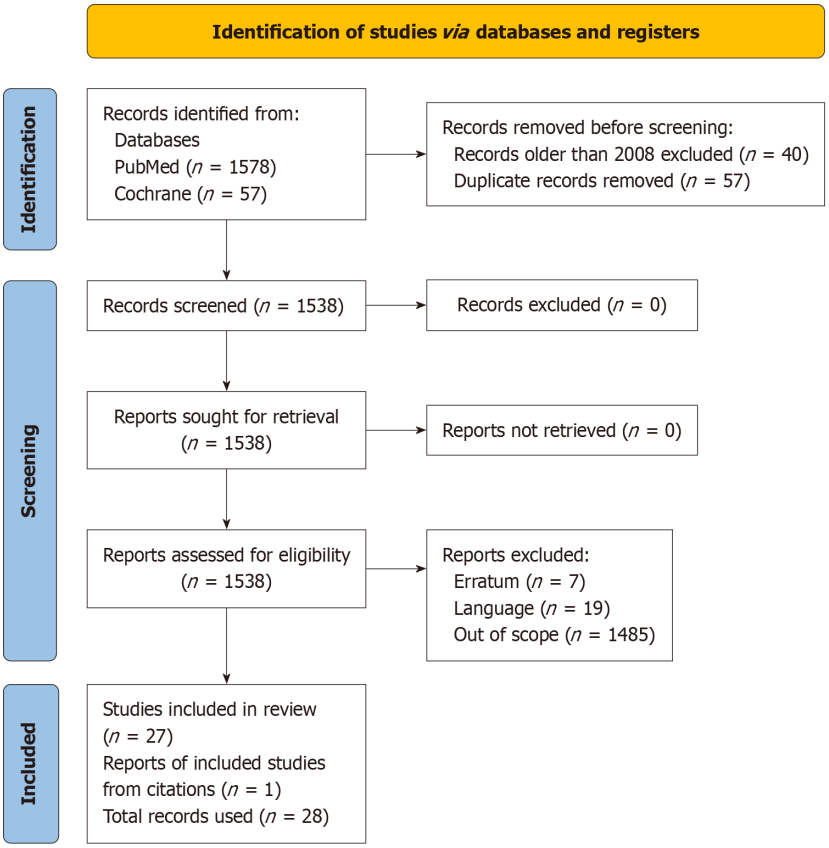

Figure 1 Search strategy with PRISMA.

the Australian population revealed that, involutional entropion exhibits modest corneal abnormalities, with 95.1% of cases showing either normal corneal epithelium or superficial punctate keratopathy. Vision loss is an uncommon consequence, occurring in 1% of participants in this study, all of whom had previous corneal disease[7].

Various surgical techniques have been delineated for the treatment of entropion[3-6]. The selected treatment must be suitable for the type of entropion being treated. The following are the most prevalent procedures employed in management[6].

Spastic entropion

Spastic eyelid closure enables the orbicularis oculi muscle to dominate the opposing function of the lower eyelid retractors, causing the lid margin to invert and exacerbating ocular surface irritation due to the mispositioned eyelashes. Spasm of the muscle of Riolan, resulting from irritation, and insufficient support of the eyelid by the globe are the primary pathophysiological changes. The treatment strategy initially necessitates the elimination of the source of

discomfort. Minimal botulinum toxin treatments (about 5 U of BOTOX®) are highly successful to treat spastic entropion by attenuating the oculi muscles (mainly the pretarsal orbicularis).

Quickert-Rathbun sutures can be considered for numerous instances of spastic entropion and certain occurrences of involutional entropion when the patient declines or is medically unfit for more decisive interventions. Full-thickness lid sutures, typically composed of gut, are employed anteriorly from the inferior fornix towards the lashes in order to rotate the eyelid edge away from the globe. The tissue response to the intestinal suture facilitates the formation of a scar in the eyelid that preserves the eyelid in an everted posture. Skin and muscle excision procedures, along with Wheeler's operation, are alternative options when initial treatments fail to induce disease regression; Wheeler orbicularis transplantation involves horizontal shortening of the orbicularis muscle and skin, and for the placement of orbicularis straps that can be used to prevent displacement within tarsal structures[6].

Involutional or senile entropion

Anatomical causes responsible for entropion due to aging encompass laxity of the lids horizontally, overriding of the oculi muscle (mainly orbicularis) and wrong insertion of the lower eyelid retractors. The alterations, mainly induced by aging, lead to the inward rotation of eyelid margins, causing the eyelashes to contact the external eyeball including the cornea. This continual irritation results in harm to the ocular surface structures. Orbicularis oculi muscles, tarsus, lower lid retractors, and canthal tendons ensure the horizontal stability of the lower lid. Any deterioration or flexibility in these components may result in the inward turning of the lid. The lower eyelid retractors similarly confer stability vertically, in which laxity may lead to rotation inwardly. The pinch test is commonly employed to evaluate the horizontal laxity severity. Diverse non-surgical and surgical interventions have been utilized to address senile entropion, contingent upon anatomical deficiencies, and to alleviate irritation resulting from misaligned eyelashes induced by the inward-turned eyelid. Conservative methods encompass the administration of lubricating eye drops, the application of contact lenses, and the injection of Botulinum toxin. Nevertheless, conclusive treatment generally necessitates surgical intervention.

Patients typically exhibit gyration of the posterior eyelid retractors, resulting in eyelid inversion akin to spastic entropion. The involution of the orbital soft tissues, especially the orbital fat, may result in involutional enophthalmos, subsequently causing an abberant eyelid posture with entropion.

Various surgical techniques are utilized to rectify involutional entropion. One of the most straightforward and accessible methods entails the application of full-thickness lid-everting sutures, referred to as Quickert sutures. This approach produces anterior rotational torque, modifying the orientation of eyelashes and inhibiting the preseptal orbicularis oculi muscle from dominating. The principal disadvantage is its elevated recurrence rate. A commonly employed technique is the transconjunctival or transcutaneous reinsertion of the lower eyelid retractors, referred to as Jones retractor plication. The method entails the reattachment of the separated lower eyelid retractors to the tarsal plate anterior margin. Although it has the advantage of direct visibility of the afflicted structures and facilitates the excision of the surplus skin and of the pretarsal orbicularis muscle, it is frequently criticized for its intricacy, time demands, and risk in causing eyelid retraction or secondary ectropion.

Surgical alternatives vary from transient, office-based interventions, such as the Quickert suture technique, to more enduring remedies, including the Weis operation, lateral canthal tendon tightening, and lateral tarsal strip method. The latter encompasses all 3 senile entropion etiological elements. These include lower eyelid retractor disinsertion, horizontal eyelid laxity, and overriding orbicularis oculi muscles[6,7].

Early attempts by Bick resulted in development the term "orbital tarsal disparity," associating eyelid flexibility and age-related orbital volume reduction with ectropion and entropion. He demonstrated that lower eyelid entropion may be temporarily rectified by injecting saline into the muscle cone; nonetheless, lid shortening has been considered as a better and more effective treatment. The surgery entails a complete tissue triangular excision at the lateral canthus, followed by the reattachment of the tarsal plate to the lateral canthal tendon, contingent upon eyelid flexibility[8]. In 1977, Tenzel *et al* [9] introduced a lateral canthal tendon sling for the treatment of involutional ectropion, which was subsequently refined by Anderson into the "tarsal strip" method. Both the tarsal strip and the Bick's treatments laterally shorten the eyelid; however, Bick's technique circumvents the lateral canthal tendon and does not conceal the tarsal plate[10].

Han *et al*[11], reported a non-incisional blepharoptosis correction method utilizing buried transconjunctival sutures (which plicate the Müller and superior levator palpebral muscles and may be used in advancing the levator aponeurosis to ameliorate blepharoptosis), posited that, given the anatomical similarity between the upper and lower eyelids—where the Müller and levator palpebral muscles in the upper lid correspond to the lower eyelid retractor in the lower eyelid—a non-incisional correction technique for upper lid blepharoptosis can be adapted to address lower eyelid involutional entropion by reinforcing the attenuated or dehisced lower eyelid retractor. The author employed a buried-suture method on the lower lid to fortify the weakened or disinserted lower eyelid retractors, utilizing three knots for precise defect correction. To avert overriding of the preseptal orbicularis oculi muscle, the technique involved excising an orbicularis oculi muscle strip through a minimal subciliary incision thereby integrating the underlying orbicularis oculi muscle into the sutures for optimal closure of the skin.

Qurban *et al*[12] conducted a quasi-experimental study proposing a modified surgical approach for entropion repair with an external tamponade, resulting in good outcomes, little recurrence, and symptomatic alleviation.

The management of senile entropion may necessitate the correction of horizontal laxity through medial and/or lateral canthal tightening, plication of lower eyelid retractors (according to Jones), transmarginal rotation (according to Weis that involves a full-thickness horizontal eyelid incision), and tucking of palpebral ligaments; a minor resection of the pretarsal orbicularis oculi may be performed simultaneously to avert further tarsal overriding.

The Weis method integrates a transverse full-thickness blepharotomy with everted sutures. Everything sutures the appropriate vertical eyelid laxity by traversing the retractor layer and constricting the lower eyelid retractors. Blepharotomy forms a scar that links the conjunctiva, skin, and the pretarsal and preseptal orbicularis oculi muscles.

Collectively, these approaches inhibit the preseptal orbicularis from dominating the pretarsal segment. The Weis method fails to treat horizontal lid laxity, which arises from the looseness of the canthal tendons and tarsal plate. Horizontal laxity may be rectified with eyelid-shortening techniques, including full-thickness wedge resection or lateral tarsal strip techniques. It is generally acknowledged that rates of recurrence tend to increase when horizontal laxity is unaddressed. In cases devoid of horizontal laxity, a straightforward reattachment of the retracted lower lid retractors may be adequate. Addressing horizontal laxity is essential to reduce the likelihood of recurrence, especially when the snapback test yields a positive result. A comprehensive preoperative assessment is crucial to exclude horizontal laxity and guarantee excellent results from the Weis operation, hence minimizing the likelihood of early recurrence[13].

Cheung *et al*[14] advanced procedure according to Hill-a technique that entails a shortening of the lateral lower lid through full-thickness excision, then fixation of an orbicular muscle strip to the lower tarsal plate border, and curettage of the anterior tarsal plate to avert orbicularis muscle overriding—by integrating pentagonal resection (PR) and inferior retractor plication (IRP) for the primary treatment of lower eyelid laxity with involutional entropion in a Chinese cohort. The combination of PR and IRP constitutes an effective surgical technique for addressing primary involutional entropion, with a minimal risk of recurrence. However, there exists a potential danger of eyelid notching following the procedure.

Cicatricial entropion

Cicatricial entropion can be defined as tarsoconjunctival scarring resulting from conditions that include ocular cicatricial pemphigoid, chronic blepharitis, trachoma, Stevens-Johnson syndrome, prolonged use of topical glaucoma medications, and prior surgical interventions. Additional indicators comprise trichiasis, forniceal shortening, and the development of symblepharon[15].

Cicatricial entropion presents a challenging treatment dilemma, as various surgical methodologies exhibit varying degrees of efficacy. It is essential that the inflammation process is not in an acute phase in individuals with Ocular Ciucatricila pemphigoid–a persistent autoimmune condition marked by advancing conjunctival fibrosis, resulting in cicatricial entropion and symblepharon development- prior to any conjunctival surgery. Manipulating the conjunctiva in these patients may provoke a return of inflammation, potentially resulting in the failure of the surgery. The choice of surgical technique is contingent upon parameters like the extent and degree of eyelid retraction, entropion, fornix and tarsus involvement, keratinization, distortion of the eyelid edge, and the advancement of the underlying pathology. Surgical techniques can be categorized into four types: (1) Posterior lamella lengthening; (2) Grayline splitting of the posterior and anterior lamellae; (3) Lid margin eversion or rotation; and (4) A combination of the 3 methods. Grayline splitting of the posterior and anterior lamellae encompasses lamellar splitting with anterior lamella excision or recession, advancement of the posterior lamella, and recession of the anterior lamella accompanied by advancement of posterior lamella; however, in the presence of metaplastic lashes in the posterior lamella, the latter technique is inapplicable. Lengthening of the posterior lamella requires the application of middle and posterior lamella grafts to achieve a flat surface for proper eye contact, hence extending the duration of the surgical procedure[16-21].

Kersten *et al*[15] characterized transverse tarsotomy and lid margin rotation as straightforward and dependable interventions for mild to moderate cicatricial entropion, achieving a success rate of 94%, but the success rate diminishes for severe cicatricial entropion.

Chi *et al*[22] refined the transverse tarsotomy technique for severe cicatricial entropion by incorporating a straightforward modification that entails 'two back cuts' at each end of the transverse tarsotomy. These back cuts facilitate greater mobility of the distal tarsal fragment, potentially enhancing the success rate in patients with severe cicatricial entropion. Kadyan *et al*[19] stated that spontaneous granulation with anterior lamellar excision in seven patients with ocular cicatricial pemphigoid was a straightforward and successful surgery; nonetheless, three individuals had residual lashes.

Wu *et al*[20] found that the functional success rate of the lamellar splitting with eyelash removal method exceeded 90% for severe, recurring, segmental cicatricial entropion. The limitation of this approach is its inapplicability in cases of metaplastic eyelashes within the posterior lamella.

Studies by Goldberg *et al*[23] reported an 80% success rate for a shared mucosal graft in their case series including severe cicatricial entropion, based on posterior lamellar lengthening. In the case series by Gu *et al*[3], posterior lamellar lid reconstruction and terminal tarsal rotation utilizing dermis allograft (acellular) for patients with severe cicatricial entropion was effective in 14 of 16 cases. Seiff *et al*[24] documented a functional success rate of 100% for the rotation of the upper eyelid tarsal margin and the extensive advancement of the posterior lamellae, integrating eyelid margin rotation with the lamellar division of the anterior and posterior lamellae.

Employing labial mucosa to separate the anterior lamella and repair both the posterior lamella and the eyelid border is an efficacious method for addressing recurrent cicatricial entropion with a minimal recurrence rate[25].

Congenital entropion

Congenital entropion is an uncommon disorder that predominantly impacts the lower eyelid. It is linked to multiple developmental defects, including hypertrophy of the pretarsal orbicularis oculi muscle, deficits in the tarsal plate, facial nerve paralysis, and dysgenesis of the lower eyelid retractors. It may also manifest concurrently with microphthalmos. In contrast to infantile entropion, which results from fat accumulation in well-nourished children and typically resolves spontaneously, congenital entropion necessitates meticulous distinction owing to its unique underlying causes[4-6].

The advancement of the posterior layer located in the lower lid retractors is an effective surgical method in addressing congenital entropion. Takahashi *et al*[26] showed in their case series that histological investigation revealed no signs of pretarsal orbicularis oculi muscle hypertrophy in cases with congenital entropion, indicating that diminishing this muscle mass may not be necessary to rectify the problem.

A revised surgical technique involving fixation of the orbicularis oculi muscle at the inferior eyelid edge was assessed for the treatment of congenital entropion of the lower lid. A study including 180 eyes of 96 patients categorized participants in 2 groups: The first group had excision of the cutaneous orbicularis oculi, while the second group underwent the modified surgical method. The second group exhibited a better success rate and a diminished rate of recurrence compared to the first group ($P < 0.05$). The results indicate that this improved technique can be an efficacious and dependable method for addressing congenital lower eyelid entropion with reduced recurrence rates[27].

The application of subciliary rotating sutures alongside a modified Hotz procedure constitutes an efficient method for rectifying congenital lower eyelid entropion. This procedure is advantageous in situations where retractor reinsertion does not yield adequate enhancement, as it circumvents manipulation of the lower lid retractor posterior layer. Furthermore, it may reduce the likelihood of overcorrection and lid retraction in specific circumstances[28].

Trichiasis, deformity and epiphora

Trachomatous trichiasis—the main cause of trichiasis—represents a critical ophthalmic public health issue, particularly in sub-Saharan Africa. Trichiasis is characterized by abnormally positioned lashes, which grow back toward the ocular surface, touching the conjunctiva or cornea.

Surgical intervention remains the mainstay of treatment, with several techniques described in the literature[29]. One of the more effective procedures involves bilamellar rotation of the tarsal that incises the tarsal plate full thickness and rotates the lash-bearing tarsus to evert the eyelid margin. Another option consists of posterior lamellar tarsal rotation (Trabut procedure), where sutures are placed above the lashes. The literature found no definitive advantage of one method over the other.

While both posterior lamellar and bilamellar tarsal rotation procedures are widely used in regions endemic of trachoma, there is no supporting evidence to suggest the superiority of one technique. Though bilamellar surgery can result in a higher rate of eyelid exposure and overcorrection, these risks remain insignificant. The procedures are both considered to be safe, in which post-operative trichiasis tends to be the most common complication reported in studies.

Non-surgical interventions, such as cryotherapy and electrolysis, used to treat minor trichiasis by targeting lash destruction, have shown lower success rates in preventing recurrence compared to bilamellar tarsal rotation surgery. Given these techniques' high costs and maintenance difficulties, they are not recommended for routine use.

While various surgical methods for trichiasis due to trachomatous exist, posterior lamellar and bilamellar tarsal rotations are commonly employed, with no definitive evidence favoring one over the other. Both are effective and safe, but post-operative trichiasis remains challenging, and non-surgical approaches offer limited efficacy[29].

Distichiasis is an eyelash abnormality in which lashes originate from meibomian gland orifices, differing from normal eyelashes that arise from the skin. It is distinct from trichiasis and other disorders like tetrastichiasis and tris trichiasis. Distichiatic lashes may cause signs and symptoms due to contact to the ocular surface and may vary in appearance. There are two types: Congenital and acquired.

Surgical management of distichiatic eyelashes involves various techniques to address the aberrant cilia. These include excision, cryotherapy, and electrocautery, often performed under high magnification to ensure precision. Historical approaches date back to 1880, where posterior and anterior lamellas were split, and the tarsoconjunctival ciliary-bearing strip was removed, giving rise to a bare eyelid margine. Later modifications included grafting of the mucous membrane, proposed in 1913 by Begle, to reduce complications such as ectropion and entropion. Subsequent methods proposed in 1960s, like Fox's technique of conjunctival flap removal and anterior lamella reattachment, showed positive outcomes but lacked data on long-term outcomes.

The transconjunctival trapdoor method was proposed to circumvent marginal complications and entropion. It allows the direct cilia root removal without the need for tarsal excision or grafting. However, its effectiveness remains undetermined due to incomplete recurrence data. In elderly patients with dermatochalasis, redundant skin excision offers an additional aesthetic benefit.

Eyelash trephination, using a Sisler ophthalmic micro trephine, is another method. It has shown a 38% rate of recurrence in patients with acquired distichiasis and trichiasis, likely due to the uncertain depth of abnormal lash roots. Direct excision along the lash's vertical axis has been successful in congenital distichiasis, achieving an 80% success rate, but it is time-consuming, requiring up to 1.5 hours per eyelid.

For acquired distichiasis with cicatricial entropion, anterior lamellar recession combined with mucosal grafting is used to reconstruct the excised area. Recurrences, trichiasis, and eyelid malposition, such as entropion, remain common complications. The unknown depth of distichiatic eyelashes poses a significant challenge, particularly in acquired cases. Advances in imaging technology, like high-frequency ultrasound, can enhance the precision of treatment options by enabling the complete removal of the cilia including the roots[30].

Epiblepharon—in—rolling of lashes and the lid margin over the superior tarsal edge—is commonly observed in East-Asian children, and as the population grows, so does the demand for surgical intervention. In managing this condition, surgeons must understand the aesthetic preferences and specific needs of Asian patients[31]. Recent findings indicate a high prevalence of astigmatism in these patients, which can lead to amblyopia; thus, early surgery and visual rehabilitation are crucial[32]. The pathophysiology of epiblepharon involves various etiological factors, and while Western surgical methods are commonly aimed at creating a lower lid crease, this can be undesirable in Asian patients. Careful selection of surgical techniques is essential to minimize muscle and skin resection, reducing the risk of eyelid retraction and ectropion. Although epiblepharon may resolve naturally over time, surgical treatment correction is necessary in patients with severe damage to the cornea due to eyelash contact. Efficient surgical techniques should prioritize reduced rates of complications and limit the formation of new lid creases[31].

According to a comparative study by Ma *et al*[33] the improvement in keratopathy observed in the surgical cohort surpassed that of the nonsurgical group, despite the greater baseline severity in the former. A reduction in with-the-rule astigmatism was noted at six months postoperatively, particularly in patients with higher baseline astigmatism. However, the magnitude of this change remained minimal, and the overall outcomes did not differ significantly from those achieved with nonsurgical management. Consequently, surgical intervention should primarily be indicated based on the severity of symptoms and the extent of keratopathy.

Among different techniques methods, Sung *et al*[34] reported successful surgical outcomes with orbicularis oculi ring myotomy and epicanthal tension-releasing procedures. The clinical correlations with altered findings and satisfactory outcomes of the method suggested that fibrosis of the medial epicanthal is the main clinical factor that causes epicanthal folds and epiblepharon. Obesity may exacerbate lower lid epiblepharon that may be effectively addressed with the L-plasty procedure and the rotating suture method. The L-plasty procedure tends to be used in cases that also show significant epicanthus[35].

Management of ptosis in patients with eyelid disorders

Lagophthalmos refers to the incomplete or impaired closure of the eyelids, a condition that disrupts normal eyelid function. Complete eyelid closure, along with an intact blink reflex, is critical for maintaining a stable tear film and preserving ocular surface health. Patients with an inability to blink effectively or fully close their eyelids are predisposed to tear film evaporation, corneal exposure, and the subsequent development of keratopathy due to exposure. If left untreated, this may progress to ulceration of the cornea and, ultimate perforation in severe cases. Early recognition of the clinical symptoms and signs of lagophthalmos, followed by early diagnosis of the underlying causes, is essential to initiate appropriate treatment and management.

Diagnosing lagophthalmos requires assessing clinical history for surgeries, trauma, infections, or systemic conditions, with sudden facial motor loss often indicating nerve paralysis. Evaluation includes examining cranial nerve function, incomplete blinking, exophthalmos and lid malposition. Slit lamp evolution of the tear film stability and of the corneal surface using tear breakup time assessment and fluorescein staining are fundamental.

The primary etiology of lagophthalmos tend to be facial nerve paralysis, resulting in paralytic lagophthalmos; facial nerve paralysis could be caused by many underlying etiologies: Infection, trauma, tumor, metabolic disorder, toxic agents, iatrogenic (for example as a consequence of eyelid surgery), neurological, congenital, idiopathic, cicatricial, nocturnal[36].

Eyelid retraction is frequently associated with thyroid eye disease, in which the Müller muscles are stimulated by hyperthyroidism, leading to a typical bilateral asymmetric stare. The infiltration of mast cells and lymphocytes, followed by fibroblastic proliferation in the levator and Müller muscles, give rise to superior temporal lid retraction, often with lateral flaring[37]. In contrast, facial nerve (seventh cranial nerve) paralysis leads to lagophthalmos, typically without eyelid retraction. This paralysis, seen in conditions such as Bell's palsy, sarcoidosis, ischemic events, or post-surgical outcomes, causes orbicularis oculi dysfunction, resulting in unopposed levator muscle action, lower lid ectropion, and epiphora due to increased reflex tear secretion and deficient lacrimal pump function from ocular surface exposure.

The surgical treatment of lagophthalmos is based on the severity and duration of the condition. In cases of corneal exposure with anticipated recovery within weeks, a temporary tarsorrhaphy may be an effective choice. In most instances, the cornea can be sufficiently safeguarded by closing the lateral one-third of the eyelids. A minimal aperture should be maintained to facilitate ongoing evaluation of the cornea and the administration of necessary topical medicines.

In instances of paralytic lagophthalmos where full eyelid closure is impaired, the insertion of a gold or platinum weight into the upper eyelid may be warranted. This method utilizes gravity to improve eyelid closure. The ideal implant weight must enable complete eyelid closure and opening, without causing ptosis in the primary gaze. Traditionally, gold weights are placed anterior to the tarsus (pretarsal area), specifically tailored for the trapezoidal tarsal shape observed in Caucasian eyes. However, in patients with a sickle-shaped tarsus, such as those of Asian descent, visible implant edges often result in suboptimal cosmetic outcomes and higher incidences of implant exposure, infection, and the need for reoperation. Recent advancements favor supratarsal placement, as this approach has demonstrated reduced visibility, lower exposure risk, and improved postoperative outcomes compared to the conventional technique[38].

In lagophthalmos resulting from upper eyelid retraction, as seen in thyroid eye illness, recession of the levator palpebrae superioris and Müller's muscles constitutes an effective surgical intervention. Options for postsurgical eyelid shortening comprise full-thickness skin grafts or advancement flaps. Moreover, scar band release and tarsal-sharing techniques are suitable for the management of cicatricial lagophthalmos. Laxity of the lower eyelid is noted in disorders such as facial nerve paralysis and floppy eyelid syndrome. Surgical therapies, including lateral tarsal strip procedures, improve the alignment of the lower eyelid with the globe, thereby decreasing scleral exposure and alleviating symptoms of epiphora[39,40].

When secondary to facial nerve paralysis lagophthalmos may require midface elevation or other facial reanimation procedures[41].

Ectropion

Ectropion denotes the outward turning of the lid margin, leading to inadequate lubrication and ocular exposure and. Patients can have signs and symptoms due to corneal dryness and inflammation. Although ultimate therapy is surgical, medicinal management offers temporary alleviation and symptomatic enhancement during the interval before surgery.

Involutional or age-related ectropion, the predominant variant, is linked to tarsoligamentous sling laxity, widespread elastin depletion, and orbicular atrophy. Surgery encompass blepharotomy with canthopexy, rotational sutures, lateral tarsal strip, and horizontal lid shortening or tightening, either medially, laterally, or both. A comprehensive understanding of the underlying factors and surgical techniques is crucial for formulating effective therapeutic approaches in

the treatment of involutional lower lid ectropion. Customizing surgical procedures to the specific etiological factors revealed during preoperative evaluation, while focusing on the primary ectropion location, markedly improves the probability of favorable results[42]. Ghafouri *et al*[43] assert that the amalgamation of a lateral tarsal strip and internal retractor reattachment utilizing full-thickness eyelid sutures proficiently addresses horizontal eyelid laxity and tarsal instability, rendering it an effective method for rectifying involutional ectropion of the lower eyelid.

Cicatricial ectropion occurs when anterior lamellar shortening from scar tissue induces traction, elongating the lid border and retracting it from the globe, akin to mechanical ectropion. Contributing variables encompass mechanical, thermal, and chemical injuries, dermatological conditions, eyelid surgery, or cosmetic interventions, frequently aggravated by actinic damage or mid-face decline resulting from habitual eye rubbing or aging.

The surgical management of cicatricial ectropion involves three essential steps: Relieving the radial strain of the lid margin, reducing the elongated lid margin to restore its appropriate alignment with the globe, and correcting the anterior lamellar insufficiency. Various eyelid shortening methods, such as pentagon excision, lateral tarsal strip, and lateral canthopexy, have been proposed to address horizontal eyelid laxity. However, recurrence or chronic ectropion rates may reach 43%, potentially due to insufficient repair of the anterior lamellar insufficiency or the choice of lid margin tightening techniques. Some surgical procedures produce more lasting results than others; nonetheless, accurate diagnosis and correction of both the lamellar deficit and the lid margin are crucial for durable success. The anterior lamellar restoration procedure seems to have a negligible impact on overall outcomes; nevertheless, studies demonstrate a significantly lower recurrence rate of ectropion in eyelids that underwent concurrent horizontal tightening and skin grafting. The Modified Bick's Procedure has proven to be safe and effective in correcting horizontal eyelid laxity, particularly when augmented with a full-thickness skin graft or a mucous membrane conjunctival flap for the anterior lamella [44].

Congenital ectropion is an exceedingly rare condition sometimes linked with other defects, such as euryblepharon and blepharophimosis, characterized by inadequate anterior lamella, diminished tarsal rigidity, and suboptimal development of canthal tendons. The repair involves methods previously mentioned for other forms of ectropion, such as horizontal lid tightening/shortening and anterior lamella grafting[42].

The lower lid positionis determined by the interaction of the bony orbit and the globe e, gravitational forces, tissue elasticity, the lateral and medial canthal ligaments, in addition to the active activity of the orbicularis oculi muscle, with the deep lateral canthal tendon being essential. As tissue elasticity declines with age, the orbicularis oculi muscle increasingly assumes responsibility for sustaining lower eyelid stability. The abrupt loss of innervation, as shown in facial palsy, leads to paralytic ectropion, which is marked by lagophthalmos, and an elevated risk of exposure keratitis. Over time, paralysis may result in anterior lamella retraction, hence worsening the disease.

Reconstructive surgery for paralytic ectropion is used to realign the lower lid to enhance closure, enhance tear drainage, maintain ocular surface lubrication, diminish vertical aperture, while also improving aesthetic results. Due to the usual tissue laxity and elongation of lateral support systems, canthoplasty with horizontal eyelid shortening is frequently advised. The lateral tarsal strip method and its modifications are frequently employed. Nevertheless, conventional methods, such as suturing to the periosteum or perforating the orbital wall, have hazards including suboptimal outcomes or injury to the globe.

Employing a periosteal flap as a substitute for the deep lateral canthal ligament presents a more secure option. It offers robust, self-sustaining support without requiring suturing or drilling within the orbit, facilitating anatomical adjustment of the lid while reducing problems. This technique can be readily integrated with other treatments and is executable under local anesthesia[45].

CONCLUSION

The main aspect emerging from this brief review of related literature is the importance of addressing the innermost pathophysiological alteration proper of that specific corneal damaging eye-lid pathology: The peculiar anatomical structure concerned by the disorder has to be identified and any surgical procedure has to be tailored upon that. Furthermore, due to the complexity of illness presentation, multidisciplinary work between ophthalmologists and plastic surgeons is crucial to achieve stable long-term results. A comparative analysis of various surgical interventions for corneal lesions secondary to eyelid pathologies reveals substantial differences in efficacy, complication rates, and long-term outcomes. Techniques such as lateral tarsal strip surgery, Quickert-Rathbun sutures, and full-thickness wedge resection exhibit variable success depending on the underlying pathology. Lateral tarsal strip surgery demonstrates exceptional efficacy in correcting horizontal eyelid laxity, boasting high success rates and low recurrence; however, potential complications include overcorrection and lid malposition. Quickert-Rathbun sutures, commonly employed for spastic and involutional entropion, provide a minimally invasive approach with rapid symptomatic relief but are associated with a higher recurrence rate compared to more definitive surgical techniques. Full-thickness wedge resection, frequently indicated for severe eyelid malposition, offers durable correction but carries risks of scarring and postoperative eyelid retraction. Additionally, posterior lamellar lengthening with mucosal grafting has shown promise in the management of cicatricial entropion, though its complexity necessitates specialized surgical expertise. Reported success rates for these procedures range from 80% to 95%, with surgical failures often attributed to inadequate preoperative assessment of horizontal and vertical eyelid laxity. The integration of advanced preoperative imaging modalities, such as OCT and high-frequency ultrasound is widely recognized as a critical tool for optimizing surgical planning and reducing postoperative complications. While textual descriptions provide valuable insights into these procedures, the incorporation of visual aids depicting anatomical changes and surgical modifications would significantly enhance

comprehension for both clinicians and trainees. A structured visual representation of these techniques, highlighting key procedural steps and anatomical considerations, may facilitate a deeper understanding of the complexities inherent in surgical decision-making for ocular reconstructive procedures.

FOOTNOTES

Author contributions: Miotti G and Quaglia D wrote the outline as co-authors; Miotti G, Quaglia D and De Marco L did the research and writing of the manuscript; Miotti G, Quaglia D, De Marco L, Parodi PC, D'Esposito F, Musa M, Tognetto D, Gagliano G and Zeppieri M assisted in the writing of the draft and final paper; Miotti G, Quaglia D, De Marco L and Zeppieri M were responsible for the conception and design of the study and completed the English and scientific editing; Miotti G, Quaglia D, De Marco L, Parodi PC, D'Esposito F, Musa M, Tognetto D, Gagliano G and Zeppieri M assisted in the editing, making critical revisions of the manuscript and viewing all versions of the manuscript. All authors provided the final approval of the article.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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S-Editor: Liu H
L-Editor: A
P-Editor: Wang WB

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World Journal of Clinical Cases

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World J Clin Cases 2025 July 6; 13(19): 99311

DOI: 10.12998/wjcc.v13.i19.99311

ISSN 2307-8960 (online)

CASE REPORT

Successful treatment of depressed esophageal squamous papilloma with interferon- alpha 2a: A case report

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Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Aghazadeh H

Received: July 19, 2024

Revised: January 27, 2025

Accepted: February 26, 2025

Published online: July 6, 2025

Processing time: 143 Days and 5.4 Hours

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Abstract

BACKGROUND

Esophageal squamous papilloma (ESP) is a rare benign tumor of the esophagus, typically characterized by an exophytic and warty appearance, with a diameter of less than 5 mm. Endoscopic resection is considered the most effective treatment for these tumors.

CASE SUMMARY

In this paper, we discussed the pathogenesis, clinical characteristics, and therapeutic options of ESP based on our experience with a case presenting a depressed appearance and treated with interferon-alpha 2a (IFNα2a) injection.

CONCLUSION

This paper reports the first successful clinical case of using the human IFNα2a for the treatment of ESP with a depressed endoscopic appearance. However, the efficacy of interferon treatment requires to validation in a large number of subsequent cases.

Key Words: Papilloma; Esophagus; Interferon-alpha 2a; Human papillomavirus; Case report

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Core Tip: Esophageal squamous papilloma (ESP) is a rare benign epithelial tumor of the esophagus, typically presenting with an exophytic and warty appearance, often measuring less than 5 mm in diameter. Endoscopic resection is regarded as the most effective treatment for these tumors. However, the complete resection rate remains low. In this paper, we reported a case of ESP located in the lower esophagus that exhibited an unusual depressed endoscopic appearance with a diameter approaching 2 cm, which showed significant therapeutic outcomes by recombinant human interferon-alpha 2a. Nevertheless, further validation of the efficacy of interferon treatment is necessary through larger-scale studies involving subsequent cases.

Citation: Jiang J, Shi HT, Wu J, Sha SM, Cai SX, Liu X. Successful treatment of depressed esophageal squamous papilloma with interferon- alpha 2a: A case report. *World J Clin Cases* 2025; 13(19): 99311
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/99311.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.99311

INTRODUCTION

Esophageal squamous papilloma (ESP) is a rare benign tumor of the esophagus. The incidence of ESP reported ranges from 0.01% to 0.45%[1]. ESP can occur throughout the esophagus, with the lower and middle esophagus being the most commonly affected regions. Endoscopically, ESP usually appears as white or grayish-white, wart-like lesion with a diameter of less than 5 mm. It is often solitary but can occasionally present as multiple lesions, and in rare cases, may involve the entire esophagus[2,3]. ESP is believed to result from a chronic inflammatory response triggered by chemical or mechanical irritants, including gastroesophageal reflux disease, smoking, alcohol consumption, caustic injury, food impaction, or human papillomavirus (HPV) infection[4]. Currently, endoscopic treatment is the primary clinical approach, with methods such as electrocoagulation, argon gas, cold forceps, and microwaves being commonly used. However, endoscopic resection is challenging for lesions larger than 2 cm, with a low complete resection and a higher likelihood of recurrence. In this paper, we report a case of ESP with a depressed growth pattern, measuring nearly 2 cm in diameter in the lower esophagus, which was completely resolved after a 1-month course of intramuscular recombinant human interferon-alpha 2a (IFNα2a) injection. To our knowledge, this is the first case of a depressed ESP successfully treated with interferon injection, as detailed below.

CASE PRESENTATION

Chief complaints

Intermittent retrosternal discomfort for more than one month.

History of present illness

A 40-year-old man presented to our hospital on December 11, 2015, with intermittent retrosternal discomfort persisting for more than one month. His symptoms were accompanied by acid reflux and heartburn but without significant nausea, vomiting, palpitations, shortness of breath, chest tightness, chest pain, fever, or night sweats. The patient had been taking oral omeprazole 20 mg once daily; however, his symptoms did not significantly improve, and he subsequently developed adverse swallowing/ dysphagia and retrosternal pain.

History of past illness

The patient reported no history of previous illness, medication use, or exposure to toxic substances.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

Upon physical examination, his vital signs were stable, and no significant abnormalities were observed in the cardiac, pulmonary, or abdominal examinations.

Laboratory examinations

Routine blood and urine laboratory test results were within normal limits. Biochemical tests, tumor markers, viral and *mycobacterium tuberculosis* DNA and antibody screening, and T-SPOT.TB results were all normal. Autoantibody screening revealed a positive Jo-1 antibody, while other markers were negative. The erythrocyte sedimentation rate was elevated at 58 mm/h, and C-reactive protein level was 2.09 mg/dL. Stool occult blood was positive. The electrocardiogram showed no significant abnormalities.

Imaging examinations

Chest and abdominal computed tomography revealed striae in the right middle lobe lung lobe, gallbladder stones, and calcified foci on the right liver lobe. Upper gastrointestinal endoscopy showed an irregular, depressed lesion in the lower esophagus near the cardia (Figure 1A), measuring approximately 2.0 cm in diameter, with 1.2% Lugol's iodine staining and no obvious unstained areas (Figure 1B). Several biopsies were obtained, and pathological findings revealed esophageal squamous epithelial papilloma proliferation with necrosis and severe acute and chronic inflammation, with numerous koilocytes (Figure 1C and D).

FINAL DIAGNOSIS

The depressed lesion in the lower esophagus was diagnosed as an HPV infection-associated esophageal papilloma.

TREATMENT

The patient received an intramuscular injection of recombinant human IFNα2a at a dose of 300 IU once every other day for 1 month.

OUTCOME AND FOLLOW-UP

Gastroscopy performed one month after treatment showed a significant reduction in the lesion (Figure 1E). After two months, scar formation was observed at the lesion site (Figure 1F). No recurrence was noted during a follow-up gastroscopy conducted 4 months later (Figure 1G).

DISCUSSION

ESP is a rare benign epithelial tumor of the esophagus. Most ESP cases lack specific clinical manifestations and are often discovered incidentally during upper gastrointestinal endoscopy performed for symptoms such as epigastric discomfort and acid reflux. Endoscopically, ESP typically presents as a single proliferative papillary bulge of approximately 2-8 mm in diameter. Studies have shown that exophytic growth, a warty appearance, and crossed vessels on the lesion surface observed under narrow-band imaging are three important features of ESP, with a diagnostic accuracy up to 88.2%[5] when all three features were present. However, there have also been reports of ESP cases with diameters exceeding 3 cm or with a flat appearance[6-9].

In this paper, we report a case of ESP in the lower esophagus near the cardia, consistent with the common site of ESP occurrence, but presenting with an unusual flat, depressed, ulcer-like appearance. The lesion measured nearly 2 cm in diameter and was difficult to distinguish from early esophageal cancer under conventional white-light endoscopy. No unstained areas were observed following local spraying with 1.2% Lugol's iodine, and subsequent pathological analysis confirmed the diagnosis of ESP. To date, no other reports have described ESP with a depressed growth pattern.

The etiology of ESP is not fully understood, and two hypotheses have been proposed[10]. The first suggests that ESP results from chronic irritation of the lower esophageal mucosa due to gastroesophageal reflux, esophagitis, esophageal hiatal hernia, or other physicochemical or mechanical injury. The second hypothesis suggests a strong association between ESP and HPV infection. Syrjänen *et al*[11] conducted a meta-analysis of 427 ESP cases from various studies, reporting that 132 cases (30%) were HPV DNA-positive, with diverse HPV serotypes identified. A study from Turkey detected HPV DNA in 7 of 38 ESP patients, including 4 cases of low-risk HPV (types 6 and 81) and 3 cases of high-risk HPV (types 16, 18, and 31)[12]. Another smaller study conducted in Mexico found that 10 out of the 14 HPV-positive ESP patients were infected with low-risk HPV (types 6 and 11) and 2 patients with high-risk HPV (type 16)[13]. Some studies have shown that the presence of koilocytes in HPV-positive tissues is significantly higher than in HPV-negative tissues, suggesting that koilocytes may have diagnostic value for HPV infection[14]. In the ESP case reported in this paper, histological examination of the lesion revealed thickened squamous epithelium with visible papillary structures and central visible fibrovascularity, without cellular anisotropy, consistent with ESP pathology. Although histological HPV DNA testing was performed, the presence of numerous koilocytes suggests a potential correlation with HPV infection.

It is generally accepted that pharmacological treatment by itself has limited efficacy, and endoscopic resection is the preferred treatment due to its effectiveness and lower recurrence rates. Depending on the lesion's size, morphology, and location, different endoscopic treatment measures can be selected. Lesions measuring 1-5 mm are typically selected for cold forceps, thermal biopsy, or argon plasma coagulation. Lesions measuring 0.5-1.0 cm can be treated with cold forceps polypectomy or endoscopic mucosal resection, which allows intact lesion retrieval for detailed pathologic evaluation. Larger lesions, particularly those exceeding 2 cm in diameter pose challenges for complete endoscopic resection, with lower success rates and a higher likelihood of recurrence. Better outcomes have been reported with alternative methods such as radiofrequency ablation or cryotherapy[15,16].

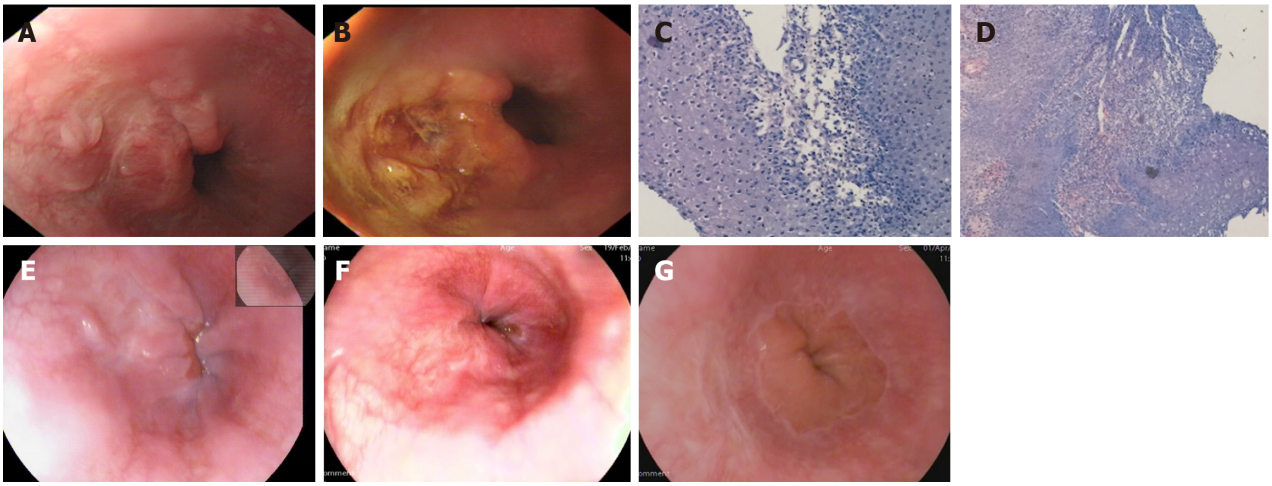

Figure 1 Gastroscopic and pathological manifestations. A: White light endoscopic manifestation before interferon treatment; B: Lugol's iodine staining at the lesion before interferon treatment; C and D: Pathological histological manifestation; E-G: Endoscopic manifestation 1 month, 2 months and 4 months after interferon α2a treatment, respectively.

For ESP associated with HPV infection that recurs after endoscopic treatment or cannot be treated endoscopically, pharmacological treatment, particularly interferon therapy, may be considered as an adjuvant treatment option. Interferon therapy has been reported to be effective in patients with papillomas of the respiratory tract or pharynx[17,18], and successful cases of bronchial papillomas treated with recombinant human IFNα2a have also been reported[19]. In this paper, we report an ESP case that exhibited an ulcer-like appearance endoscopically, measured nearly 2 cm in diameter, and was difficult to manage with curative endoscopic resection. Given the histological findings suggestive of HPV infection, the patient was treated with intramuscular injections of recombinant human IFNα2a at a dose of 300 IU once every other day for 1 month. Follow-up gastroscopy after two months showed scar formation at the lesion site, and no signs of recurrence were observed after four months, suggesting the potential effectiveness of interferon therapy.

CONCLUSION

ESP is a benign lesion that can occur at any location throughout the esophagus. Most cases present endoscopically as small, solitary, exophytic, white lesions with wart-like elevations. To date, there have been no reported cases of ESP exhibiting a depressed growth pattern. The exact etiology of ESP is not fully known, although HPV infection is considered one of the possible triggering factors. Endoscopic resection remains the primary treatment method. Currently, there are no documented cases in the literature of successful treatment of ESP using only interferon injection. In this paper, we report a case of ESP in the lower esophagus with a previously unreported depressed endoscopic appearance, which was treated with recombinant human IFNα2a, echieving significant results. However, the efficacy of interferon treatment requires further validation through larger case studies.

FOOTNOTES

Author contributions: Jiang J data analysis and writing; Shi HT literature search; Wu J histological and pathological analysis; Sha SM collation of clinical case data; Cai SX clinical data acquisition; Liu X visualization, writing-review & editing. All authors have read and approved the final manuscript. Jiang J, the first author of the paper, was the attending physician of the patient, responsible for the implementation and formulation of the diagnosis and treatment plan of the patient during hospitalization, and the operation of each gastroscopy review of the patient after treatment. She was also the author of the paper and the corresponding author of the paper. Liu X, the other corresponding author, was the superior doctor in charge of the patient during hospitalization. Professor, responsible for the formulation of treatment plan and efficacy supervision during the patient's hospitalization, as well as the formulation of follow-up plan, the two authors occupy the same important position in the whole treatment process of the patient, so they are co-corresponding authors.

Supported by Key Research & Development Program of Shaanxi Province, No. 2021SF-221.

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

Conflict-of-interest statement: 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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S-Editor: Qu XL
L-Editor: A
P-Editor: Zhang XD

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World J Clin Cases 2025 July 6; 13(19): 102212

DOI: 10.12998/wjcc.v13.i19.102212

ISSN 2307-8960 (online)

CASE REPORT

Chronic hepatitis B triggering antineutrophil cytoplasmic antibody-associated vasculitis complicated by glomerulonephritis: A case report

Ming-Ru Li, Li-Ya Li, Juan Tang, Jian Sun

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C, Grade D

Novelty: Grade B, Grade C, Grade C

Creativity or Innovation: Grade B, Grade B, Grade C

Scientific Significance: Grade B, Grade C, Grade C

P-Reviewer: Hai DNN; Hasibuzzaman MA; Naik PA

Received: October 11, 2024

Revised: January 19, 2025

Accepted: February 28, 2025

Published online: July 6, 2025

Processing time: 158 Days and 12.5 Hours

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Abstract

BACKGROUND

Hepatitis B virus (HBV) infection can lead to renal involvement, commonly manifested as HBV-associated glomerulonephritis (HBV-GN), which typically presents as nephrotic or nephritic syndrome. Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) is a systemic disease characterized by immune necrotizing inflammation of small blood vessels involving multiple organs with complex and severe clinical implications. The coexistence of HBV-GN and AAV is sporadic, with limited data existing regarding its diagnosis, management, clinical outcomes, and prognosis, especially in patients with AAV.

CASE SUMMARY

This manuscript presents the case of an older male patient who presented with persistent foamy urine lasting over two weeks. Initial clinical findings included nephrotic syndrome and renal insufficiency, which subsequently progressed to involve the lungs, immune system, hematologic system, and other organ systems. The patient was diagnosed with HBV-GN complicated by AAV, a rare and complex condition. Despite receiving comprehensive treatment, including corticosteroids, cyclophosphamide for immune regulation, plasma exchange, and immunoadsorption targeting antineutrophil cytoplasmic antibody-associated antibodies, the patient required long-term dialysis and demonstrated a poor prognosis.

CONCLUSION
HBV infection may trigger nephropathy with AAV. Early recognition and intervention are crucial for improving patient prognosis.

Key Words: Hepatitis B virus; Antineutrophil cytoplasmic antibody-associated vasculitis; Nephropathy; Complications; Immune complex; Alveolar hemorrhage; Plasma exchange; Protein A immunoadsorption; Case report

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Core Tip: This case highlights a 63-year-old man diagnosed with hepatitis B virus-related nephropathy complicated by antineutrophil cytoplasmic antibody-associated vasculitis. Despite undergoing treatments such as plasma exchange, protein A immunoadsorption, and immune modulation, the patient suffered dual renal insults, necessitating maintenance dialysis and resulting in a poor prognosis. Chronic hepatitis B virus infection may contribute to antineutrophil cytoplasmic antibody production, emphasizing the importance of early diagnosis and proactive clearance of immune complexes to improve outcomes in similar cases.

Citation: Li MR, Li LY, Tang J, Sun J. Chronic hepatitis B triggering antineutrophil cytoplasmic antibody-associated vasculitis complicated by glomerulonephritis: A case report. *World J Clin Cases* 2025; 13(19): 102212
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/102212.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.102212

INTRODUCTION

Chronic hepatitis B virus (HBV) infection affects an estimated 250-300 million individuals worldwide, with approximately 3%-5% of these patients developing renal complications. Among these, membranous nephropathy is the most common glomerular injury, although HBV infection is also associated with IgA nephropathy, cryoglobulinemia, and polyarteritis nodosa (Kussmaul-Maier disease)[1]. The HBV-related kidney involvement, termed HBV-associated glomerulonephritis (HBV-GN), commonly presents as nephrotic or nephritic syndrome. Currently, two hepatitis viruses have been linked to systemic vasculitis: HBV, which is primarily associated with classic polyarteritis nodosa, and hepatitis C virus, which is related to cryoglobulinemic vasculitis[2]. The HBV infection has a recognized tendency to induce antineutrophil cytoplasmic antibody (ANCA) production, resulting in clinical manifestations that mimic ANCA-associated vasculitis (AAV)[3]. Both HBV and AAV significantly impact renal function, increasing the likelihood of misdiagnosis or oversight of one condition during clinical evaluation. Simultaneous occurrence of HBV-GN and AAV is infrequent[2-4], with limited data available on diagnosis, management, clinical outcomes, and prognosis. Here, we report a 63-year-old Chinese man who was diagnosed with AAV complicated by glomerulonephritis. After comprehensive treatment with antiviral, immunotherapy, and plasma exchange, the patient's prognosis was still poor. This case demonstrates a complex clinical scenario at the intersection of nephrology and infectious diseases, where concurrent HBV-GN and AAV complicate the diagnostic process. It underscores the need for heightened clinical awareness and offers a practical diagnostic approach to aid physicians in identifying and managing such rare cases.

CASE PRESENTATION

Chief complaints

The patient reported foamy urine persisting over two weeks and generalized swelling lasting 4 days.

History of present illness

Approximately two weeks prior, the patient experienced the onset of foamy urine without an identifiable cause, accompanied by bilateral lumbar and abdominal distension, and increased nocturia (5-6 times/night). Over the last 4 days, the patient developed facial and bilateral lower limb swelling, which progressively worsened.

History of past illness

The patient had a longstanding history of gouty arthritis, managed intermittently over several years.

Personal and family history

The patient had unremarkable familial or personal history, with no notable medical conditions or genetic predispositions.

Table 1 Laboratory data at the time of initial hospitalization

Items	Result	Reference values
Sedimentation (mm/hour)	91	0-28
CRP (mg/L)	27.66	0-6
WBC (× 10^9/L)	8.95	3.5-9.5
Neutrophils	6.97	1.8-6.3
PLT (× 10^9/L)	167	125-350
Hb (g/L)	106	130-175
D-dimer (mg/L)	5.65	< 0.55
PCT (ng/mL)	0.215	< 0.045
Albumin (g/L)	22.9	40-55
Serum creatinine (mol/L)	387	57-111
Blood urea nitrogen (mmol/L)	16.8	3.1-9.5
24-hour urine protein (g/L)	12.397	<0.15
Proteinuria	+++	Negative
Hematuria	+++	Negative
Cholesterol (mmol/L)	9.24	< 6.22
Triglyceride (mmol/L)	2.74	< 1.7
AFP (ng/mL)	7.98	< 7

CRP: C-reactive protein; WBC: White blood cell; PLT: Platelet; Hb: Hemoglobin; PCT: Procalcitonin; AFP: Alpha fetoprotein.

Physical examination

On admission, physical examination revealed facial and bilateral lower extremity edema. Blood pressure was elevated at 181/97 mmHg. No significant abnormalities were noted in pulmonary auscultation or findings.

Laboratory examinations

Initial laboratory testing identified significant abnormalities (Table 1), including proteinuria (3 +), hematuria (3 +), hypoalbuminemia (22.9 g/L), elevated serum creatinine (Scr) (387 μmol/L), increased blood urea nitrogen (16.8 mmol/L), and hypercholesterolemia (9.24 mmol/L). Complement analysis showed a reduced C4 level (0.4 g/L). Immunological studies revealed positive perinuclear ANCA and an elevated anti-myeloperoxidase antibody IgG level of 380 AU/mL (Table 2).

Imaging examinations

Ultrasound of the urinary system showed standard kidney dimensions with enhanced parenchymal echogenicity and reduced blood flow signals.

FINAL DIAGNOSIS

HBV triggering AAV complicated by glomerulonephritis.

TREATMENT

The patient was started on a treatment regimen that included methylprednisolone (40 mg/day) for inflammation control, cyclophosphamide (0.6 g) for immunosuppression, ceftriaxone (1 g/day) for infection control, and enoxaparin (4000 IU/day) for anticoagulation at the beginning of the hospitalization. Furthermore, supportive treatments included renal protection, detoxification, antihypertensive therapy, gastric protection, calcium supplementation, albumin infusion, and intermittent diuretics. This comprehensive treatment approach reduced Scr to 228 mmol/L and significantly improved systemic edema.

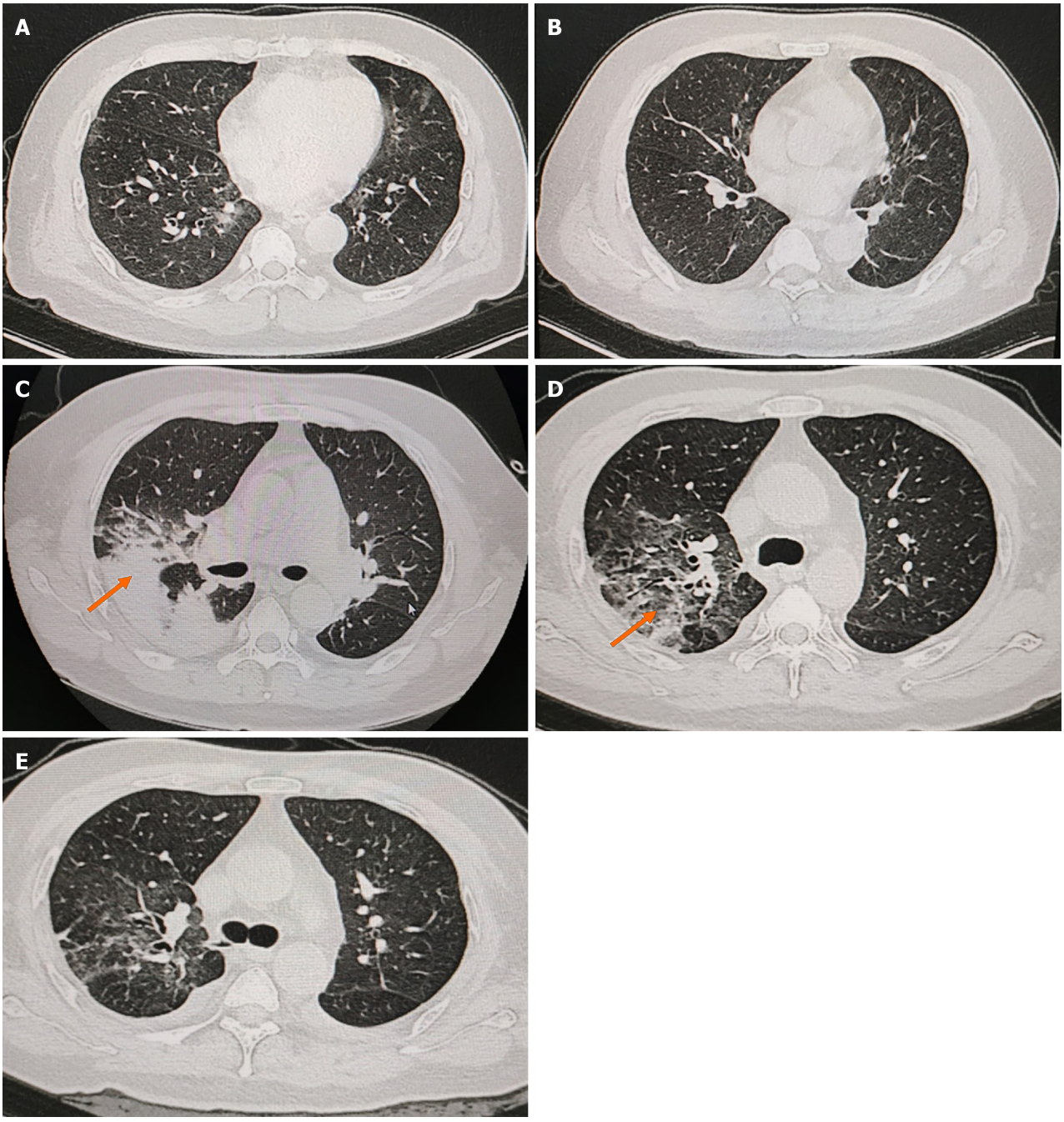

Figure 1 Computed tomography imaging images at the time of initial hospitalization and disease progression. A and B: High-resolution computed tomography (CT) images to consider viral infections in both lungs; C: Pulmonary artery imaging on March 23, 2023, reveals multiple inflammations in both lungs are significantly more advanced than before. CT angiography imaging of the pulmonary arteries reveals no significant abnormalities. The orange arrow shows prominent solid exudative changes in the right upper lung; D: Multiple inflammations in both lungs are significantly more resorbed than before; E: High-resolution CT of the lungs, performed on April 13, 2023, demonstrates partial resolution of the lesions in the upper and dorsal segments of the right upper and lower lobes, along with a small amount of bilateral pleural fluid effusion. Moreover, partial distension of the adjacent lower lungs is observed.

During hospitalization, the patient developed complications, including fever, dyspnea, and pulmonary hemorrhage (Figure 1). These symptoms necessitated transfer to the intensive care unit, where noninvasive ventilatory support was initiated to manage respiratory distress. According to the result of next-generation sequencing of alveolar lavage fluid, the treatment regimen was revised to include methylprednisolone (20 mg/day), meropenem (1 g/8 hour) combined with moxifloxacin (0.4 g/day) for antimicrobial therapy, and trimethoprim-sulfamethoxazole (0.48 g/day) for prophylaxis against *Pneumocystis jirovecii*. Entecavir (0.5 mg/5 day) was administered for antiviral treatment. Additional interventions included plasma transfusions to improve coagulation, intravenous immunoglobulin to enhance immune function, and plasmapheresis combined with six sessions of protein A immunoadsorption, performed between March 29 and April 12. Supportive care measures were also implemented, including renal protection and symptomatic management. The patient showed clinical improvement following treatment.

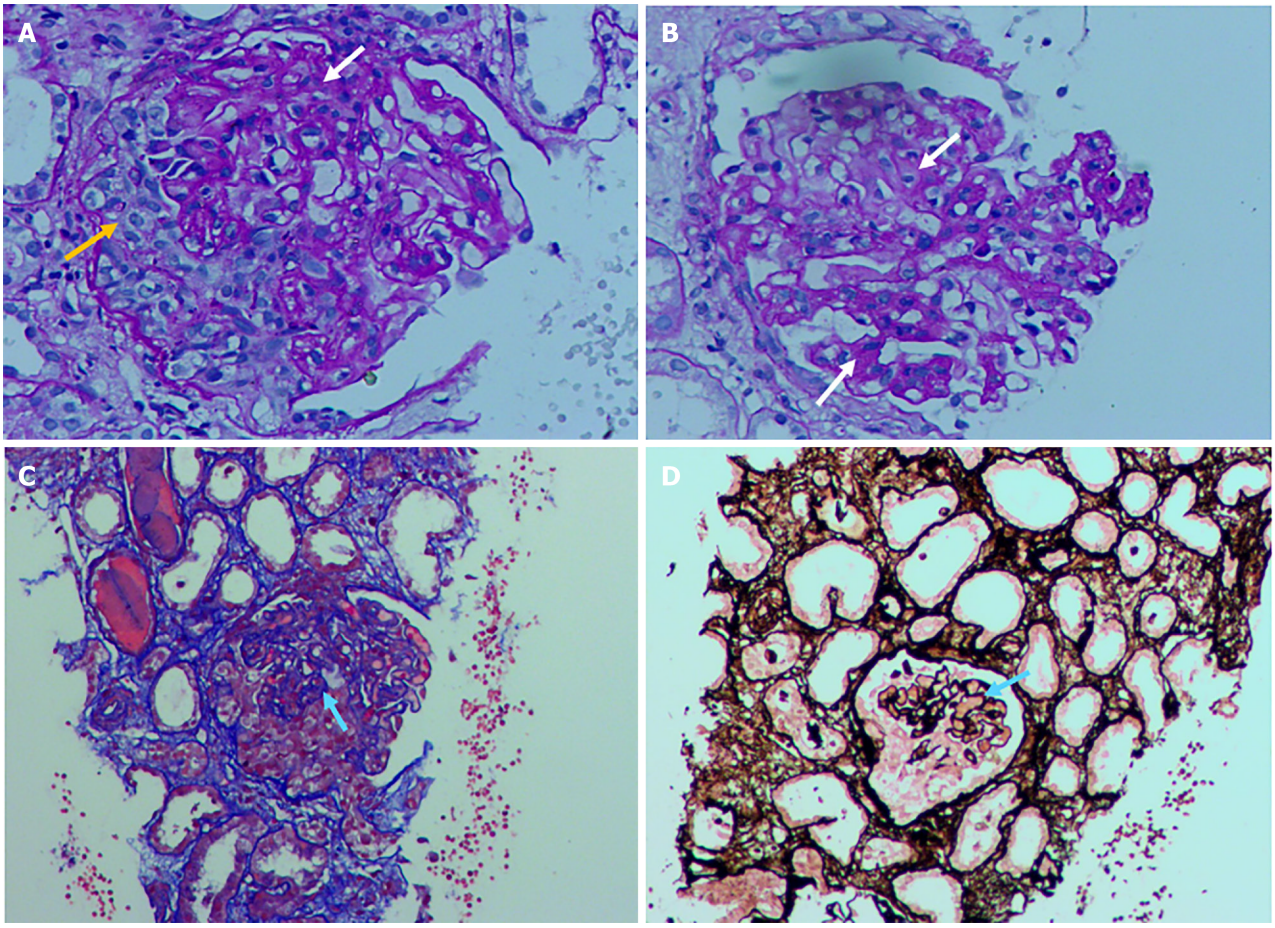

Figure 2 Light microscopic picture of renal pathology. The light microscopy specimen in this case reveals the presence of five glomeruli, including three marginal glomeruli with crescentic lesions (3/5), while only two intact glomeruli are observed. PASM-Masson staining: Glomeruli with suspected erythrophilic deposits, segments with suspicious "pegs". Renal tubular interstitium with severe chronic lesions, multiple small foci of tubular atrophy, basement membrane thickening, some tubular epithelial cells with large nuclei, and some cells with intranuclear inclusion bodies. Focal renal tubular epithelial cells with brush border detachment, some renal tubular epithelial cells with fine apparent granular degeneration and vacuolar degeneration, and tubular lumen with visible protein tubular pattern. Interstitial fibrosis and edema, multifocal infiltration of single nucleated cells, and eosinophils are seen in small foci. Segmental or total hyaline degeneration of small arteries. A and B: Periodic acid-Schiff stain of glomeruli, fibrous necrosis and crescent formation can be seen; C: Masson-Trichrome, glomeruli with suspected erythrophilic deposits, segments with suspicious "pegs"; D: Periodic-acid silver methenamine. White arrows: Fibrinoid necrosis; yellow arrows: Fibrocellular crescent; blue arrow: Basement membrane thickening.

OUTCOME AND FOLLOW-UP

Five months post-discharge, the patient's edema had resolved; however, renal function showed no significant recovery, necessitating ongoing maintenance hemodialysis.

DISCUSSION

The underlying mechanisms of nephropathy in chronic HBV infection remain unclear. The condition is thought to result from the deposition of immune complexes (ICs)[5], with genetic predisposition potentially contributing to susceptibility [6]. The patient presented with multiorgan involvement, and renal pathology revealed crescent formation, suggesting a combination of HBV-GN and AAV-related renal damage. However, AAV typically manifests as necrotizing and crescentic glomerulonephritis without IC deposition[7]. However, renal biopsy findings (Figure 2) in this case revealed membranous changes accompanied by crescent formation. Granular deposition of IgA, IgM, C3, C1q, and IgG was observed in the mesangium and capillary loops alongside the granular presence of HBV markers (HBsAg, HBcAg, HBeAg) within the same regions. Electron microscopy (Figure 3) further confirmed the presence of IC deposits in subepithelial, intramembranous, subendothelial, and mesangial locations. These findings suggest that, in addition to neutrophil-mediated endothelial cell injury induced by ANCA[7], HBV infection contributes to IC formation and deposition within blood vessels, leading to progressive vascular wall damage over time. This process may trigger vasculitis and associated renal manifestations. The underlying pathogenesis likely involves a combination of direct viral invasion of vascular endothelial cells, IC-mediated vascular injury, and autoimmunity-mediated activation of autoreactive B cells and regulatory T cells[5]. This cascade of events, coupled with local complement activation and recruitment

Table 2 Autoimmune work-up

Items	Result	Reference values
ANA antibody	1:160 (+)	Negative
Anti-SS-A	±	Negative
Anti-dsDNA	Negative	Negative
Anti-SM	Negative	Negative
Anticardiolipin IgG (GPLU/mL)	57.7	0-8
C3 (g/L)	0.88	0.79-1.52
C4 (g/L)	0.4	0.16-0.38
p-ANCA	+	Negative
Anti-MPO	+	Negative
IgG4 (g/L)	4.52	0.03-2.01
Lupus anticoagulant	Negative	Negative
Anti-β2 glycoprotein 1 antibody	Negative	Negative
Serum anti-phospholipase A2 receptor antibody	Negative	Negative
HBsAg(ng/mL)	0.01	0-0.5
HBsAb (MIU/mL)	99.23	0-10
HBeAg (PEIU/mL)	0.01	< 0.1
HBeAb (PEIU/mL)	0.02	< 0.15
HBcAb (PEIU/mL)	3.06	< 0.7
HBV-DNA (IU/mL)	< 20	< 20

ANA: Antinuclear antibody; SS-A: Sjögren's syndrome A; SM: Smith; p-ANCA: Perinuclear antinuclear cytoplasmic antibody; MPO: Myeloperoxidase.

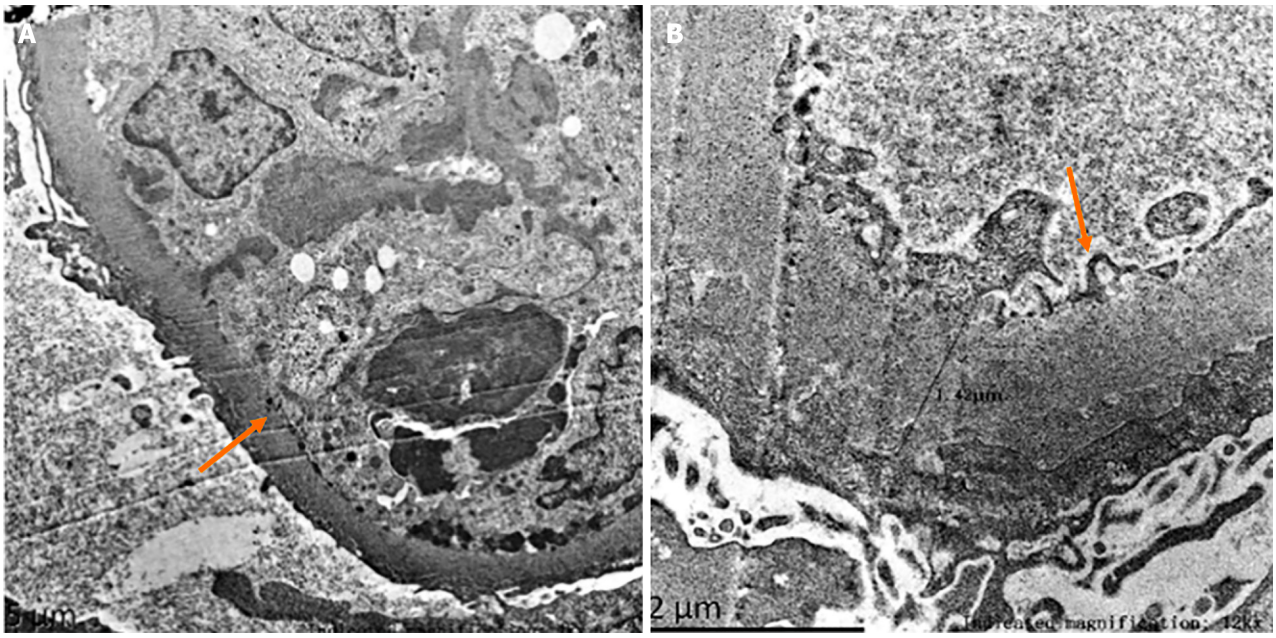

Figure 3 Electron microscopic picture of renal pathology. Electron microscopy reveals mild to moderate glomerular mesangial hyperplasia accompanied by segmental endothelial cell proliferation and neutrophil infiltration. Multiple immune complexes are identified, along with diffuse basement membrane thickening, the formation of small pegs, extensive fusion of pedicles, and the characteristic double-tracking and layering pattern. Multifocal renal tubular atrophy is observed, along with edema, vacuolar degeneration in some tubular epithelial cells, interstitial edema, focal fibrous tissue hyperplasia, and scattered inflammatory cell infiltration. A: Diffuse basement membrane thickening (orange arrow); B: The formation of small pegs (orange arrow).

of inflammatory cells[8], results in blood vessel damage. A retrospective study involving 153 patients with AAV reported that those with positive HBcAb levels had a substantially greater risk of relapse and poorer survival rates, particularly in cases of eosinophilic granulomatosis with polyangiitis[9]. Chronic HBV infection induces ANCA production, resulting in clinical manifestations resembling AAV[3]. Moreover, patients with concurrent HBV infection have a heightened risk of poor prognosis compared with those without HBV infection. The patient's HBV DNA concentration was reported as < 20 IU/mL, however, it could trigger rapidly progressive and severe pathology. Although such low levels of viral replication may not cause significant hepatitis, they can stimulate the immune system, resulting in a chronic inflammatory state that may contribute to the development of vasculitis and glomerulonephritis. Moreover, an individual's genetic predisposition and immune response may influence the clinical manifestations of HBV infection[6]. Therefore, when a rapid decline in renal function occurs, the possibility of HBV-associated rapidly progressive glomerulonephritis should be considered, renal biopsy should be promptly carried out to find the basis, and antiviral and immunotherapy should be initiated promptly. This case exemplifies the critical importance of early renal function monitoring in patients with HBV infection.

However, in patients with concurrent HBV infection, the use of immunosuppressants poses the risk of rapid viral replication[8]. Elevated viral loads or persistent infection can facilitate immune complexes (IC) formation, with subsequent deposition in medium and small arteries[10], creating a self-perpetuating cycle of inflammation and tissue damage. Antiviral therapy is pivotal in addressing this issue. In the present case, treatment with entecavir, corticosteroids, and cytotoxic agents improved systemic edema, although no significant recovery in renal function was observed. Generally, clearing HBsAg from the bloodstream mitigates liver and kidney involvement[11]. However, a subset of patients may experience disease progression, resulting in chronic renal insufficiency[12]. Emerging evidence suggests that a combination of antiviral and immunosuppressive therapies can reduce proteinuria in patients with HBV-GN without altering HBV replication or impairing liver and kidney function[13]. However, the short duration of observation in these studies highlights the need for further evaluation of long-term outcomes. Patients with elevated Scr, alanine aminotransferase levels, and reduced estimated glomerular filtration rate derive more significant benefits from entecavir therapy [14]. This finding underscores the essential role of antiviral treatment in managing HBV-associated renal complications. Combining plasmapheresis with antiviral therapy can significantly expedite the clearance of ICs, providing benefits in case of acute organ failure[15]. In this case, the kidneys experienced a dual hit, and despite receiving interventions such as protein A immunoadsorption, corticosteroids, and cyclophosphamide, targeting AAV antibodies, the renal function could not be restored, necessitating long-term dialysis and resulting in a poor prognosis. An analysis of this case highlights several factors that may influence patient outcomes, including treatment strategies, the extent of renal involvement, the type and titer of ANCA, the level of viral replication control, the timing of therapeutic interventions, and disease activity scores[4]. Early clearance or control of HBV-related ICs may facilitate recovery in patients with HBV-associated nephropathy and reduce the risks of renal insufficiency and vasculitis, ultimately improving patient outcomes[16,17]. However, immunosuppressive therapy carries the risk of secondary infections, as it diminishes immune defenses[18]. These infections can progress rapidly, with atypical clinical presentations, complicating timely diagnosis[19]. Therefore, prompt microbiologic evaluation and immediate treatment of new or worsening symptoms are crucial. This case underscores the challenges of diagnosing and managing co-occurring HBV-GN and AAV. The rarity of this dual presentation limits clinical experience, which may delay accurate diagnosis and appropriate treatment. Both conditions may involve multiple organ systems, including renal damage, and their overlapping clinical manifestations further complicate the identification of specific etiologies. The detection and localization of ICs are essential for diagnosing HBV-GN; however, these diagnostic tests can be technically demanding and are not always widely available. Furthermore, treating AAV requires the use of immunosuppressive agents, which increases the risk of HBV reactivation, leading to potential therapeutic conflicts[20]. Selecting an appropriate antiviral regimen to control HBV replication without exacerbating renal damage or aggravating AAV activity remains a significant challenge. The rarity of co-morbid conditions such as HBV-GN and AAV, coupled with the absence of specialized treatment guidelines and robust evidence, underscores the need for further research into optimal therapeutic approaches.

The co-occurrence of HBV-GN and AAV is exceedingly rare, and this case serves as a valuable reference for developing practical diagnostic and therapeutic strategies. It highlights the importance of improving physicians' awareness and diagnostic capabilities when managing uncommon clinical scenarios. This case provides a deeper understanding of HBV-associated renal diseases, including HBV-GN and its potential association with AAV. The insights from this case provide a foundation for future research into the pathogenesis, diagnostic techniques, therapeutic measures, and prognostic factors associated with HBV-GN and AAV co-morbidity.

CONCLUSION

In cases of occult HBV infection, both the virus itself and unresolved ICs can trigger nephropathy and vasculitis-related clinical manifestations, potentially leading to misdiagnosis or inappropriate treatment. This situation necessitates heightened vigilance and a comprehensive approach during clinical diagnosis and treatment.

FOOTNOTES

Author contributions: Li MR collected the materials and drafted the manuscript; Li LY and Tang J revised the content of the manuscript; Sun J contributed to critically revising the manuscript for important intellectual content and offered unique insights into the clinical data and valuable suggestions for improving the manuscript; and all authors gave final approval for the version to be submitted.

Supported by the Natural Science Foundation of Hunan Province, China, No. 2023JJ30842.

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

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

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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S-Editor: Bai Y
L-Editor: A
P-Editor: Yu HG

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World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2025 July 6; 13(19): 103585

DOI: 10.12998/wjcc.v13.i19.103585

ISSN 2307-8960 (online)

CASE REPORT

Wernicke encephalopathy presenting as a stroke mimic: A case report

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Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C, Grade C, Grade C

Novelty: Grade B, Grade C, Grade C

Creativity or Innovation: Grade B, Grade C, Grade C

Scientific Significance: Grade B, Grade B, Grade B

P-Reviewer: Chen S; Itoh K; Jayachandran S

Received: November 25, 2024

Revised: February 16, 2025

Accepted: February 24, 2025

Published online: July 6, 2025

Processing time: 115 Days and 15.7 Hours

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Abstract

BACKGROUND

Several conditions may present with acute neurological symptoms, thus mimicking the presentation of stroke. Although the underlying disorder can be diagnosed after careful medical, neurological, and radiological examinations, a few conditions, such as Wernicke encephalopathy (WE), may present a particular diagnostic difficulty. WE is a neurological disorder caused by deficiency of thiamine (B1 vitamin), most often resulting from alcoholism, malnutrition, hyperemesis gravidarum or bariatric surgery. The diagnosis of WE in a certain historical, clinical setting is easily suggested, but in a few cases presenting with acute neurological deficits, it can be particularly challenging.

CASE SUMMARY

We present the case of a 63-year-old man who was brought to the emergency department after developing weakness of the left extremities, dizziness and a confusional state, which had lasted for approximately 30 minutes. The patient had a similar episode of a confusional state approximately two months earlier; at that time, a transient ischemic attack was suspected and he was started on aspirin. The initial clinical evaluation and imaging findings were unremarkable for stroke, but the patient's symptoms, history of chronic alcohol abuse and abnormal liver function tests prompted the consideration of WE. Magnetic resonance imaging findings in subthalamic areas and electroencephalogram data of diffuse delta activity supported this diagnosis.

CONCLUSION

Through this case report, we aim to underscore the importance of considering WE

as a differential diagnosis in patients presenting with symptoms suggestive of stroke, especially when the presentation is atypical or when risk factors for thiamine deficiency are present. Since intravenous thiamine significantly improves outcomes, delayed recognition and treatment in some cases might be deleterious.

Key Words: Wernicke encephalopathy; Stroke mimic; Thiamine deficiency; Magnetic resonance imaging findings; Alcohol abuse; Case report

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Core Tip: Wernicke encephalopathy (WE) is a neurological disorder caused by the deficiency of thiamine (B1 vitamin), most often resulting from alcoholism, malnutrition, hyperemesis gravidarum or bariatric surgery. The diagnosis in a certain clinical setting might be easy, but in a few cases presenting with acute neurological deficits it can be particularly challenging. A 63-year-old male presented to the emergency department with left limbs weakness, dizziness and confusion that lasted 30 minutes. Brain magnetic resonance imaging (MRI) was performed and revealed hyperintense signals in several sequences, involving mammillary and hypothalamic regions, and adjacent midbrain and subthalamic nuclei. Therefore, based on the history taking, symptoms of confusion and ataxia, as well as MRI findings, WE was diagnosed. Parenteral thiamine was started as well as diuretics for hepatic cirrhosis.

Citation: Roçi E, Mara E, Dodaj S, Vyshka G. Wernicke encephalopathy presenting as a stroke mimic: A case report. *World J Clin Cases* 2025; 13(19): 103585
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/103585.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.103585

INTRODUCTION

Stroke is one of the most common diseases, affecting one in four people during their lifetime. Several nonvascular medical conditions, such as stroke mimics, acute neurological deficits and acute ischemic stroke, have been described. Stroke mimics, especially when they correspond to a hypothetical vascular distribution, result in false-positive stroke cases[1,2]. Stroke mimics account for approximately 20%–30% of all suspected stroke presentations, of which more than three-quarters are of a neurological nature and only a few are of functional origin[3]. When symptoms are brief and resolve quickly, especially when magnetic resonance imaging (MRI) findings are normal, stroke mimics can be more challenging to differentiate from stroke. A hint at a diagnosis should be that suddenness at onset is not always evident, as is the fluctuating severity of symptoms and the presence of systemic signs such as altered levels of consciousness, drowsiness, agitation, fever, *etc.*[4]. Correct clinical evaluation and medical history, as well as the use of laboratory data and brain scan tomography, led to a lower percentage of stroke mimic admissions (4%–6.5%); the use of MRI, particularly diffusion weighted imaging, has reduced it to approximately 1%[5,6].

Wernicke encephalopathy (WE), first described in 1881, is a severe and potentially life-threatening neurological disorder caused by thiamine (vitamin B1) deficiency[7]. The prevalence among the general population is estimated to be 0.4%–2.8%, with a slight predominance in males[8]. Fifty percent of cases are caused by chronic alcohol consumption, and the rest are caused by malnutrition, hyperemesis, liver disease, gastrointestinal surgery, *etc.* The classical triad of WE is described as ophthalmoplegia and/or nystagmus, gait ataxia, and confusion or delirium[9,10]. It affects both the central and peripheral nervous systems. WE is associated with high rates of morbidity and mortality. Approximately 85% of patients with WE and associated Korsakoff syndrome may experience complications, and approximately 20% of them may die. Even though delirium is likely to resolve after thiamine replacement, ataxia and ophthalmoplegia may continue and sometimes be permanent[7]. Fewer than 10% of WE patients manage to recover after long-term hospitalization, whereas others may experience long-term neurological sequelae such as ataxia and Korsakoff psychosis, which significantly worsen their quality of life[7,10].

These findings highlight the importance of recognizing pathology and its early diagnosis to treat and prevent disease complications in time.

CASE PRESENTATION

Chief complaints

We present the case of a 63-year-old man who was brought to the Emergency Department after he developed weakness of the left extremities, dizziness and confusion, which lasted approximately 30 minutes. His spouse noted that approximately two months earlier, the patient had a similar episode of confusion that lasted 20 minutes.

History of present illness

A neurological consultancy raised the suspicion of a transient ischemic attack (TIA), and the patient was given aspirin.

History of past illness

The patient did not report having a history of comorbidities including hypertension, diabetes mellitus, hyperlipidemia or stroke-inducing lifestyle behaviors, such as alcohol abuse and smoking.

Personal and family history

His family history was significant for cerebrovascular disease, as his father had suffered a massive stroke in his 60s.

Physical examination upon admission

Upon arrival at the Emergency Department, the patient was alert but appeared slightly disoriented. He denied experiencing dizziness at the time of examination. His vital signs were stable, with a blood pressure of 138 mmHg/82 mmHg, heart rate of 78 beats per minute, respiratory rate of 16 breaths per minute, and oxygen saturation of 98% on room air.

Neurological examination revealed that his pupils were isochoric and reactive to light, with intact extraocular movements and no evidence of nystagmus. Remainder cranial nerve examination showed symmetrical facial movements, normal gag reflex, and preserved tongue mobility. Motor strength was graded as 5/5 in the right extremities and 4+/5 in the left upper and lower extremities. There was mild dysmetria and ataxia observed in the left upper extremity during finger-to-nose testing, and the patient had difficulty performing rapid alternating movements on the left side. The patient also exhibited a leftward drift in the outstretched arm test and showed an unsteady gait with a tendency to veer towards the left side. Romberg's test was mildly positive, indicating impaired balance. Deep tendon reflexes were symmetric with slightly brisk reflexes on the left side. Babinski's sign was negative bilaterally. Sensory examination, including light touch, pain, temperature, and proprioception, was normal. No signs of meningeal irritation were present.

Laboratory examinations

Computed tomography (CT) of the head and CT angiography of the supraaortic vessels did not reveal any acute lesions. Based on the acute presentation, a prior history of transient neurological deficits (probably due to TIA and acute stroke were suspected. Therefore, the patient was admitted to the neurology ward.

Laboratory investigations, including a complete blood count, basic metabolic panel, coagulation profile, and lipid panel, were unremarkable except for anemia with red blood cells 4.08 × 10^6/μL (normal range 4.4-5.9 × 10^6/μL), thrombocytopenia with platelet count 77 K/μL (150-400 K/μL). Coagulation tests showed prothrombin time (Quick time) at 59% (70%-110% without anticoagulation), international normalized ratio: 1.45 (0.85-1.15 without anticoagulation), and a D-Dimer level of 2.17 μg/mL (< 0.5 μg/mL).

Liver function tests were abnormal, with total bilirubin at 2.47 mg/dL (0.3-1.2 mg/dL), direct bilirubin at 1.16 mg/dL (0.1-0.5 mg/dL), alanine aminotransferase at 35 U/L (< 55 U/L), aspartate aminotransferase at 51 U/L (5-34 U/L), glutamyl transpeptidase at 83 U/L (12-64 U/L), and lactate dehydrogenase at 258 U/L (125-200 U/L). Renal function tests showed urea at 30.4 mg/dL (18-55 mg/dL) and creatinine at 0.61 mg/dL (0.72-1.25 mg/dL).

During the hospital stay, the patient experienced a few episodes of confusion lasting an average of 15–20 minutes, without accompanying signs or symptoms.

Imaging examinations

The results from an electroencephalogram examination revealed diffuse delta waves. Abdominal ultrasound revealed a coarse hepatic parenchyma, gallbladder sludge, ascites, and an enlarged spleen. Transthoracic echocardiogram revealed concentric hypertrophy of the left ventricle with type I diastolic dysfunction. MRI of the head revealed hyperintense signals in several sequences, such as those shown below, involving the mammillary and hypothalamic regions and adjacent midbrain and subthalamic nuclei (Figure 1).

MULTIDISCIPLINARY EXPERT CONSULTATION

His relatives reported that he had been recovering from alcoholism and that he had abused alcohol for the past 25 years. Past medical history, information and laboratory findings revealing elevated liver enzymes, elevated bilirubin, decreased prothrombin time, and low serum albumin and protein. An abdominal ultrasound revealed hepatic cirrhosis and ascites, and an MRI showed hyperintense signals bilaterally in the hypothalamic and subthalamic areas. Therefore, WE was diagnosed.

The patient received intravenous thiamine (500 mg every 8 hours for the first 24-48 hours, followed by 250 mg daily) for WE, diuretics for ascites (spironolactone 100mg/daily and furosemide 80 mg/daily), and benzodiazepines (diazepam 10 mg every 6-8 hours as needed).

FINAL DIAGNOSIS

On the third day of hospitalization, the patient experienced an episode of hematemesis. Emergent esophagogastroduo-

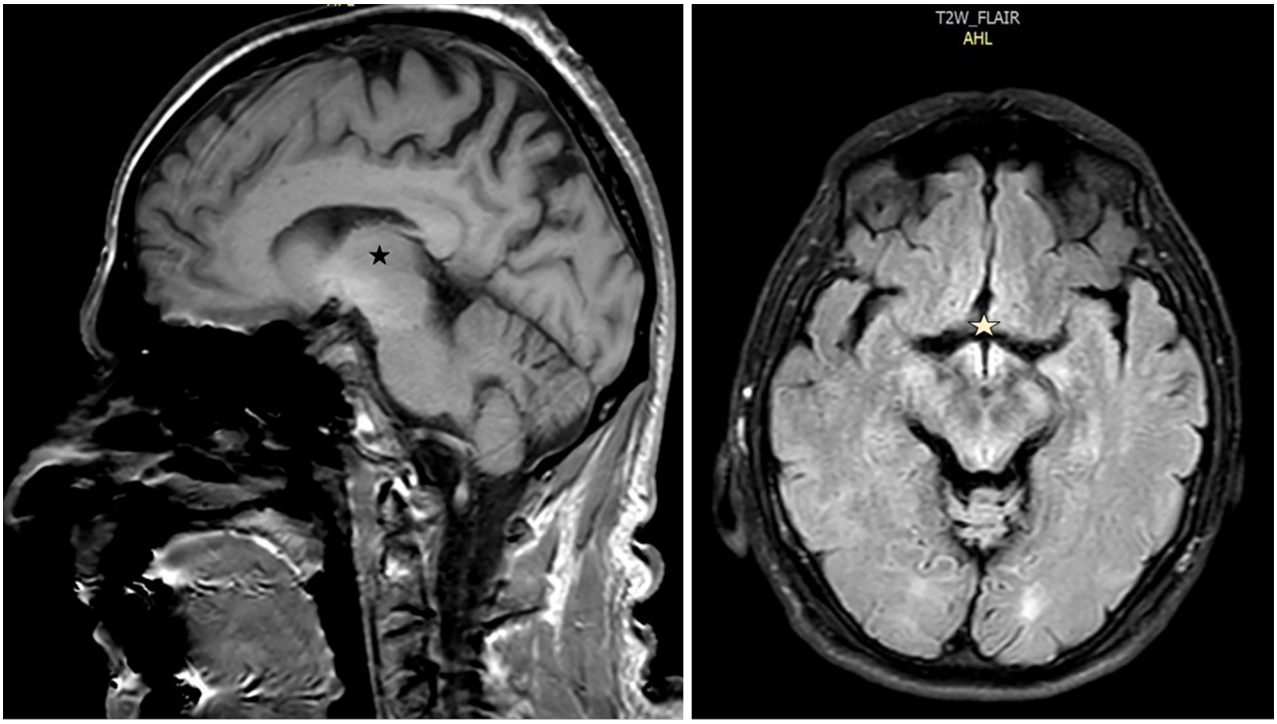

Figure 1 Magnetic resonance imaging of the head showing hyperintense signals in the fluid attenuation inversion recovery sequence, involving hypothalamic structures (mammillary bodies, right inset), subthalamic and adjacent midbrain areas. Left inset: Sagittal images (black star); right inset: Axial images (yellow star).

denoscopy revealed three esophageal varicose veins and one gastroesophageal varicosity, with no active bleeding. Ligation of the varicose veins was recommended and subsequently performed, with no surgical complications.

TREATMENT

The patient was transferred to the intensive care unit (ICU) for one week. During his ICU stay, he continued the same treatment regimen, including thiamine, diuretics, and diazepam for alcohol withdrawal, with additional treatments as needed, such as fluids, electrolyte management, preemptive antibiotic use (Ceftriaxone 2 g/daily), and close monitoring of his liver function, coagulation status, inflammation and infection markers.

As treatment progressed, there was gradual improvement in his mental status, and he began to show more alertness and responsiveness. By the end of his ICU stay, there was significant improvement in both his neurological and systemic status. His confusion and disorientation continued to improve, although he still required monitoring for withdrawal symptoms. His liver function tests remained elevated, but the patient's overall condition stabilized.

OUTCOME AND FOLLOW-UP

Upon discharge, he was stable and had no particular complaints. The medical team advised his referral to an outpatient rehabilitation service for long-term therapy for alcohol-dependent patients.

DISCUSSION

WE is a critical medical condition resulting from thiamine deficiency. Thiamine is a vitamin that is highly important for maintaining membrane integrity. After crossing the blood-brain barrier (BBB), it forms thiamine pyrophosphate, the active metabolite, which serves as a coenzyme for multiple enzymes in the Krebs cycle (tricarboxylic acid cycle) and the pentose phosphate pathway (PPP)[11-13].

Thiamine deficiency decreases intracellular thiamine diphosphate, leading to decreased activity of the Krebs cycle and PPP. Consequently, adenosine triphosphate (ATP) production decreases, as do DNA/RNA and nicotinamide adenine dinucleotide phosphate synthesis, increasing the vulnerability of cells to oxidative stress. Furthermore, there is an accumulation of toxic intermediates such as lactate, alanine and glutamate, decreasing the cellular pH and causing electrolytic disequilibrium, which ultimately results in cytotoxic edema[7,14]. Moreover, vasogenic edema is caused by

Table 1 Key diagnostic distinctions between ischemic stroke and Wernicke encephalopathy

	Ischemic stroke	WE
Origin	Vascular	Metabolic
Mechanism	Thrombotic or embolic occlusion of a cerebral artery which interrupts blood flow depleting the brain from of oxygen and glucose, which leads to disrupted adenosine triphosphate synthesis and energy deficiency, as well as impaired ion homeostasis and acid-base imbalance. Cytotoxic edema is developed rapidly after ischemic stroke, followed by vasogenic and mixed edema	Krebs cycle (tricarboxylic acid cycle) and the pentose phosphate pathway due to thiamine deficiency leading to both vasogenic and cytotoxic edema
Associated risk factors	High blood pressure, atrial fibrillation, cardiac failure, diabetes mellitus, vasculopathies, hypercoagulability, carotid stenosis, dyslipidemia *etc.*	Chronic alcoholism, hyperemesis gravidarum, gastric surgery procedures, anorexia nervosa *etc.*
Clinical presentation	Depends on the vascular territory: Dysarthria, aphasia, hemiparesis, hemianopia, hemi paresthesia, ataxia *etc.*	Typical triad: Confusion, ophthalmoplegia, ataxia
Laboratory findings	No specific changes. Changes of international normalized ratio, prothrombin time, activated partial thromboplastin time if specific anticoagulation therapy is taken, elevated d-dimer or fibrinogen activity may be found	Low thiamine concentration in blood, low red blood cell transketolase activity. Elevated transaminases, bilirubin and glutamyl transpeptidase, and low serum concentration of hepatic proteins in chronic alcoholism
Radiological features	Vascular territory. CT perfusion: Hypoperfusion of the affected area. CT: Hypodensity. MRI findings: Hypointense in T1, Hyperintense in T2/FLAIR. High diffusion weighted imaging signal, with corresponding low ADC. Radiological findings corresponding to encephalomalacia of the affected area	Non-vascular territory. CT perfusion: Normal. CT is normal in the majority of WE cases in the acute phase of the disease. MRI findings: Symmetrical bilateral. Hyperintensities of medial thalami, mammillary bodies, and periaqueductal region in T2/FLAIR. Atrophy of the mammillary bodies may be absent initially but is a typical finding. ADC varies from normal to reduced but less than that in most cases of ischemic stroke. Reversal of radiological findings with the adequate treatment
Treatment	Anticoagulants, antiplatelet drugs, symptomatic measures such as antihypertensive and/or antidiabetic agents *etc.*	Thiamine replacement

ADC: Apparent diffusion coefficient; CT: Computed tomography; FLAIR: Fluid attenuation inversion recovery; MRI: magnetic resonance imaging; WE: Wernicke encephalopathy.

disruption of the BBB because of tight junction malfunction, which allows intravascular fluid to penetrate the cerebral parenchymal extracellular space; this occurs because astrocytes are damaged following ATP depletion, oxidative stress and hyperexcitability due to excessive glutamate concentrations in synapses[13,15]. Some studies have focused on the inflammation process due to microglial hyperactivity and the production of proinflammatory cytokines in response to vitamin B1 deficiency. This overstimulation of microglia occurs due to a lack of inhibition by cholinergic neurons, since the bioavailability of acetylcholine may decrease in thiamine deficiency (Table 1)[16,17].

Antemortem and postmortem studies have shown a tendency of WE to affect specific regions of the brain, and the most affected areas are the thalamus and periventricular region in almost 85% of cases, the periaqueductal area in 59%–65% of cases, the mammillary bodies in approximately 45%, the midbrain tectum in 37% of cases, the cranial nerve nuclei (18%), and, less frequently, the cerebellum (5%)[14,18,19]. Butterworth *et al*[20] suggested that these areas were more sensitive to vitamin B1 deficiency due to their high rates of oxidative and thiamine-related metabolism.

Similar to these reports, the MRI findings of our patient revealed involvement of the mammillary body, subthalamic and adjacent midbrain areas.

Owing to the severity of WE symptoms, if not properly treated, complications such as Korsakoff psychosis and even death may occur. However, it is not always easy to detect and diagnose the disease in time. Many factors contribute to non-timely diagnosis, such as the variability of symptoms. In fact, the classical triad of WEs is present in only one-third of cases[12]. Similarly, alcoholism, which is the condition most closely related to WE, is associated with only half of WE patients[21]. Therefore, nonalcoholic WE patients are more likely to present different symptoms and atypical MRI findings. In addition, in nonalcoholic patients, an altered level of consciousness is the only clinical presentation, which can lead to delayed or missed diagnoses[18,19].

In fact, histopathological studies admit that many cases of WE may not be diagnosed[22,23]. In addition to Korsakoff psychosis, WE-associated complications include hepatic encephalopathy, epileptic seizures, central pontine myelinolysis, and posterior reversible encephalopathy syndrome[9]. Unusual sites of brain lesions on MRI can also be confusing for doctors and delay diagnosis. Moreover, bilaterally symmetrical lesions of the medial thalami, which are typical of WE, can be misdiagnosed as top-of-the-basilar syndrome, deep cerebral venous thrombosis, Creutzfeldt–Jakob disease, metronidazole-induced encephalopathy or paramedian thalamic syndrome[7,22,23].

Even though WE patients in the acute phase present with delirium, to the best of our knowledge, most guidelines on delirium do not include thiamine deficiency as one of the possible causes. Furthermore, in the alcohol disorders guidelines, delirium is mentioned mostly in relation to alcohol withdrawal syndrome, leading to misdiagnosis of WE delirium, which can also present similar attention deficits, speech difficulty, altered levels of consciousness, and gait ataxia. Concomitant conditions in WE patients, such as infections, can also mask the typical clinical presentation of WE [10,24,25].

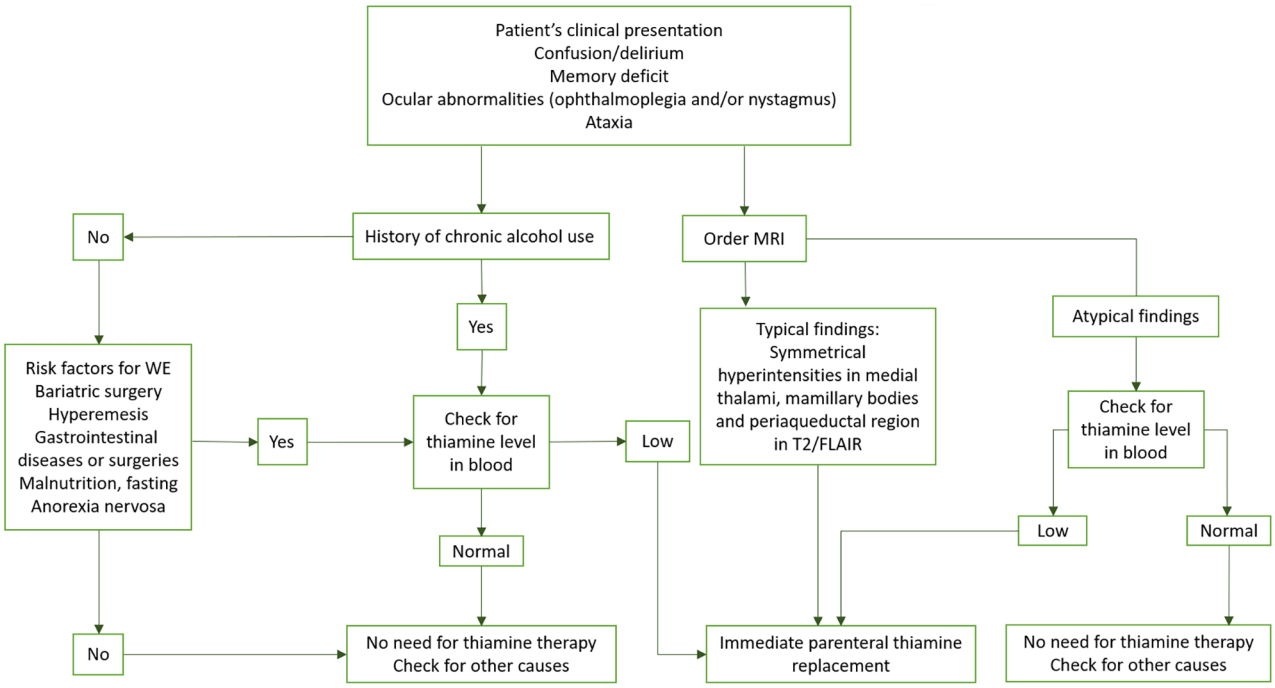

Figure 2 Algorithm: Practical diagnostic and therapeutic approach to a patient with Wernicke encephalopathy. FLAIR: Fluid attenuation inversion recovery; MRI: Magnetic resonance imaging; WE: Wernicke encephalopathy.

Neurological examination can be difficult to perform correctly on these patients, and diagnostic confirmation is often delayed. Repeated clinical evaluations, a high degree of clinical suspicion, a good medical history and recognition of the predisposing conditions are needed to prompt the diagnosis and initiate treatment with thiamine as soon as possible[9].

The European Federation of Neurological Societies guidelines recommend the administration of 200 mg intravenous thiamine diluted with 100 mL of normal saline or 5% dextrose, given over 30 minutes three times per day[26]. The recommended treatment in the United States is 100 mg of parenteral thiamine three to seven days in the treatment phase, followed by oral thiamine for as long as the patient continues consuming alcohol. In the United Kingdom, the proposed treatment is intravenous thiamine 500 mg every 8 hours or 12 hours for 2 days to 3 days[27]. Parenteral administration of 250 mg thiamine for 5 days should be maintained in patients with neuropsychiatric symptoms. Higher doses are not correlated with better outcomes than intermediate or lower doses are[28]. Even if the duration is not fixed, it is suggested that intravenous thiamine replacement should be prolonged in comatose patients. Oral vitamin B1 at a dose of 50 mg to 100 mg must be continued in patients with alcohol addiction or those who have undergone bariatric surgery. Magnesium supplementation should also be administered because of its deficiency in alcohol-dependent WE patients[12]. These guidelines are summarized in the below algorithm (Figure 2).

CONCLUSION

This case highlights the importance of considering WE in the differential diagnosis of any patient presenting with acute neurological symptoms, especially when a background of alcohol abuse or risk factors for thiamine deficiency are identified. The overlapping clinical features of stroke and WE, such as confusion, ataxia, and focal neurological deficits, can easily lead to misdiagnosis. Awareness of the pathophysiology, clinical presentation, laboratory abnormalities, and characteristic MRI features of WE are essential for early recognition and treatment. The immediate administration of thiamine is crucial, as delays can result in irreversible damages. Encephalopathy gradually diminishes, but residual neurologic deficits such as ocular abnormalities and memory deficit, are very common. Therefore, multidisciplinary teams and specialized centers are so much needed as well as educating and encouraging alcohol abstinence is very important.

FOOTNOTES

Author contributions: Roçi E, Mara E and Dodaj S were responsible for patient diagnosis, treatment and follow up, drafting of the manuscript; Mara E and Vyshka G were responsible for manuscript writing and review of literature; all of the authors read and approved the final version of the manuscript to be published.

Informed consent statement: The study participant's legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare no conflict of interest in publishing the manuscript.

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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S-Editor: Luo ML
L-Editor: A
P-Editor: Li X

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World Journal of Clinical Cases

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World J Clin Cases 2025 July 6; 13(19): 103844

DOI: 10.12998/wjcc.v13.i19.103844

ISSN 2307-8960 (online)

CASE REPORT

Unusual foreign body in the buccal mucosa: A case report

Ashwag Yagoub Aloyouny, Hamad Nasser Albagieh, Randa Aleyoni, Ghadah Jammali, Khawlah Alhuzali

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade D

Novelty: Grade A, Grade B

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade B

P-Reviewer: Agarwal P; Bin Nabhan A

Received: December 3, 2024

Revised: February 1, 2025

Accepted: February 20, 2025

Published online: July 6, 2025

Processing time: 106 Days and 17.2 Hours

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Abstract

BACKGROUND

Intraoral honeybee stings are very rare. Stings by these insects occur 25% of the time in the head and neck region. In addition, a stinger intraorally can lead to persistent irritation, inflammation, and secondary infections if not promptly excised.

CASE SUMMARY

We report the case of a 52-year-old female patient who was stung in her mouth by a honeybee, causing a local irritation. The patient presented with a one-month history of pain, swelling, and redness in the left buccal mucosa. Inadvertently retained, the stinger was discovered during a clinical evaluation following initial treatment for facial swelling and erythema. After the stinger was removed, the patient's symptoms resolved without complications.

CONCLUSION

This case emphasizes the importance of thorough examination and prompt management of insect stings to prevent prolonged discomfort and potential complications.

Key Words: Intraoral bee sting; Local irritation; Buccal mucosa; Oral cavity; Facial swelling; Case report

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Core Tip: Stings from honeybees are extremely rare inside the oral cavity. These insects sting in the head and neck area less than 25% of the time compared to other body parts. Furthermore, if a stinger is not removed promptly, it may cause chronic discomfort, inflammation, and secondary infections. We present a 52-year-old female patient who had a local irritation after being stung in the mouth by a honeybee. Shortly after removing the stinger, the patient's symptoms disappeared without any issues.

Citation: Aloyouny AY, Albagieh HN, Aleyoni R, Jammali G, Alhuzali K. Unusual foreign body in the buccal mucosa: A case report. *World J Clin Cases* 2025; 13(19): 103844
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/103844.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.103844

INTRODUCTION

The order Hymenoptera includes many species of bees, wasps, and ants. They usually attack and sting either for defense or to paralyze their prey[1]. Stings by these insects occur 25% of the time in the head and neck region, but the incidence of insect stings intraorally is infrequent. Allergic reaction to insect stings ranges from a minimal response to a life-threatening reaction, depending on the allergic status of the victim, the toxicity and amount of venom injected into the victim's body, and the site of the sting. Stings within the oral cavity are particularly concerning due to the proximity to vital structures such as the airway, which can lead to severe complications if not promptly and properly managed[2]. The venom from a honeybee sting comprises various toxic and allergenic components, such as melittin, phospholipase A2, hyaluronidase, histamine, and apamin, which contribute to the inflammatory and potentially systemic effects observed following such stings[3,4]. Moreover, a stinger within the oral cavity can lead to persistent irritation, inflammation, and secondary infections if not promptly removed[3]. In this paper, the author presents a rare case of an intraoral bee sting in the left buccal mucosa of an adult female patient with a one-month history of a retained bee stinger. The work has been reported in line with the SCARE criteria[5].

CASE PRESENTATION

Chief complaints

A 52-year-old female patient was referred to the oral medicine clinic for evaluation of painful swelling and redness in the left buccal mucosa.

History of present illness

The patient had a one-month history of localized pain, swelling, and redness in the left buccal mucosa. The patient mentioned that she was visiting a honey hive farm in Egypt. As she was eating soft bread dipped in honey, she experienced an excruciating sting inside her mouth as she opened it wide to take a bite. She reported that she discontinued chewing the bread and spat out the bolus immediately. A few hours later, she had a left facial swelling. The intraoral soreness persisted for a month before the patient sought help.

History of past illness

The patient denied past surgical, medical history or genetic conditions. She also had no allergies, no psychosocial history, and was not taking any treatment.

Personal and family history

The patient was not aware of any family health history of inherited conditions.

Physical examination

Extraoral examination: The extraoral examination revealed pain on palpation of the left buccinator muscle area. The left submandibular lymph node was also palpable, firm, and slightly tender on palpation, with no localized warmth, measuring 1 cm × 1 cm in diameter, mobile, and not fixed to the surrounding tissues.

Intraoral examinations: Intraoral examination revealed a solitary, yellowish-white, 0.2 cm × 0.2 cm vesicle on the left anterior buccal mucosa surrounded by a red halo; the lesion was painful and tender to palpation (Figure 1A).

Laboratory examinations

The blood test revealed normal results: A red blood cell count of 3.9 × 10^6/mL, a hemoglobin count of 13.2 g/dL, a platelet count of 448 × 10^3/mL, a white blood cell count of 16.7 × 10^3/mL, segmented neutrophil 42%, and lymphocytes 71%.

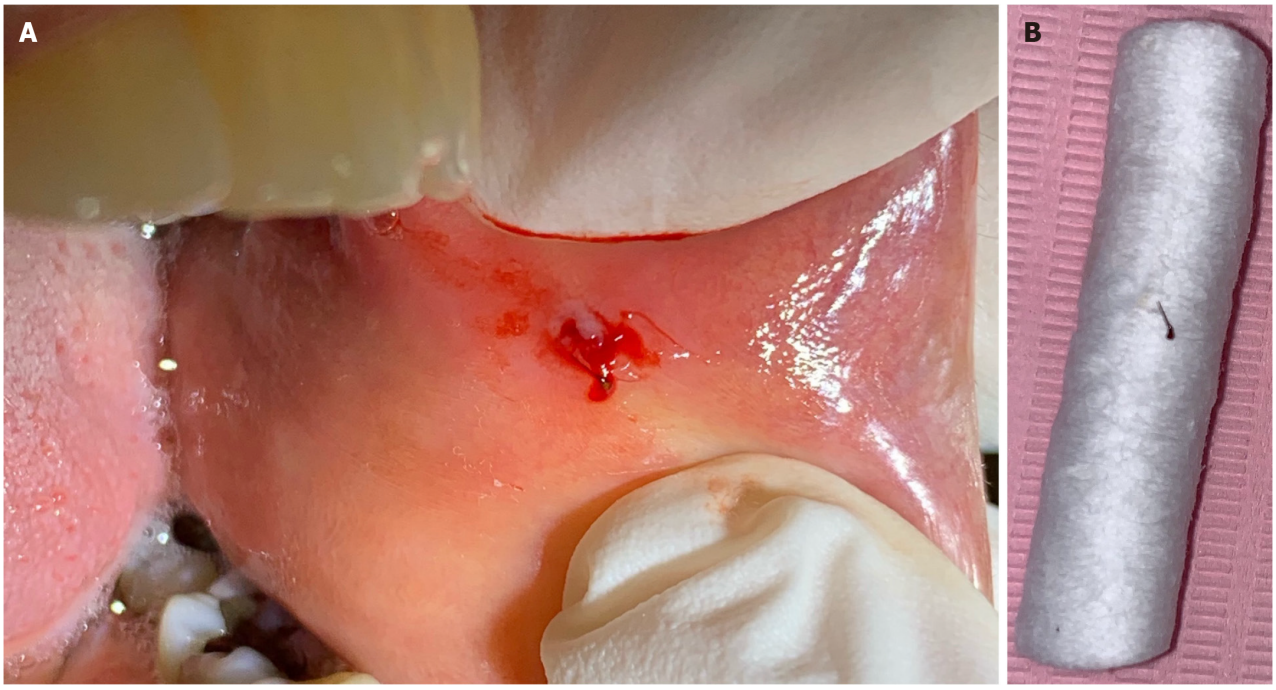

Figure 1 Clinical photos of the honeybee stinger. A: A clinical intraoral photo of a 2-mm black, long, thin foreign body came out with the pus and blood from the vesicle on the left buccal mucosa, B: A honeybee stinger on a cotton roll.

Imaging examinations

An orthopantomogram radiographic imaging was taken, which showed normal bony structures. The patient refused to go through fine needle aspiration for the involved lymph node. In addition, the excisional biopsy procedure was not accepted by the patient.

FINAL DIAGNOSIS

As part of the foreign body detection workup, diagnostic procedures were carried out to reach the definitive diagnosis. The foreign body was analyzed under the microscope; it was determined to be the honeybee's stinger (Figure 2). The final diagnosis of the oral vesicle is an intraoral localized infection caused by a long-standing foreign body in the left buccal mucosa.

TREATMENT

The patient signed a consent form before starting the treatment. The procedure was performed by an oral medicine consultant who identified as a diplomate in the American Board of Oral Medicine. After the anesthetic solution was applied around the vesicle, a small incision was performed through the blister to release the entrapped pus. Surprisingly, a 2-mm black, long, thin foreign body came out with the pus and blood (Figure 1A). The area was checked and washed with normal saline to remove any other irritants. Finally, the incision was stitched with one resorbable suture. After investigation, and based on the patient's history, the foreign body turned to be a honeybee stinger (Figure 1B). The patient was unaware of the bee sting because she had not observed the bee before or shortly after feeling the pinch in her mouth. Moreover, she only knew about the bee sting when the stinger was removed in the oral medicine clinic. Luckily, no other sites of the body were affected, there was only one sting in the oral cavity and no evidence of earlier reactions to bee stings.

OUTCOME AND FOLLOW-UP

At one-week and then four-week recall visits, the facial swelling completely resolved, and the sting site healed well without any clinical signs of complications.

Figure 2 A microscopic photo of the foreign body confirmed a honeybee stinger.

DISCUSSION

Local irritation in the oral cavity is not uncommon; it can be induced by different materials such as food, toys, graphite, dental materials, and oral care goods. However, a foreign body from a living organism inside the mouth is rare[6]. For instance, a retained insect part in the buccal mucosa is unexpected. Honeybee insects belong to the Hymenoptera order and are commonly found in nature. Honeybee stings are common because these insects possess a stinging part at the tail end of the body, which can only move forward because of its complex anatomy. Moreover, the honeybee can deliver around 50 ng of venom[3,4]. The venom toxicity increases when the stinging bee apparatus remains longer and deeper in the victim's tissue[7]. Usually, the insect's venom contains histamine, acetylcholine, dopamine, serotonin, numerous enzymes, polypeptide toxins, and kinins[1]. Most bee stings heal with no complications. However, a few cases present with either slight local irritation (measuring < 5 cm in diameter), which results in discomfort and pruritic urticarial lesion, or significant local irritation (measuring > 5 cm in diameter) that lasts for more than one day. Bee stings may also cause a mild systemic reaction, including erythema, urticaria, nausea, or diarrhea; a severe systemic response may lead to anaphylactic shock. Bee stings might cause immediate hypersensitivity reaction within two hours after the sting or delayed hypersensitivity reactions that occur two hours after the insect attack[8].

When dealing with these cases, it is important to assure the patient and take a thorough history and examination. First, immediate management should involve removing the local irritant, which is the bee stinger. Pharmacological treatment should be prescribed depending on the case. Antihistamines can reduce allergic reactions and minimize swelling, while corticosteroids could be administered to reduce severe inflammation and prevent airway compromise[2]. Analgesics should be given to manage pain, and antibiotics might be prescribed if there is evidence of secondary infection or if the patient is at high risk of infection[7]. There should be follow-up with the patient to monitor the healing process and ensure no complications arise. In this case report, the patient had a sizeable local irritation caused by a delayed-hypersensitivity reaction that included the left side of the face, albeit without airway obstruction; the swelling lasted for six days and subsided with therapy. Consequently, it was found that the patient had a retained bee stinger whose extraction was delayed for a month due to impaired visualization. A slight local irritation around the foreign body inside the mouth continued until it was extracted at the oral medicine clinic.

CONCLUSION

Bee stings inside the oral cavity are exceedingly rare. Usually, patients are aware of insect stings when they happen or shortly after the incident. In this case, the patient reported that she was at a honey hive farm when she opened her mouth wide to take a bite and felt a searing sting inside her mouth. Facial swelling immediately followed intraoral soreness, which was probably caused by an allergic reaction to something in the environment. In this instance, the likelihood of getting stung by bees is increased when visiting a honey hive farm without adopting any safety measures. We urge dentists to take a complete patient history and make a thorough clinical examination during each dental visit for any suspicious lesions.

FOOTNOTES

Author contributions: Aloyouny AY was the patient's oral medicine specialist, reviewed the literature, and contributed to data collection, data interpretation, and manuscript drafting; Albagieh HN, Aleyoni R, Jammali G, and Alhuzali K contributed in manuscript drafting and revision of the manuscript. All authors issued final approval for the version to be submitted.

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 report no relevant conflicts of interest for this article.

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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S-Editor: Wei YF
L-Editor: A
P-Editor: Zhang XD

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World Journal of Clinical Cases

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World J Clin Cases 2025 July 6; 13(19): 103946

DOI: 10.12998/wjcc.v13.i19.103946

ISSN 2307-8960 (online)

CASE REPORT

Brain and scalp metastasis of cervical cancer in a patient with human immunodeficiency virus infection: A case report

Hui-Qiong Huang, Feng-Ming Gong, Chun-Tang Sun, Yu Xuan, Lin Li

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C, Grade D

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade B, Grade B

P-Reviewer: Yang L; Yata VK

Received: December 5, 2024

Revised: January 28, 2025

Accepted: February 19, 2025

Published online: July 6, 2025

Processing time: 104 Days and 15.2 Hours

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Abstract

BACKGROUND

Cervical cancer is the most commonly diagnosed cancer worldwide and the most common cancer in females living with human immunodeficiency virus (HIV). Cervical cancer is classified as an acquired immune deficiency syndrome-defining disease. Brain metastases (BMs) from cervical cancer are extremely rare, with an incidence rate of approximately 0.63%, and there is limited information on optimal treatment protocols and patient outcomes. Since brain lesions are sequestered behind the blood-brain barrier, multimodal treatment approaches are crucial to help improve the prognosis of cervical cancer in patients with BMs who are also living with HIV.

CASE SUMMARY

A 42-year-old Chinese female with HIV infection was diagnosed with stage IIIC1r cervical cancer in March 2022 based on the International Federation of Gynecology and Obstetrics system. Fourteen months after undergoing the initial treatment with concurrent chemotherapy and radiotherapy in January 2024, the patient presented to a local hospital with a severe explosive headache. The patient underwent craniotomy and postoperative pathological examination confirmed metastasis of cervical squamous cell carcinoma to the brain on February 1, 2024. Following surgery, the patient received external beam radiotherapy for the metastatic lesions. The patient has been under observation for 7 months with no evidence of tumor recurrence.

CONCLUSION

Females living with HIV are more than three times more likely to be diagnosed

with cervical cancer. Due to the scarcity of cervical cancer BMs, therapeutic protocol experience is limited. In addition to the existence of the blood-brain barrier, the treatment of cervical cancer BMs appears to be exceptionally complex, and a multi-modal treatment approach consisting of chemotherapy, surgery, and radiation may help prolong patients' life. For females living with HIV, antiretroviral therapy should be prioritized, as recommended by the Center for Disease Control in China. An intact immune system and a high $CD4^+$ count are positive indicators of treatment response and tumor reduction. The overall survival of patients with cervical cancer after brain metastasis is approximately 3-5 months. However, owing to multimodal therapy and the use of antiretroviral therapy, the patient reported in this case showed no signs of recurrence after prolonged follow-up.

Key Words: Brain metastasis; Cervical cancer; Antiretroviral therapy; Multi-modal treatment; Case report

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Core Tip: A 42-year-old Chinese female patient with human immunodeficiency virus infection, was diagnosed with stage IIIC1r cervical cancer based on the International Federation of Gynecology and Obstetrics. Fourteen months after concurrent chemotherapy and radiotherapy, the tumor metastasized to the brain. The patient underwent a craniotomy and radiotherapy for postoperative metastatic lesions. Metastasis of cervical cancer to the brain is relatively rare, and the treatment of cervical cancer brain metastases is complicated. A multimodal treatment approach consisting of chemotherapy, surgery, and radiotherapy may need to be considered to prolong such patients' life. Additionally, antiretroviral therapy should be implemented for females living with human immunodeficiency virus.

Citation: Huang HQ, Gong FM, Sun CT, Xuan Y, Li L. Brain and scalp metastasis of cervical cancer in a patient with human immunodeficiency virus infection: A case report. *World J Clin Cases* 2025; 13(19): 103946
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/103946.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.103946

INTRODUCTION

Cervical cancer is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths among females worldwide, with a global incidence of approximately 570000 new cases and 311000 deaths in 2018[1]. Human papillomavirus (HPV) is the main causative agent of cervical cancer, causing 99.7% of all cervical cancer cases, with high-risk HPV types 16 and 18 accounting for 75%[2]. In 2020, an estimated 37.7 million people globally (uncertainty range 30.2-45.1 million) will be infected with the human immunodeficiency virus (HIV)[3]. Among HIV-infected women, cervical cancer is the most commonly detected malignancy and is classified as an acquired immunodeficiency syndrome (AIDS)-defining disease. Persistent HPV infection is closely associated with advanced HIV infection, which is featured by a weakened immune system due to a reduction in the number of $CD4^+$ T-helper lymphocytes, a hallmark of AIDS progression[4].

Cervical cancer metastatic lesions in the brain are relatively rare, but the risk of brain metastasis is increased in patient with AIDS due to immune deficiency, with reports suggesting a more aggressive form of cervical cancer with advanced stages and more susceptible to distant metastases in patients with HIV associated immunosuppression[5,6]. In this paper, we report a case of cervical cancer complicated by AIDS and eventually developing into scalp metastasis. Additionally, we discuss the characteristics, treatment, and outcomes of cervical cancer in patients with AIDS.

CASE PRESENTATION

Chief complaints

A 42-year-old Chinese female patients with HIV infection was diagnosed with stage IIIC1r cervical cancer based on the International Federation of Gynecology and Obstetrics system in March 2022.

History of present illness

The patient's clinical symptoms included unusual vaginal bleeding persisting for six months prior to hospital admission.

History of past illness

The patient was diagnosed with AIDS in 2014 and has since been on antiretroviral therapy (ART) under the care of the Chinese Centre for Disease Control, and was tested for $CD4^+$ cell levels regularly for adjustment of ART regimens.

Personal and family history

The patient declared no significant personal or family medical history.

Physical examination

Gynecological examination revealed a cervical enlargement of approximately 4.5 cm in diameter, with infiltration into the parametria, but not extending to the pelvic wall or involving the vagina.

Laboratory examinations

HPV tests were positive for HPV 16 and HPV 18. Histopathology of a cervical biopsy indicated poorly differentiated squamous cell carcinoma.

Imaging examinations

Pelvic magnetic resonance imaging (MRI) revealed a cervical mass with a segmental absence of cervical stroma, a lesion protruding downward into the vaginal vault, and indistinct boundaries from the anterior rectal wall. The bilateral obturator lymph nodes were also enlarged (Figure 1).

FINAL DIAGNOSIS

Following the revised 2018 International Federation of Gynecology and Obstetrics staging system, the patient was diagnosed with stage IIIC1r cervical cancer, considering the pelvic lymph node metastasis.

TREATMENT

The patient underwent radical concurrent chemoradiotherapy based on the National Comprehensive Cancer Network guidelines. External pelvic radiotherapy was delivered at a dose of 45 Gy divided into 25 fractions (1.8 Gy) over the whole pelvis and 55 Gy for the lymph nodes which was divided into 25 fractions of 2.2 Gy, using the intensity-modulated radiation therapy technique. Concurrently, according to the National Comprehensive Cancer Network guidelines, the patient received weekly cisplatin chemotherapy at a dose of 40 mg/m^2. Additionally, a high-dose rate of intravaginal irradiation using an iridium (Ir192) of 30 Gy divided into 5 fractions was also administered. The patient tolerated the treatment well, experiencing only moderate nausea and vomiting, and grade 3 myelosuppression according to the scale of the Ration Therapy Oncology Group. Subsequent follow-ups were conducted every 3 months. Pelvic MRI revealed good local control of the tumor (Figure 1) and no complaints of discomfort during the follow-up period were reported. The patient was still on ART under the care of the Chinese Centre for Disease Control.

OUTCOME AND FOLLOW-UP

However, 14 months after the initial treatment by January 2024, the patient presented with symptoms of explosive headache for 2 days and was admitted for emergency treatment at a local hospital. An MRI scan of the brain revealed a solitary lesion measuring 3.1 cm × 0.9 cm on the right side of the head between the right parietal skull and dura mater, accompanied by edema of the surrounding soft tissues (Figure 2). The patient underwent tumor resection surgery of the affected area on February 1, 2024. Postoperative pathological examination indicated cervical squamous cell carcinoma metastasis, which was consistent with the patient's medical history (Figure 3). Postoperatively, the patient received external radiotherapy for the metastatic lesions, at a dose of 45 Gy divided into 25 fractions of 1.8 Gy from March 1, 2024 to April 10, 2024. Due to the patient's deteriorating physical condition and economic constraints, she decisively declined further chemotherapy and any other additional treatment strategies suggested. The patient remained under clinical follow-up for 7 months, with no signs of relapse.

DISCUSSION

Cervical cancer is a major global health and financial concern, and has one of the world's highest annual incidence rates and a poor prognosis. Buoyed by growing global optimism about the possibility of reducing cervical cancer worldwide, the World Health Organization's Cervical Cancer Elimination Strategy has set ambitious targets for all countries to achieve the following by 2030: 90% of girls fully vaccinated against HPV before the age of 15, 70% of women screened by the age of 35 and again by the age of 45, and 90% of women with detected precancerous lesions treated ("90-70-90")[7].

Over the past four decades, the HIV/AIDS epidemic has become, and will continue to be, one of the world's most serious public health, development, and economic challenges. In 2020, an estimated 37.7 million people (uncertain range 30.2-45.1 million) were living with HIV, of whom 53% were young and adult women[8]. Females living with HIV are more than three times more likely to be diagnosed with cervical cancer[9]. Persistent infection with HPV is associated with advanced HIV infection, which is characterized by a weakened immune system due to low CD4$^+$ T-helper

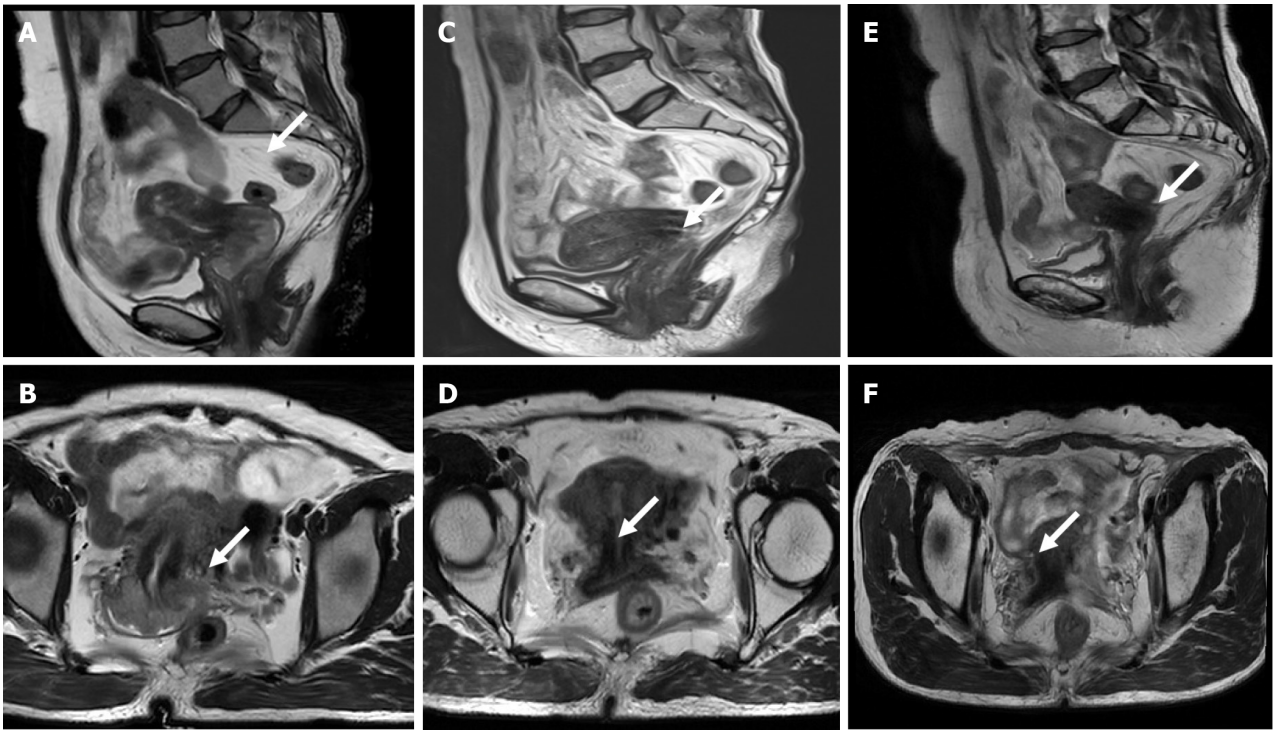

Figure 1 Pelvic magnetic resonance imaging with intravenous contrast. A and B: A cervical mass with segmental absence of cervical stroma and an unclear local boundary with the anterior wall of the rectum (white arrows); C and D: An almost normal cervix after concurrent chemotherapy and radiotherapy treatment; E and F: Magnetic resonance imaging revealed good local control of the tumor, and the size of the uterus slightly decreased 1 year after the treatment (white arrows).

lymphocyte counts—a hallmark of AIDS[4].

Approximately 16% of cervical cancer cases metastasize to distant sites[10], and despite the high rate of invasion, brain metastases (BMs) are relatively rare, estimated at 0.63%[11]. In recent years, the incidence of cervical cancer with BMs has increased. This has been attributed to improved treatment of the primary cancer, which has led to prolonged survival periods[12]. The risk of brain metastasis increases when tumors are poorly differentiated or concomitant with other conditions, such as immune deficiency, as seen with the patient in the present case who had AIDS. Although the interplay between HPV and HIV infections is complex, their synergistic effects in advancing cervical cancer pathology have been well-documented. Evidence indicates that immunosuppression in females with HIV infection results in more aggressive cervical cancer, often presenting at advanced stages[5,6]. Notably, HIV plays an indirect role in oncogenesis, primarily through immune suppression, which enhances the effects of high-risk HPV[13]. This role is supported by the evidence that cervical cancer is associated with a lower $CD4^+$ cell count and lack of an ART among females living with HIV. The route of spread of cervical cancer to the brain is likely to be haematogenous. However, there are many other factors that need to be considered, including tumour emboli and host immune response[12,14]. The median interval between the diagnosis of cervical cancer and the detection of BMs has been reported to be 17.5 months[15], and the overall survival of patients with cervical cancer after the diagnosis of BMs is approximately 3-5 months[11].

Although BMs from cervical cancer are uncommon, recognizable patterns of symptoms are still observed in patients with such metastases. These symptoms include increased intracranial pressure, headache, nausea, vomiting, seizures, and weakness in the extremities[16]. The patient in this case presented with explosive headache. Because brain lesions are sequestered behind the blood-brain barrier, they differ from other tumors. However, the treatment of BMs from cervical cancer is comparable to that of BMs from other cancers. Treatment for BMs from cervical cancer is multidisciplinary, involving a combination of craniotomy, whole-brain radiation therapy, stereotactic radiosurgery, and chemotherapy. However, which treatment provides the most desirable outcome depends on various clinical factors such as the location and size of the BMs. Surgery is usually preferred when there is a solitary lesion. Systemic treatment is favorable for patients who are poor surgical candidates or have multiple lesions[14]. According to Ikeda *et al*[17], surgical excision of the brain lesions followed by radiotherapy results in a better survival rate than radiotherapy alone. Palliative therapies such as gamma-knife radiosurgery have focused on neurological symptom control[18]. Chemotherapy comprising a platinum-based regimen, often in combination with an angiogenesis inhibitor such as bevacizumab, is the first-line treatment for patients with recurrent, metastatic, or advanced cervical cancer.

Due to the poor physical condition of the patient in the presented case and her resolute refusal of chemotherapy, the patient only underwent surgical and radiotherapy treatments. Immunotherapies and targeted therapies typically improve survival in recurrent cases. Ni *et al*[19] described a rare case of BMs in a patient with cervical cancer treated with zimberelimab in combination with anlotinib after radiation therapy with temozolomide, and the patient had a progression-free survival period of nearly 10 months. However, there is limited information on the efficacy and survival benefit of these therapies in patients with HIV infection[19]. An intact immune system and a high $CD4^+$ count are positive

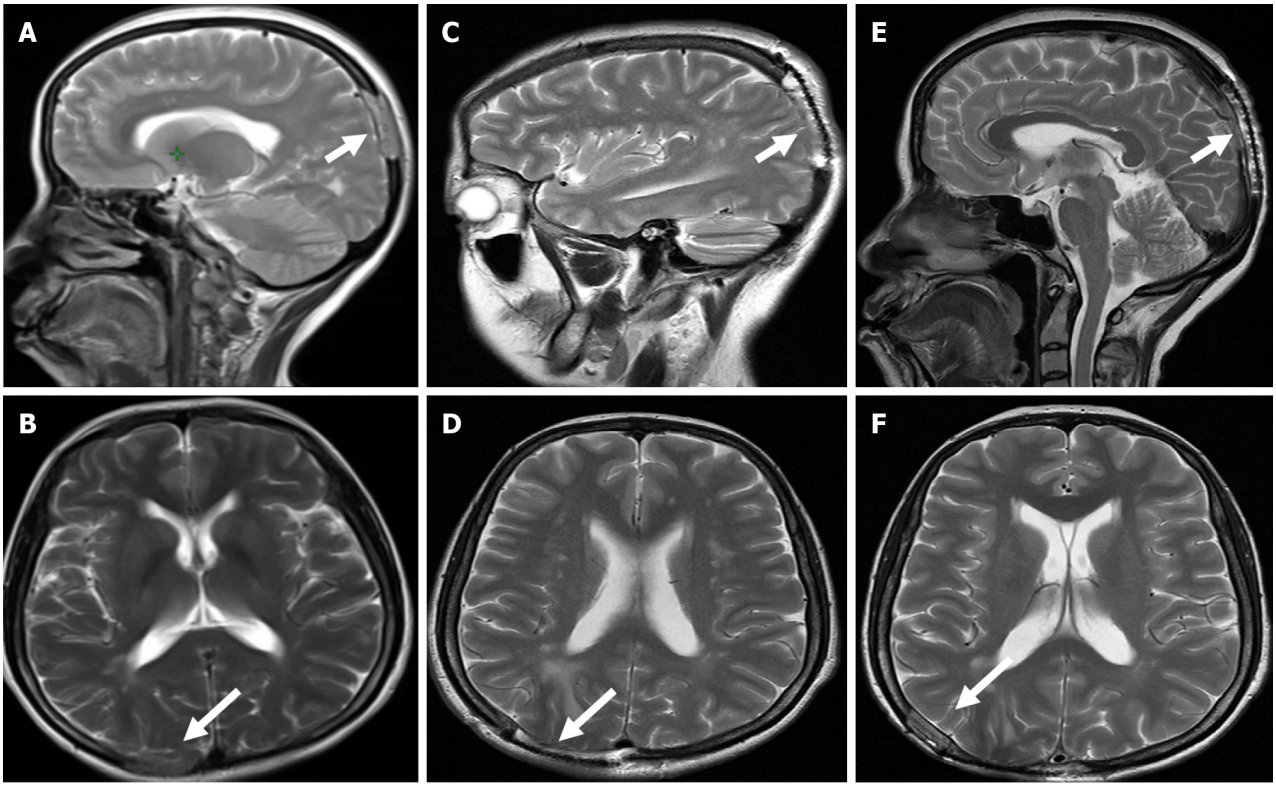

Figure 2 Images of brain magnetic resonance imaging. A and B: Patchy high signal shadow was observed between the right parietal bone and adjacent soft tissues, with limited diffusion (white arrows); C and D: Brain magnetic resonance imaging before radiotherapy showed postoperative changes, and a cranial bone flap can be seen; E and F: Brain magnetic resonance imaging images obtained 6 months after the treatment (white arrows).

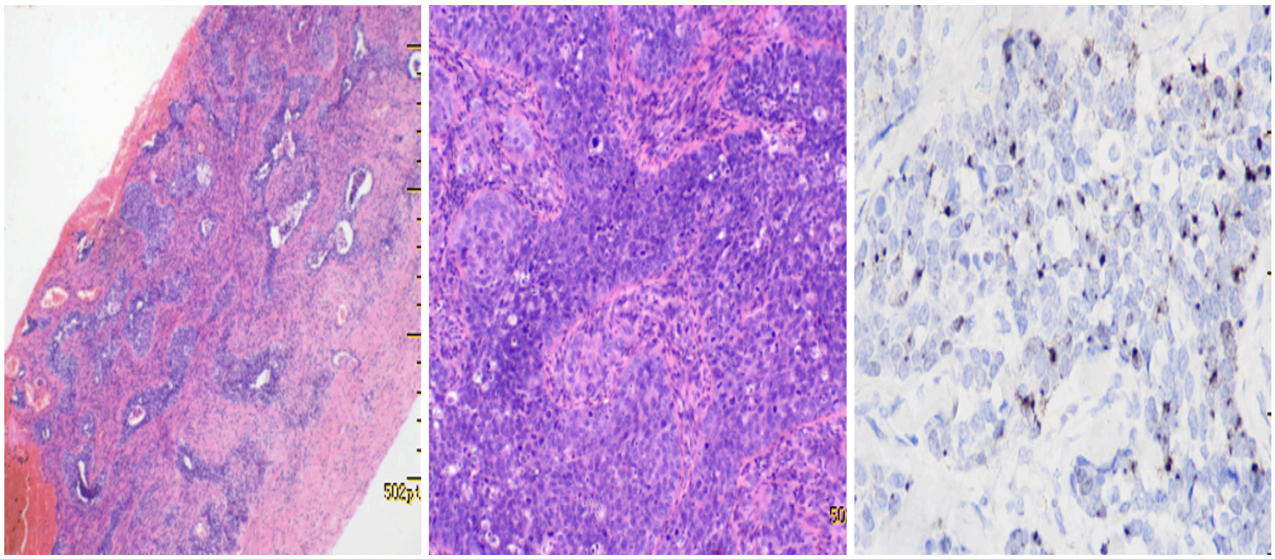

Figure 3 Pathological pictures of the patient. Histology of serous carcinoma of the meningeal metastases shows endometrioid gland lined by columnar cells with eosinophilic cytoplasm and pseudostratified nuclei (hematoxylin and eosin × 400, left). Multi-subtype *in situ* hybridization showing spotty and patchy positive signals in the cytoplasm of tumor cells (right).

indicators of treatment response and tumour reduction[20].

The associated acute treatment toxicity of radiotherapy among HIV-positive female patients was seen to be an independent significant risk factor for interrupted or delayed treatment, resulting in most of patients not completing their prescribed therapies[21]. There were no significant differences in treatment outcomes, treatment response, or toxicity between females living with HIV on ART and HIV-negative women[22,23].

CONCLUSION

Females living with HIV are more likely to be diagnosed with cervical cancer. Due to the scarcity of cervical cancer BMs, therapeutic protocol experience is limited. In addition to the existence of the blood-brain barrier, the treatment of cervical cancer BMs appears to be unusually difficult. Even so, our patient showed good tolerance to our treatment, and the multimodal treatment approach consisting of chemotherapy, surgery, and radiation provides a potential option for prolonging life. The major limitations of this study are the absence of follow-up data beyond 7 months, and the patient's decision to forgo chemotherapy, which is the most important component of multimodal treatment protocols.

FOOTNOTES

Author contributions: Huang HQ wrote the manuscript; Gong FM designed the research study; Huang HQ, Xuan Y, and Li L analyzed the data; Sun CT made supervisory contributions to the manuscript; and all authors thoroughly reviewed and endorsed the final manuscript.

Supported by the Sichuan Science and Technology Program, No. 2022NSFSC0797.

Informed consent statement: Written informed consent was obtained from the patient for the publication of this case report.

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

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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S-Editor: Bai Y
L-Editor: Wang TQ
P-Editor: Zhang XD

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World J Clin Cases 2025 July 6; 13(19): 104083

DOI: 10.12998/wjcc.v13.i19.104083

ISSN 2307-8960 (online)

CASE REPORT

Delayed diagnosis of pulmonary tuberculosis with pleuritis due to ampicillin/sulbactam: A case report

Munechika Hara, Toshitsugu Yashiro, Yasuaki Yashiro

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade C

P-Reviewer: He YL

Received: December 12, 2024

Revised: February 6, 2025

Accepted: February 24, 2025

Published online: July 6, 2025

Processing time: 97 Days and 16.6 Hours

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Abstract

BACKGROUND

Tuberculosis (TB) remains a global health concern despite decreasing incidence. Delayed TB diagnosis can exacerbate patient outcomes and lead to broader public health issues such as mass infections. Differentiation between TB and bacterial pneumonia is often complicated by variable clinical and radiological manifestations of TB, leading to diagnostic delays.

CASE SUMMARY

An 89-year-old, Japanese male patient with a history of diabetes mellitus, hypertension, and hypothyroidism presented with right-sided chest pain. Based on the elevated inflammatory response, right pleural effusion, and infiltrating shadow in the lung field, the diagnosis of right pleurisy was made and the antibiotic, ampicillin/sulbactam, was administered. The patient's condition, inflammatory reaction, and right pleural effusion temporarily improved. However, persistent low-grade fever and malaise prompted further evaluation, revealing repeated right pleural effusion and inflammatory response. A right thoracentesis was performed; the patient was diagnosed with tuberculous pleurisy as a result of exudative effusion with lymphocyte predominance, elevated adenosine deaminase levels, and positive *Mycobacterium TB* polymerase chain reaction test. Anti-TB treatment, including isoniazid, rifampicin, and ethambutol was initiated, leading to significant clinical improvement. The patient successfully completed a 12-month course of TB therapy without recurrence or deterioration.

CONCLUSION

There are cases of TB wherein temporary improvement apparently could be shown through treatment with antimicrobial agents other than anti-TB drugs, necessitating careful evaluation in atypical cases of bacterial pneumonia.

Key Words: Antibiotics; Ampicillin/sulbactam; Pneumonia; Tuberculosis; Tuberculous pleuritis; Case report

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Core Tip: There are cases of tuberculosis (TB) wherein diagnosis is delayed because they appear to improve temporarily after using an antimicrobial other than fluoroquinolone. In cases of pneumonia that follow an atypical course, such as one that improves after treatment with antibacterial drugs but then worsens again, reevaluating the possibility of TB is extremely important.

Citation: Hara M, Yashiro T, Yashiro Y. Delayed diagnosis of pulmonary tuberculosis with pleuritis due to ampicillin/sulbactam: A case report. *World J Clin Cases* 2025; 13(19): 104083
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/104083.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.104083

INTRODUCTION

Although the global incidence of tuberculosis (TB) is decreasing, it remains an important cause of death among infectious diseases[1]. Delayed TB diagnosis not only worsens prognosis but also causes social problems such as infection to surroundings. Symptoms of TB are often characterized by prolonged cough, chest pain, fatigue, weight loss, fever, and night sweats[2]. Radiographic findings are commonly associated with pulmonary TB, such as upper lobe cavitary lesions and centrilobular nodules[3]. However, these clinical and radiological findings are not specific for TB; we often detect TB without these findings[2,3]. Therefore, distinguishing TB from bacterial pneumonia is sometimes challenging in the clinical practice[4]. Fluoroquinolones are commonly used for community-acquired pneumonia; it is well known that their partial effectiveness against TB can delay diagnosis and affect prognosis[5,6]. In contrast, the impact of antimicrobials other than fluoroquinolones on the course of TB is not well known. Herein, we report a case of pulmonary TB with pleuritis wherein the diagnosis was delayed due to administration of sulbactam/ampicillin.

CASE PRESENTATION

Chief complaints

An 89-year-old Japanese man was referred to our hospital due to intermittent right chest pain, low grade fever, and fatigue since discharge from hospitalization for pneumonia 2 months ago.

History of present illness

The patient was referred to our hospital three months before this admission for right chest pain that lasted for five days. This was based on the right chest pain, elevated inflammatory response, infiltrative shadows in the lower lobes of the right lung, and right pleural effusion on a chest computed tomography (Figure 1A). A sputum culture could not be submitted due to poor sputum expectoration. Thoracentesis was not performed because the pleural effusion was small, as observed on chest ultrasonography, and a risk of lung penetration existed. Diagnosis of bacterial pneumonia and pleurisy was made; the administration of the antibiotic sulbactam/ampicillin 9 g/day was started. Eight days after administration of sulbactam/ampicillin, his symptoms and radiological findings improved (Figure 1B). Therefore, the patient was discharged and followed up by his family doctor. However, during follow-up, his symptoms, including right chest pain, low grade fever, and fatigue, recurred. He was diagnosed with a relapse of pleurisy, and antibiotics, including fluoroquinolones, were prescribed by his primary physician. Although temporary improvement was achieved with oral fluoroquinolone, his symptoms recurred after treatment discontinuation. Therefore, the patient was referred to our hospital 2 months after his initial discharge.

History of past illness

The patient had a history of hypertension, hypothyroidism, and diabetes mellitus. Hypertension was well controlled with cilnidipine (20 mg, qd), and levothyroxine sodium hydrate (25 μg, qd) had been administered for hypothyroidism. His diabetes was controlled with linagliptin (5 mg, qd). He had surgery for colon cancer seven years ago.

Personal and family history

He had no history of smoking, allergies, or notable family history of respiratory or malignant diseases.

Physical examination

Physical examination revealed a body temperature of 36.1 °C, pulse rate of 67/min, blood pressure of 113/48 mmHg, respiratory rate of 22/min (mildly labored), and O_2 saturation of 92% on ambient air. No murmurs were heard; the lungs were clear on auscultation. There were no rashes, joint swelling, or limb deformities suggestive of autoimmune diseases.

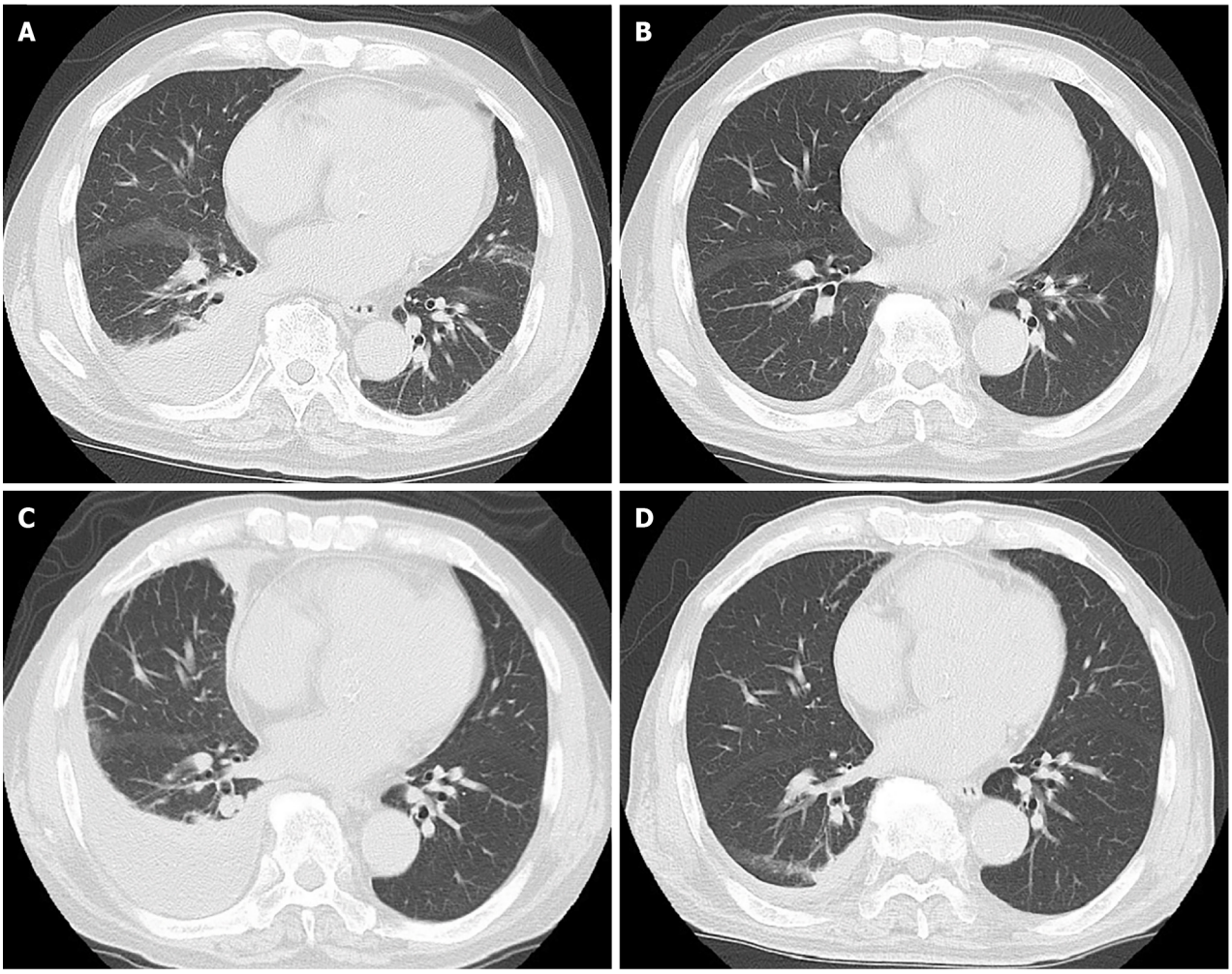

Figure 1 Chest computed tomography. A: Showing infiltrative shadows in the lower lobes of the right lung, right pleural effusion; B: Obtained one month after treatment with ampicillin/sulbactam showing decreased right pleural effusion; C: Obtained 2 months after various antibiotic treatments showing the reappearance of the right pleural effusion; D: Obtained six months after the initiation of antituberculosis drugs showing decreased right pleural effusion.

Laboratory examinations

Laboratory tests showed a re-elevated inflammatory response, a white blood cell count of 9400/μL, with 77.6% segmented neutrophils, a C-reactive protein level of 13.6 mg/dL, a high hemoglobin A1c level of 7.6%, and renal dysfunction, with blood urea nitrogen levels of 22 mg/dL and creatinine levels of 1.18 mg/dL. Interferon-gamma release assays (IGRA) were withholding judgment. The right pleural effusion had reaccumulated and had increased further compared with his previous hospitalization; right thoracentesis was performed to collect a pleural fluid sample. The pleural fluid examination revealed an elevated lymphocyte ratio of 91%, a serum protein level of 7.9 g/dL, and a lactate dehydrogenase (LDH) level of 200 U/L, as well as a pleural fluid protein level of 5.3 g/dL, an LDH level of 818 IU/L, and exudative effusion. Pleural fluid cytology did not reveal any malignant findings. The pleural fluid adenosine deaminase level was high at 107.6 U/L. Although Ziehl–Neelsen staining of the pleural fluid yielded negative results, a polymerase chain reaction test of *Mycobacterium TB* (*Mtb*) was positive.

Imaging examinations

Chest CT scan showed an infiltrative shadow in the lower right lobe and increased right pleural effusion (Figure 1C).

FINAL DIAGNOSIS

Pulmonary TB with pleuritis.

TREATMENT

Isoniazid (0.3 g, qd), rifampicin (0.6 g, qd), and ethambutol (0.75 g, qd) were administered. Pyrazinamide was not

administered because of the patient's age and poor vitality at treatment initiation.

OUTCOME AND FOLLOW-UP

The patient's general condition gradually improved and the right pleural effusion decreased due to anti-TB drugs, (Figure 1D). Acid-fast bacterium culture was positive in sputum and pleural fluid and was isoniazid- and rifampicin-susceptible. Two months after the initiation of three-drug therapy, the treatment was switched to two-drug therapy comprising isoniazid and rifampicin for 10 months. After completion of 12 months of TB treatment, careful follow-up has been performed every six months; no flare-ups of chest pain or other symptoms or re-accumulation of pleural effusions have been observed. Careful follow-up was scheduled to be continuously performed for 2 years after completing treatment.

DISCUSSION

An estimated 10.6 million people were ill with TB worldwide in 2022, increasing to 10.3 million in 2021 from 10.0 million in 2020, following a decline between 2010 and 2020[7]. This reversal of progress up to 2020 is thought to reflect the impact of disruption in essential TB services during the coronavirus disease 2019 pandemic worldwide. Whereas some countries have reduced the burden of TB disease to fewer than 10 cases per 100000 people per year, the incidence of TB remains high in low-income countries[7]. Furthermore, in 2022, the total number of deaths caused by TB was 1.30 million globally, and TB remains the second leading cause of death worldwide from a single infectious agent[7].

The characteristics of TB symptoms include prolonged cough, chest pain, weakness or fatigue, weight loss, fever, and night sweats[8]. However, these symptoms are not specific to TB; in many cases, these symptoms do not occur[2], particularly in older individuals, who are less likely to present with classic symptoms of cough, hemoptysis, fever, and night sweats than are younger adults[9]. Although imaging findings of pulmonary TB are characterized by a predominance of upper lobe cavitary and centrilobular nodules, these characteristics are not present in some cases. Furthermore, cases of TB without these radiological findings are also reported[3]. Therefore, TB diagnosis is often delayed because TB can be misdiagnosed as common community-acquired pneumonia. A delayed TB diagnosis leads to delayed initiation of appropriate treatment, resulting in a worsened prognosis and resistance to anti-TB drugs. Furthermore, social problems such as nosocomial and mass infections can occur because of delayed diagnosis. Early diagnosis and prevention of TB spread are critical components of public health strategies. Community-level interventions, such as health promotion activities and educational sessions, can encourage individuals to seek screening and treatment. These activities and sessions have shown some success in increasing detection of TB cases[10].

In the present case, no significant symptoms other than right-sided chest pain were observed at the time of initial examination, and no cavity shadows or centrilobular nodules characteristic of TB were observed on imaging. Furthermore, a sputum test for acid-fast bacilli could not be performed because of poor sputum production and a pleural fluid test was not performed because of the small amount of pleural effusion at the time of initial examination. Bacterial pleurisy was initially diagnosed based on physical and radiological findings, followed by the administration of ampicillin/sulbactam, which resulted in an approximately 3-month delay in establishing a definitive TB diagnosis. In the present case, the submission of sputum smear and culture tests by attempting to induce sputum at the time of initial hospitalization, as well as analysis of gastric fluid specimens and IGRA, could have led to TB diagnosis and avoided the delay in diagnosis caused by the use of ampicillin/sulbactam.

Fluoroquinolones are used to treat community-acquired pneumonia and achieve temporary improvement in TB symptoms, resulting in a delay in the correct diagnosis of TB, further affecting prognosis[5,6]. Additionally, the use of antimicrobial agents other than fluoroquinolones, such as penicillin with beta-lactamase inhibitors and carbapenems, can lead to delayed TB diagnosis due to temporary improvements in symptoms and radiological findings of TB[11,12]. Previous studies have discussed the delayed diagnosis of TB caused using these antimicrobial agents, their direct and partial effects on TB, the possibility that these agents can effectively treat co-infections caused by other bacteria, and the time-consuming process of determining the effectiveness of the prescribed antimicrobials[5]. In the present case, a bacteriological examination could not be submitted at the time of admission 2 months ago, and the possibility that there was co-infection with bacteria other than TB and that ampicillin/sulbactam had an effect on those bacteria cannot be ruled out. Furthermore, clinical findings of TB can improve temporarily depending on various factors such as the patient's immune status, underlying disease, and natural course of TB[13,14]. TB manifests with various clinical conditions in its natural history; approximately 5%–10% of infected people develop active TB[15]. Symptoms and radiological findings of TB are non-specific particularly in older adults, wherein TB diagnosis is more often delayed and mortality is higher[16]. The present case was also an older adult (89-year-old) and was on treatment for diabetes. Factors such as age, immune status, and background disease might have influenced the course of this temporary improvement in TB.

On the other hand, one of the mechanisms by which TB is resistant to beta-lactams is that TB produces beta-lactamases [17,18]. With these researches as a background, the *in vitro* activity of beta-lactam and beta-lactamase inhibitors against TB and their clinical efficacy against multidrug-resistant TB have been reported[19-23]. Even in the present case, the clinical course of the right pleural effusion, in which *Mtb* was subsequently detected, temporally decreased after ampicillin/sulbactam administration, suggesting the possibility that ampicillin/sulbactam was temporarily effective against *Mtb*.

In this case, IGRA at the time of pleurisy relapse showed borderline levels. IGRA is *in vitro* blood test that measures T cell release of interferon-gamma following stimulation by antigens unique to *Mtb* and a few other mycobacteria[24]. IGRA has specificity > 95% for diagnosis of TB infection, since it is not affected by Bacillus Calmette–Guérin vaccination or most nontuberculous mycobacteria[25]. However, human immunodeficiency virus infection, aging, low lymphocyte counts, and the use of immunosuppressive drugs can cause false negatives[26-28]. In this case, the patient was 89-year-old man. This may have been one of the reasons why the IGRA result was inconclusive. If IGRA had been performed at the time of the initial hospitalization, the possibility of TB would have been considered based on the results of the judgment pending; a TB diagnosis could have been made with additional tests such as thoracentesis. In terms of treatment, in this case, given the patient's age of 89, we chose to treat him with isoniazid, rifampicin, and ethambutol rather than pyrazinamide. However, in recent years there have been reports that pyrazinamide regimens can be safely used in older adults, and the use of pyrazinamide was considered an important option[29]. In addition, a 4-month regimen of rifapentine and moxifloxacin has been non-inferior to standard therapy and is expected to become a treatment option in the future[30].

A clinical course that appears to have temporarily improved with treatment other than anti-TB drugs can lead to the assumption that the patient does not have TB, which is disadvantageous. To prevent delayed TB diagnosis, appropriate bacteriological tests should be performed at the initiation of pneumonia treatment. However, difficulty in obtaining samples can occur, as in this case. Therefore, when the condition of patients is improved with antibiotics other than anti-TB drugs while the clinical findings repeatedly worsen or an atypical course of bacterial infection occurs, a reassessment should be performed to determine whether the patients could have TB.

CONCLUSION

TB remains an important differential disease for respiratory tract infections; sometimes it is very difficult to distinguishing it from bacterial pneumonia is sometimes very difficult. As in this case, there are cases of TB wherein it appears that a temporary improvement has been achieved through treatment with antimicrobial agents other than anti-TB drugs due to various factors, such as the patient's immune status and natural course of TB. To prevent delays in TB diagnosis, appropriate sample submissions for bacteriological examination, including testing for acid-fast bacilli, are required before initiating antibiotics in cases of pneumonia. When it is difficult to submit samples at the start of pneumonia treatment, re-evaluation for TB infection is necessary in cases of an atypical course, such as relapse after temporary improvement in pneumonia with antimicrobial agents against common bacteria.

FOOTNOTES

Author contributions: Hara M contributed to conceptualization, data curation, investigation, methodology, resources, supervision, writing–original draft, and writing–review and editing; Yashiro T, Yashiro Y contributed to investigation and writing–review and editing.

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

Conflict-of-interest statement: The authors declare that they have no conflict of interest 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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S-Editor: Liu H
L-Editor: A
P-Editor: Li X

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World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2025 July 6; 13(19): 104148

DOI: 10.12998/wjcc.v13.i19.104148

ISSN 2307-8960 (online)

CASE REPORT

Unexpected finding of cholecystogastric fistula in a patient undergoing laparoscopic cholecystectomy: A case report

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Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C, Grade D, Grade E

Novelty: Grade B, Grade B, Grade D, Grade D

Creativity or Innovation: Grade B, Grade B, Grade C, Grade D

Scientific Significance: Grade B, Grade C, Grade D, Grade E

P-Reviewer: Luthra H; Muñoz RA; Shukla A

Received: December 12, 2024

Revised: February 1, 2025

Accepted: February 20, 2025

Published online: July 6, 2025

Processing time: 97 Days and 23.4 Hours

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Abstract

BACKGROUND

Gallbladder stones are a common occurrence, with a prevalence of approximately 10% in the Pakistani population. A rare but potentially fatal complication of gallstones is cholecystogastric fistulas. The underlying mechanism involves chronic inflammation due to cholelithiasis, causing gradual erosion and eventually leading to fistula formation.

CASE SUMMARY

We present a rare case of a cholecystogastric fistula in a 40-year-old female patient, successfully managed with an open surgical approach. The patient initially presented with a 6-month history of intermittent epigastric pain, nausea, and vomiting, which worsened over time. Laboratory investigations and abdominal ultrasound confirmed cholelithiasis, and laparoscopic cholecystectomy was planned. However, intraoperative findings revealed a cholecystogastric fistula, a rare complication of chronic gallstone disease. Given the dense adhesions between the gallbladder and the stomach, the procedure was converted to an open surgery. The fistula was divided, and a cholecystectomy was performed, along with primary repair of the gastric defect using a double-layer suture and reinforcement with an omental patch. The patient recovered uneventfully and was discharged

on the third postoperative day.

CONCLUSION
This case highlights the importance of considering cholecystogastric fistula in patients with vague gastrointestinal symptoms and chronic cholelithiasis. The report discusses diagnostic challenges, surgical approaches, and a review of the current literature on managing such rare but serious complications of gallstones.

Key Words: Cholecystogastric Fistula, Gallstones, Cholecystectomy, Fistula, Open Surgery, Adhesions; Case report

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Core Tip: A rare and potentially fatal complication of gallstones, cholecystogastric fistulas often present with vague, non-specific symptoms and are commonly diagnosed intraoperatively. Early recognition through imaging, such as computed tomography scans showing pneumobilia and atrophied gallbladder, is crucial for proper surgical planning. The choice between open or laparoscopic surgery and a single-stage or two-stage procedure depends on factors like adhesion severity, surgeon expertise, and patient comorbidities. Early cholecystectomy is essential in preventing complications related to chronic cholecystitis.

Citation: Ali S, Anjum A, Khalid AR, Sultan MA, Noor S, Nashwan AJ. Unexpected finding of cholecystogastric fistula in a patient undergoing laparoscopic cholecystectomy: A case report. *World J Clin Cases* 2025; 13(19): 104148
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/104148.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.104148

INTRODUCTION

Gallbladder stones are a common occurrence, with a prevalence of approximately 10% in the Pakistani population[1]. A rare but potentially fatal complication of gallstones is cholecystogastric fistulas. The underlying mechanism involves chronic inflammation due to cholelithiasis, causing gradual erosion and eventually leading to fistula formation[2]. This process often involves the impaction of gallstones in Hartmann's pouch, which may erode through the gallbladder wall and form a fistula to an adjacent organ. Most cholecystogastric fistulas are discovered unexpectedly during surgery, with a 92.1% incidence of intraoperative diagnosis due to their non-specific clinical presentation[3]. In the context of gallstones, the overall incidence of bilioenteric fistulas varies between 0.15 and 8%[3,4]. These fistulas most commonly occur between the gallbladder and the duodenum (cholecystoduodenal, 77%-90%) or the colon (cholecystocolonic, 8%-26.5%), while the cholecystogastric type is notably rare (approximately 2%)[4].

Imaging techniques such as computed tomography (CT) scans can be used to diagnose bilioenteric fistulas by showing suggestive symptoms like pneumobilia and an atrophied gallbladder[5]. The most commonly employed treatment approach involves surgical intervention, typically cholecystectomy and fistula repair. This can be accomplished through open or laparoscopic surgery[6-8]. The decision to perform a single-stage procedure, which includes stone removal, cholecystectomy, and fistula repair, *vs* a two-stage procedure, where cholecystectomy is delayed, remains a subject of debate[9]. This case report aims to present our experience with a cholecystogastric fistula and provide a comprehensive review of the current literature regarding its presentation, diagnosis, and surgical management.

CASE PRESENTATION

Chief complaints

A 40-year-old female presented with a 6-month history of intermittent epigastric pain, nausea, vomiting, indigestion, and frequent belching. The symptoms were non-specific initially but later became associated with meals. Vomiting became more frequent, occurring two to three times a week, and the pain became more persistent, starting to affect her daily routine.

History of present illness

The patient reported a gradual onset of symptoms over the past 6 months. Initially, the epigastric pain and discomfort were intermittent and non-specific, but gradually, it became increasingly associated with meals. She also had nausea and vomiting, with the latter occurring two to three times a week on average. Additionally, she also noted a sensation of indigestion and frequent belching. These symptoms progressively worsened, leading to significant discomfort and affected her daily activities. Due to the persistence and worsening nature of the symptoms, she sought medical attention for further evaluation.

History of past illness

The patient did not have a history of chronic medical conditions such as diabetes, hypertension, or liver disease. There were no previous surgeries or procedures related to the gastrointestinal system, and there was no prior history of peptic ulcer disease, gastrointestinal bleeding, or chronic pancreatitis. On abdominal ultrasound, the patient was diagnosed with cholelithiasis.

Personal and family history

Gallstones were documented in the patient's mother and maternal aunt in the past.

Physical examination

The patient appeared mildly distressed due to abdominal discomfort but was in no acute distress at rest. Vital signs were stable: Temperature 37.1 °C, blood pressure 120/75 mmHg, heart rate 88 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 98% on room air. On abdominal examination, there was no palpable mass or hepatomegaly; however, there was slight epigastric pain. Murphy's sign was positive, indicating potential gallbladder inflammation. There was no rebound tenderness or guarding, and bowel sounds were normal with no signs of peritoneal irritation. No signs of jaundice or ascites were noted.

Laboratory examinations

Laboratory tests revealed a normal total leukocyte count of 7.1 × 10^9/L, indicating no significant systemic inflammatory response. Liver function tests showed slightly elevated alanine aminotransferase (59 U/L) and aspartate aminotransferase (49 U/L) but normal alkaline phosphatase, gamma-glutamyl transferase, and total bilirubin levels. Since lipase and amylase levels were normal, pancreatitis was ruled out. These findings, the patient's clinical symptoms, and imaging results supported the diagnosis of cholelithiasis without significant active inflammation (Table 1).

Imaging examinations

Figures 1 and 2 show the intraoperative view of the cholecystogastric fistula. The dense adhesions between the gallbladder and the stomach antrum are visible. The fistulous tract is identified during the dissection, confirming the diagnosis of cholecystogastric fistula. This image was taken before the fistula was divided, and a cholecystectomy was performed.

FINAL DIAGNOSIS

The patient was diagnosed with cholecystogastric fistula secondary to cholelithiasis and was confirmed intraoperatively.

TREATMENT

The patient initially underwent elective laparoscopic cholecystectomy, during which a cholecystogastric fistula was identified intraoperatively. The laparoscopic dissection was challenging due to the presence of dense adhesions between the gallbladder, stomach, and surrounding structures, making visualization and safe separation difficult. Attempts at laparoscopic dissection revealed limited working space and significant tissue fibrosis, increasing the risk of inadvertent perforation or injury to adjacent structures. Given these intraoperative challenges, the decision was made to immediately convert to open surgery for better visualization and safer dissection. Upon opening the abdomen, extensive adhesiolysis was required to carefully separate the gallbladder from the stomach without causing additional injury. The fistula tract was found to be thickened and inflamed, necessitating meticulous dissection to avoid excessive bleeding and gastric perforation extension. Following the successful division of the fistula, antegrade dissection of the gallbladder was performed. However, friable tissue and underlying inflammation complicated the closure of the gastric defect. A double-layer suture technique using Vicryl 2.0 was applied to ensure a secure closure. The first layer provided mucosal apposition, while the second layer reinforced serosal integrity, reducing the risk of postoperative leakage.

Additionally, an omental patch was mobilized and sutured over the repair site to enhance healing and minimize tension on the closure. Careful hemostasis was maintained throughout the procedure, and saline irrigation was used to clear any residual bile and prevent contamination. A closed suction drain was placed near the repair site to monitor for any potential leakage or postoperative complications. The patient recovered uneventfully, with no signs of infection or leakage. She was discharged on the third postoperative day with a prescription for analgesics for pain management and a proton pump inhibitor to prevent gastric irritation and discomfort.

OUTCOME AND FOLLOW-UP

At the 10-week follow-up, the patient reported no complications or recurrence of symptoms. She was fully recovered, with no signs of infection or gastrointestinal distress. A repeat abdominal ultrasound confirmed normal findings, and her liver function tests remained normal. The patient was advised to continue with a healthy diet and lifestyle, with regular

Table 1 Laboratory investigations

Test	Result	Normal range
White blood cell count/total leukocyte count	7.1 × 10^9/L	4.0-11.0 × 10^9/L
Hemoglobin	13.7 g/dL	12.0-16.0 g/dL
Platelet count	210 × 10^9/L	150-400 × 10^9/L
Alanine aminotransferase	59 U/L	7-56 U/L
Aspartate aminotransferase	49 U/L	10-40 U/L
Alkaline phosphatase	53 U/L	30-120 U/L
Gamma-glutamyl transferase	61 U/L	10-71 U/L
Total bilirubin	0.7 mg/dL	0.3-1.0 mg/dL

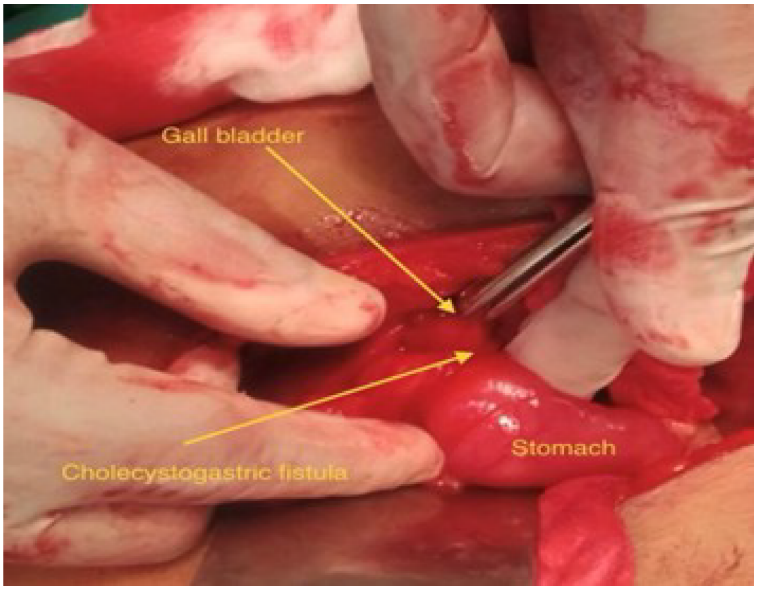

Figure 1 Intraoperative view demonstrating a well-defined cholecystogastric fistula located between the gallbladder's fundus and the stomach's antrum. The fistulous tract appears thickened and inflamed, with dense adhesions between the gallbladder and surrounding tissues.

follow-up visits as needed.

DISCUSSION

Cholecystoenteric fistulas, particularly cholecystogastric fistulas, are a rare but potentially life-threatening complication of chronic cholecystitis caused by gallstones. These fistulas result from chronic inflammation leading to gradual erosion of the gallbladder wall, eventually forming a fistula with adjacent organs, such as the stomach, colon, or duodenum. The incidence of bilioenteric fistulas in patients with gallstones ranges from 0.15% to 8%, with cholecystogastric fistulas accounting for only 2% of cases[2,4]. Diagnosing cholecystogastric fistulas remains challenging due to their non-specific symptoms, which can overlap with other gastrointestinal conditions such as peptic ulcer disease, gastritis, and gastroesophageal reflux disease. Symptoms like epigastric pain, nausea, vomiting, and dyspepsia may be attributed to more common conditions, leading to delays in diagnosis. In many cases, the fistula is only identified intraoperatively, as in our case, where laparoscopic surgery was converted to open surgery due to dense adhesions and unexpected intraoperative findings. Imaging modalities are crucial in detecting bilioenteric fistulas, particularly in patients with long-standing gallstone disease. Ultrasonography is often the first-line imaging modality commonly used to diagnose cholelithiasis. However, it has limited sensitivity in detecting fistulous tracts or complications such as biliary-enteric communications. CT scans, particularly with contrast, are more effective in detecting pneumobilia, atrophied gallbladder, and abnormal communication between the gallbladder and gastrointestinal structures. A CT scan may also reveal thickened gallbladder walls, which suggests chronic inflammation and fibrosis, key contributors to fistula formation[5].

In our case, the diagnosis was made intraoperatively after converting a laparoscopic procedure to open surgery due to dense adhesions. Surgical management typically involves cholecystectomy and repair of the fistula. While both laparoscopic and open surgical approaches are employed, open surgery is preferred in cases with extensive adhesions, as it

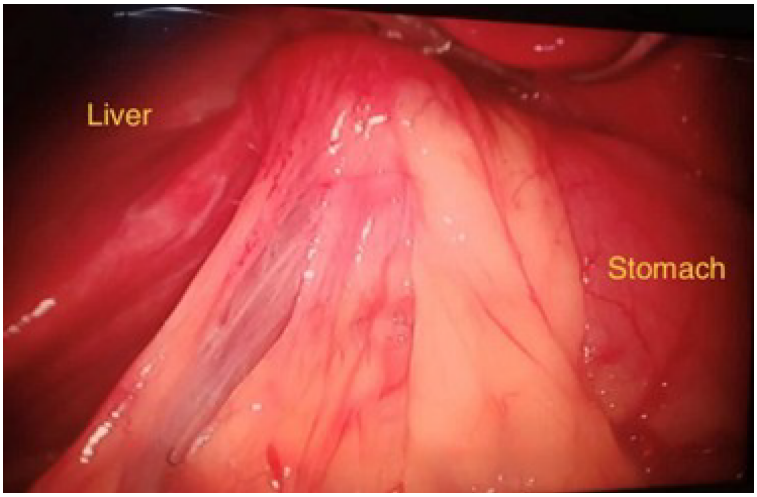

Figure 2 Intraoperative view showing a cholecystogastric fistula covered by omentum. The omental tissue adheres to the fistulous tract, likely as a protective response to chronic inflammation.

provides better visualization and dissection[7]. Some studies, however, report the feasibility of laparoscopic management with minimal conversion rates[7].

A key aspect of managing cholecystogastric fistulas is choosing between a single and two-stage approach. In a single-stage surgery, the fistula is repaired, gallstones are removed, and the cholecystectomy is performed in one operation, generally preferred if the patient's clinical condition allows[9]. The two-stage procedure, where the fistula is first addressed, followed by cholecystectomy at a later date, may be required in cases with extensive inflammation or comorbidities. Both approaches have benefits, but the choice depends on patient factors such as comorbid conditions, surgeon expertise, and the extent of the adhesions and inflammation[9].

Additionally, primary fistula repair using a double-layer closure has been proven effective. An omental patch over the repair can reinforce the closure and reduce the risk of recurrence[10]. In our case, we performed a double-layer closure with Vicryl 2.0 and reinforced it with an omental patch, which resulted in an uneventful recovery.

A study by Aguilar-Espinosa *et al*[11] highlighted that cholecystoenteric fistulas can lead to serious complications such as sepsis, gallstone ileus, and peritonitis, particularly in patients who are in poor general condition. The study emphasizes that prompt diagnosis and surgical intervention are crucial in reducing morbidity and preventing life-threatening complications[11].

In conclusion, cholecystoenteric fistulas should be considered in patients with a prolonged history of vague gastrointestinal symptoms, particularly in the presence of gallstones. Early diagnosis with appropriate imaging, such as CT scans, is crucial for surgical planning. The surgical approach should be tailored to the patient's condition, with open surgery preferred in cases of extensive adhesions. However, laparoscopic repair can be an option in select cases. The decision between single-stage and two-stage surgery should be made based on the clinical condition of the patient and the extent of the fistula.

CONCLUSION

Cholecystogastric fistula, though rare, is a serious complication of chronic cholelithiasis that can present with vague, non-specific symptoms, making diagnosis challenging. In our instance, extensive adhesions led to the shift from laparoscopic to open surgery, and the fistula was discovered intraoperatively. Early diagnosis and appropriate imaging, such as CT scans, are crucial in surgical planning. The degree of adhesions, the patient's clinical state, and the surgeon's experience all influence the decision between single-stage *vs* two-stage surgery and laparoscopic or open surgery. Our patient was successfully repaired with a double-layer closure and omental patch, with no postoperative complications. This case emphasizes the importance of considering cholecystogastric fistula in patients with chronic cholelithiasis with prolonged gastrointestinal symptoms and the need for individualized surgical management.

FOOTNOTES

Author contributions: Sultan MA and Noor S contributed to data curation and methodology; Khalid AR contributed to manuscript writing, editing, and data collection; Ali S and Anjum A contributed to data analysis, resources, and software; Nashwan AJ contributed to conceptualization and supervision. All authors have read and approved the final manuscript.

Informed consent statement: Informed consent has been obtained from the patient.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

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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S-Editor: Liu H
L-Editor: Filipodia
P-Editor: Guo X

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World Journal of Clinical Cases

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World J Clin Cases 2025 July 6; 13(19): 104294

DOI: 10.12998/wjcc.v13.i19.104294

ISSN 2307-8960 (online)

CASE REPORT

Lumbar methicillin-resistant *Staphylococcus aureus* infection caused by a peripherally inserted central catheter: A case report

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Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Ravi AK

Received: December 17, 2024
Revised: January 21, 2025
Accepted: February 18, 2025
Published online: July 6, 2025
Processing time: 89 Days and 18.1 Hours

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Abstract

BACKGROUND

Peripherally inserted central catheters (PICCs) are widely used for administering chemotherapy to breast cancer patients due to their long-term indwelling capability, versatility in drug administration, and flexibility. PICCs infection are a relatively common occurrence, yet there were no reported instances that it can metastasise to the lumbar spine.

CASE SUMMARY

This case report describes a breast cancer patient who developed a methicillin-resistant Staphylococcus aureus lumbar vertebral infection secondary to a PICC-related infection during chemotherapy. Following PICC removal, bacterial culture confirmed the presence of highly virulent methicillin-resistant Staphylococcus aureus. The patient presented with fever and severe lumbar pain. Lumbar magnetic resonance imaging revealed paraspinal muscle edema from L1 to L3 with abnormal signal intensity in the affected regions, suggestive of vertebral osteomyelitis. Prompt initiation of appropriate antibiotic therapy based on the culture results led to significant improvement in the patient's lumbar pain.

CONCLUSION

This case highlights the importance of vigilant infection prevention and control measures to minimize the risk of PICC-related complications, such as bloodstream infections and subsequent metastatic infections.

Key Words: Peripherally inserted central catheter; Methicillin-resistant Staphylococcus aureus infection; Lumbar magnetic resonance imaging; Breast cancer; Chemotherapy;

Case report

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Core Tip: Peripherally inserted central catheters (PICCs) are used for chemo in breast cancer patients because they last a long time, can be used for different drugs, and are flexible. This case report describes a breast cancer patient who developed a methicillin-resistant *Staphylococcus aureus* infection in their spine during chemotherapy. A culture of the wound after removing the PICC showed methicillin-resistant *Staphylococcus aureus*. The patient had a fever and severe back pain. A magnetic resonance imaging showed that the muscles around the lumbar vertebrae were swollen and had an abnormal signal. This is a sign of vertebral osteomyelitis. The patient's pain improved when they started antibiotics based on the culture results. This case shows the importance of infection prevention and control to avoid complications from PICCs.

Citation: Yuan XX, Tan QQ, Chen C, He QQ, Li YN. Lumbar methicillin-resistant *Staphylococcus aureus* infection caused by a peripherally inserted central catheter: A case report. *World J Clin Cases* 2025; 13(19): 104294
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/104294.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.104294

INTRODUCTION

The utilization of peripherally inserted central catheters (PICCs) in breast cancer patients receiving chemotherapy has been shown to effectively reduce the frequency of peripheral venipuncture[1], alleviate patient discomfort, and address the challenges of intravenous (IV) infusion associated with compromised peripheral vascular access[2]. Additionally, PICCs facilitate the administration of multi-cycle chemotherapy regimens, ensuring the uninterrupted progression of treatment. However, inadequate maintenance of PICCs can lead to significant complications, including catheter-related bloodstream infections (CRBSIs), which are relatively common and serious[3]. CRBSIs can be difficult to manage and may result in patient deterioration, potentially progressing to sepsis in severe cases[4]. Therefore, preventing CRBSIs is paramount, and timely treatment is essential once an infection occurs. This case report presents a patient with breast cancer who developed a PICC-related methicillin-resistant *Staphylococcus aureus* (MRSA) lumbar vertebral infection during chemotherapy. The patient was admitted to our hospital for management of these complications. By sharing this clinical case and its management strategies, we aim to provide healthcare professionals with valuable insights to improve vascular access management for breast cancer patients and reduce the incidence of catheter-related infections.

CASE PRESENTATION

Chief complaints

Two weeks after chemotherapy, the patient experienced severe lower back pain, limited mobility and a persistent rise in body temperature for no apparent reason.

History of present illness

The patient was a 63-year-old female who was admitted to our department for the administration of chemotherapy following a surgical procedure for right breast cancer, in addition to the development of a fever.

History of past illness

She underwent a radical mastectomy on the right side of her body, along with breast-conserving surgery and axillary lymph node dissection, at an external medical facility. The postoperative pathological examination revealed the presence of invasive ductal carcinoma (stage II/III), and the intention was to administer chemotherapy drugs for the purpose of treatment. Following a comprehensive evaluation, it was deemed that there were no contraindications to the insertion of a PICC. The procedure was subsequently performed by a PICC specialist nurse under local anaesthesia in the basilic vein of the left upper arm. In an external medical facility, the patient received the chemotherapy regimens paclitaxel liposome + lobaplatin + trastuzumab for injection in the first, second, and third cycles. Subsequently, she completed 10 rounds of whole breast radiation therapy with a tumor absorption dose of 20 Gary. In our medical facility, the patient underwent the fourth cycle of chemotherapy, which consisted of paclitaxel liposome, lobaplatin, and trastuzumab for injection.

Personal and family history

She underwent a radical mastectomy on the right side of her body, along with breast-conserving surgery and axillary lymph node dissection, at an external medical facility. Subsequently, she completed 10 rounds of whole breast radiation therapy with a tumor absorption dose of 20 Gary.

Physical examination

The body temperature was 39.4 °C.

Laboratory examinations

The test results demonstrated the following: The C-reactive protein level was 121 mg/L, the erythrocyte sedimentation rate was 86 mm/hour, the leukocyte count was 7.09 × 10^9/L. The results of the blood culture were as follows: The MRSA infection was classified as "+".

Imaging examinations

The lumbar magnetic resonance imaging (MRI) revealed the presence of edema in the left paraspinal muscle from L1 to L3, accompanied by abnormal internal signals and no evidence of fluid levels.

FINAL DIAGNOSIS

Considering the possibility of lumbar spine infection in conjunction with orthopedic consultation. The results of catheter bacterial culture are consistent with those of blood culture (Table 1).

TREATMENT

Therapeutic interventions included level-I nursing care, lumbar immobilization, and a lumbar elastic bandage. The patient was isolated in a single-patient room with restricted visitation. The room was disinfected with ultraviolet light three times daily per standard protocol. To prevent cross-infection, masks for both the patient and visitors were replaced regularly, among other precautionary measures. Given the patient's critical condition and high dependency, family members were informed of their status and provided regular updates. Vital signs were closely monitored, and laboratory tests, including liver and kidney function tests, complete blood count, and procalcitonin, were performed frequently. Any abnormalities were addressed promptly.

Based on the results of the drug sensitivity test (Table 1), the patient received IV cefazolin sodium 2.5 g twice daily diluted in 100 mL of 0.9% sodium chloride solution. After three days, the patient's fever persisted, and lumbar pain showed no significant improvement. In consultation with the pharmacy department, the treatment regimen was changed to IV vancomycin 0.5 g daily diluted in 100 mL of 0.9% sodium chloride solution, along with oral Xinnuoming and Xinstigmine. The patient's infection symptoms and lumbar pain significantly improved. After two days, the fever resolved, and the lower back pain subsided. The treatment was continued for six days, leading to further improvement in infection and pain. Vancomycin was discontinued, and oral administration of Xinnuoming was continued. During this period, the patient's blood count, biochemistry, and C-reactive protein were monitored twice (Table 2), procalcitonin levels were monitored continuous (Table 3). Vancomycin blood levels and lumbar MRI were assessed once. Additionally, fluid, electrolyte, acid-base balance, and nutritional support were provided. The patient and their family members were educated about the potential causes of lumbar MRSA infection related to PICC placement and the available treatment options for lumbar pain. This was done to alleviate their anxiety and instill confidence in the recovery process. After completing active treatment, the patient's self-care ability improved to moderate dependence, and they were discharged in stable condition.

OUTCOME AND FOLLOW-UP

The patient was readmitted to our department for advanced-stage targeted therapy. They received an IV infusion of 440 mg trastuzumab *via* a disposable needle puncture without complications. A follow-up lumbar MRI was performed. The radiology report indicated resolution of the bilateral psoas abscesses and improvement in the lumbar intervertebral space infection. The patient's self-care ability improved to mild dependence. The patient received monthly targeted therapy at our department, resulting in significant improvement. Initially, the patient experienced severe lower back pain, limiting their mobility. Over time, the pain gradually subsided, and the patient was able to walk independently with assistance. By the third visit, the patient had regained normal mobility and was pain-free. The treatment demonstrated notable efficacy.

DISCUSSION

The factors contributing to the development of MRSA lumbar spine infection during chemotherapy were analyzed in the present study. The patient's compromised immune system, a consequence of cancer treatment, renders them susceptible to external pathogens[5]. Contact with external pathogens can lead to infection, which may extend to the catheter[6]. Skin tissue damage during catheter insertion can trigger inflammatory reactions, compromising the body's defense mechanisms and facilitating bacterial invasion through the bloodstream[7]. Pathogens on the skin's surface may migrate

Table 1 Blood and catheter bacterial culture + drug sensitivity

Sample type	Project application	Result	Antibacterial drugs	Sensitivity	KB (mm), MIC (mg/L)	Cut off point R	Cut off point S
Blood	Bacterial culture + drug sensitivity	*Staphylococcus aureus* (+); MRSA (+)	Penicillin G	R	≥ 0.5	≥ 0.25	≤ 0.12
			Ciprofloxacin	S	1	≥ 4	≤ 1
			Moxifloxacin	S	≤ 0.25	≥ 2	≤ 0.5
			Gentamicin	S	≤ 0.5	≥ 16	≤ 4
			Clindamycin	R	≥ 8	≥ 4	≤ 0.5
			Compound sulfamethoxazole	S	≤ 10	≥ 76	≤ 38
			Linezolid	S	2	≥ 8	≤ 4
			Benzylpenicillin	R	≥ 4	≥ 4	≤ 2
			Levofloxacin	S	0.5	≥ 4	≤ 1
			Vancomycin	S	1	≥ 16	≤ 2
			Erythromycin	R	≥ 8	≥ 8	≤ 0.5
			Tetracycline	S	≤ 1	≥ 16	≤ 4
			Tigecycline	S	≤ 0.12	-	-
			Rifampicin	S	≤ 0.5	≥ 4	≤ 1
Catheter	Bacterial culture + drug sensitivity	*Staphylococcus aureus* (+++); MRSA (+)	Penicillin G	R	≥ 0.5	≥ 0.25	≤ 0.12
			Ciprofloxacin	I	2	≥ 4	≤ 1
			Moxifloxacin	S	≤ 0.25	≥ 2	≤ 0.5
			Gentamicin	S	≤ 0.5	≥ 16	≤ 4
			Clindamycin	R	≥ 8	≥ 4	≤ 0.5
			Compound sulfamethoxazole	S	≤ 10	≥ 76	≤ 38
			Linezolid	S	2	≥ 8	≤ 4
			Quinupristin/dalfopristin	S	≤ 0.25	≥ 4	≤ 1
			Benzylpenicillin	R	≥ 4	-	≤2
			Levofloxacin	S	1	≥ 4	≤ 1
			Vancomycin	S	1	≥ 16	≤ 2
			Erythromycin	R	≥ 8	≥ 8	≤ 0.5
			Tetracycline	S	≤ 1	≥ 16	≤ 4
			Tigecycline	S	≤ 0.12	-	-
			Rifampicin	S	≤ 0.5	≥ 4	≤ 1

KB: Kirby-Bauer (disk diffusion method); MIC: Minimum inhibitory concentration; MRSA: Methicillin-resistant *Staphylococcus aureus*; S: Sensitive; I: Intermediate; R: Resistant.

to the catheter tip along the puncture site[8]. Additionally, contact between the catheter and unsterilized surfaces can introduce bacteria, increasing the risk of catheter-related infections. The deposition of fibrinogen within the PICC catheter creates a favorable environment for microbial growth, promoting bacterial colonization and infection[9].

Aseptic operation techniques were not strictly adhered to by specialist nurses during PICC catheter insertion, and the puncture site and surrounding area were not adequately disinfected[10]. When changing the PICC dressing, aseptic principles were not followed, and a dislodged catheter was reinserted without proper sterilization[11]. Furthermore, PICC flushing and locking with prefilled 10 mL normal saline syringes using a pulsatile method before and after drug administration were performed without adhering to sterile techniques, and the catheter outlet site was not repaired using sterile methods[12].

Table 2 Blood count, biochemistry, and C-reactive protein were monitored twice

Report date	Report item name	Result	Normal reference value
Blood count			
During treatment	White blood cell count (10^9/L)	12.10	3.50-9.50
	Neutrophil (%)	77.5	40.0-75.0
	Lymphocyte (%)	11.6	20.0-50.0
	Monocyte (%)	10.7	3.0-10.0
	Eosinophil (%)	0.1	0.4-8.0
	Absolute neutrophil count (10^9/L)	9.38	1.80-6.30
	Absolute monocyte count (10^9/L)	1.30	0.10-0.60
	Absolute eosinophil count (10^9/L)	0.01	0.02-0.52
	Red blood cell count (10^{12}/L)	2.94	3.80-5.10
	Hemoglobin level (g/L)	94	115-150
	Hematocrit (%)	26.7	35.0-45.0
After treatment	White blood cell count (10^9/L)	9.58	3.50-9.50
	Neutrophil (%)	85.6	40.0-75.0
	Lymphocyte (%)	8.8	20.0-50.0
	Eosinophil (%)	0.2	0.4-8.0
	Absolute neutrophil count (10^9/L)	8.20	1.80-6.30
	Absolute lymphocyte count (10^9/L)	0.84	1.10-3.20
	Red blood cell count (10^{12}/L)	2.80	3.80-5.10
	Hemoglobin level (g/L)	90	115-150
	Hematocrit (%)	27.3	35.0-45.0
Biochemistry			
Pre-treatment	Emergency K test (mmol/L)	4.49	3.6-5.0
	Emergency Na test (mmol/L)	134.8	137-145
	Emergency CI test (mmol/L)	97.7	98.0-107.0
	Emergency Ca test (mmol/L)	1.96	2.1-2.55
	Emergency CO2-CP test (mmol/L)	28	22.0-30.0
	Emergency blood glucose test (mmol/L)	7.30	3.6-5.8
	Emergency creatinine test (μmol/L)	58.10	20-110
	Emergency urea nitrogen test (mmol/L)	4.1	2.5-6.1
	Emergency aspartate aminotransferase test (U/L)	29	17-59
During treatment	Emergency UA test (μmol/L)	236	143-440
	Emergency K test (mmol/L)	4.64	3.5-5.5
	Emergency Na test (mmol/L)	135.4	135-150
	Emergency Cl test (mmol/L)	104.5	95-115
	Emergency Ca test (mmol/L)	2.16	2.08-2.60
	Emergency CO2-CP test (mmol/L)	24.6	21.0-31.0
	Emergency glucose test (mmol/L)	5.74	3.90-6.10
	Emergency creatinine test (μmol/L)	71	45-115
	Emergency urea nitrogen test (mmol/L)	5.0	2.6-8.3
	Emergency AG test (mmol/L)	10.94	6.00-22.00

	Emergency osmolality test (mmol/L)	285.8	280-320
	Emergency phosphorus test (mmol/L)	1.14	0.81-1.55
CRP			
During treatment	CRP (mg/L)	63.20	0-8
After treatment	CRP (mg/L)	28.40	0-8

K: Potassium; Na: Sodium; CI: Chloride; Ca: Calcium; CO2-CP: Carbon dioxide combining power; UA: Uric acid; AG: Anion gap; CRP: C-reactive protein.

Table 3 Procalcitonin levels were monitored continuous

Report item name	Result	Normal reference value
PCT (ng/mL)	7.31	0-0.05
	1.29	
	0.48	
	0.23	
	0.1	
	0.07	

PCT: Procalcitonin.

Building on our analysis of the causes of PICC CRBSIs, it is recommended that if a patient presents with systemic symptoms such as fever and altered blood count following catheter insertion, especially if *Staphylococcus aureus*, a common pathogen in CRBSIs, is isolated, a diagnosis of PICC catheter-related infection should be considered, and the catheter should be promptly removed[13]. In this case, the patient was diagnosed with a PICC CRBSI based on bacterial culture results. The infection had disseminated hematogenously to the adjacent paraspinal muscles. Furthermore, pre-existing lumbar spine lesions may have contributed to secondary lumbar infection, manifesting as fever and lower back pain.

The surrounding environment and all surgical equipment must be rigorously disinfected. Preoperatively, the area should be exposed to ultraviolet light for 30 minutes, and personnel should avoid walking or cleaning the floor near the operating area[14]. Surgical staff must wear sterile gloves, hats, and masks, and clean the arm where the PICC line will be inserted with 75% alcohol followed by iodine disinfection[15]. A strict aseptic technique must be maintained throughout the PICC insertion procedure. Additionally, the selected PICC catheter should have a smooth surface, high quality, and good biocompatibility to minimize vascular wall damage and infection risk[16]. Nurses should educate patients and their families on the importance of catheter care, including proper catheter protection and timely dressing changes. Upon the insertion of a PICC catheter, the implementation of compulsory follow-up protocols has demonstrated substantial efficacy. Regular alterations of the dressing represent a fundamental component of this follow-up regimen. Such dressing changes are to be executed at predetermined intervals, commonly every seven days or in accordance with the specific protocol of the institution. In conjunction with dressing changes, the persistent surveillance of potential infections is critical. This entails vigilant monitoring of the patient's body temperature, as an abrupt rise may signify an incipient infection. The regular performance of blood tests, including the assessment of white blood cell counts and C-reactive protein levels, is mandatory. Should any irregularities be identified, immediate initiation of further diagnostic measures, such as blood cultures, is required. The catheter should be removed promptly once treatment goals are achieved to minimize indwelling time[17]. Implementing effective infection prevention strategies is crucial to reduce the risk of PICC-related bloodstream infections.

CONCLUSION

PICC has the advantages of long indwelling time, suitability for a wide range of infusion drugs, good catheter elasticity and no impact on quality of life. In the chemotherapy cycle of breast cancer patients, it is one of the most important lifelines. Therefore, good catheter maintenance and reducing the incidence of PICC infections are important health measures. If a PICC catheter infection occurs, it should be removed immediately and anti-infection treatment should be given. If there are secondary lesions in other parts, they should be detected in time, and psychological care for patients and their relatives should be done well to reduce patients' nervousness and anxiety. Reduce patient suffering in addition to the disease and avoid medical disputes.

FOOTNOTES

Author contributions: Yuan XX and Li YN study conception and drafted the manuscript; Yuan XX and Tan QQ contributed equally to this article, they are the co-first authors of this manuscript; Tan QQ and Chen C contributed data acquisition to the manuscript; He QQ contributed critical revisions to the manuscript; He QQ and Li YN contributed equally to this article, they are the co-corresponding authors of this manuscript; and all authors have read and approved the final manuscript.

Supported by the Shandong Province Medical and Health Technology Development Plan, No. 202204011069.

Informed consent statement: Written informed consent was obtained from the patients/their parents for the publication of this case report.

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

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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Country of origin: China

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S-Editor: Bai Y
L-Editor: A
P-Editor: Zhang XD

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World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2025 July 6; 13(19): 104400

DOI: 10.12998/wjcc.v13.i19.104400

ISSN 2307-8960 (online)

CASE REPORT

Diced cartilage in capsula based on diced cartilage in fascia technique: A case report

Henri Stephan, Hady Rihani, Elie Dagher, Jad El Choueiri

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade B

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade C

P-Reviewer: Jin H; ROY M

Received: December 19, 2024

Revised: February 3, 2025

Accepted: February 18, 2025

Published online: July 6, 2025

Processing time: 90 Days and 8.3 Hours

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Abstract

BACKGROUND

The Turkish Delight technique, initially described by Erol in 2000, involves the use of diced cartilage wrapped in oxidized cellulose (Surgicel™) for nasal grafting in secondary rhinoplasty.

CASE SUMMARY

This paper presents a novel adaptation called Diced Cartilage in Capsula, where diced cartilage is wrapped in the periprosthetic capsule material formed from a previous breast augmentation procedure instead of fascia, a technique based on the Diced Cartilage in Fascia method. Utilizing autologous, biocompatible material minimizes foreign body reactions and enhances graft integration. This innovative approach demonstrates the potential for specific practices in cosmetic surgery by optimizing patient-specific resources and improving surgical outcomes.

CONCLUSION

The report compares traditional Turkish Delight applications with this new method, discussing biocompatibility, technique efficacy, and benefits in rhinoplasty.

Key Words: Diced Cartilage in Capsula; Diced Cartilage in Fascia; Turkish delight; Periprosthetic capsule; Rhinoplasty; Case report

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Core Tip: This study introduces the Diced Cartilage in Capsula (DCIC) technique, an innovative adaptation of the Diced Cartilage in Fascia method. By utilizing periprosthetic capsule material instead of fascia, DCIC offers a biocompatible, autologous alternative for nasal dorsum augmentation in rhinoplasty. This approach minimizes foreign body reactions, reduces additional donor site morbidity, and enhances graft integration. The technique is particularly valuable in patients undergoing concurrent breast implant revision surgery, offering a novel way to repurpose biological material for improved surgical outcomes.

Citation: Stephan H, Rihani H, Dagher E, El Choueiri J. Diced cartilage in capsula based on diced cartilage in fascia technique: A case report. *World J Clin Cases* 2025; 13(19): 104400
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/104400.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.104400

INTRODUCTION

Secondary septorhinoplasty requires a large amount of tissue, and autogenous costal cartilage is one type of grafting material that can be used in this case[1-3]. The innovation of the "Turkish Delight" technique by Erol[4] in 2000 marked a significant advance in rhinoplasty, particularly in the use of diced cartilage wrapped in oxidized cellulose (Surgicel™) for nasal grafting. This method was distinguished by its adaptability and efficacy in addressing both aesthetic and structural deficiencies of the nasal framework. Several other techniques are also available[5-7], but building upon this technique in particular, the Diced Cartilage in Fascia (DCIF) method introduced the use of fascia from the rectus abdominis or temporalis fascia as a wrapping material[8].

In this case presentation, we introduce a further evolution of this technique, termed Diced Cartilage in Capsula (DCIC), where diced cartilage is wrapped in periprosthetic capsule material harvested from a previous breast augmentation mastopexy. This innovative approach leverages autologous, biocompatible material, potentially reducing the risk of foreign body reactions and enhancing graft integration while minimizing surgical scarring by eliminating the need for additional donor site harvesting[4]. This approach not only maintains the volume and shape of the graft but also minimizes complications such as visibility and palpability post-surgery. This simple technique is indicated for patients requiring various rhinoplasty procedures with dorsum augmentation, including primary, revision, or post-traumatic cases, in combination with revision breast surgery or in patients with breast implants requiring rib grafts.

CASE PRESENTATION

Chief complaints

This case involves a 42-year-old healthy female patient with no known history of food or drug allergies and no history of smoking or alcohol consumption.

History of present illness

She presented for a revision rhinoplasty to address nasal deformities, including pollybeak deformity, a droopy tip with alar notching, and an over-resected bony dorsum (Figure 1). She was also dissatisfied with the results of her breast surgery due to lateral displacement of the implants and bilateral breast bottoming out.

History of past illness

Prior to presentation, the patient had undergone rhinoplasty elsewhere 10 years ago and an augmentation mastopexy with retropectoral 275cc full-profile nanotextured Motiva implants 3 years ago.

FINAL DIAGNOSIS

Given these concerns, we decided to combine the secondary rhinoplasty with the breast revision in the same surgery under general anesthesia.

TREATMENT

During the breast revision surgery, a 4 cm × 4 cm fragment of the periprosthetic capsule was harvested, along with a rib graft from the right 5th rib. A novel technique called DCIC was employed for nasal dorsum augmentation. This technique aims to augment the nasal dorsum while minimizing the risk of graft warping or visibility.

Figure 1 View photos of the patient before and after surgery. A: Pre-operative side view photos of the patient; B: Post-operative (6 months) side view photos of the patient; C: Pre-operative three-quarter view photos of the patient; D: Post-operative (6 months) three-quarter view photos of the patient.

The surgical procedure began with a revision mastopexy with implant exchange. A right submammary fold incision was made, and the periprosthetic capsule was identified. The intact implant was removed. A 4 cm × 4 cm fragment of the capsule was harvested and defatted. The cartilage of the right 5th rib was identified and meticulously dissected in a subperichondrial plane (Figure 2A). The entire rib cartilage was harvested (Figures 3 and 4). A Valsalva maneuver was performed to confirm the absence of a pleural injury. The perichondrium was approximated using Vicryl 2/0 simple sutures, and the pectoralis muscle aponeurosis was sutured. The retropectoral implant pocket was reduced laterally on both breasts, and new Mentor textured (Siltex) 325cc Xtragel high-profile implants were inserted. An inverted-T mastopexy was then performed.

The rhinoplasty began with reopening the previous incision, followed by meticulous dissection of the nasal structures. Supratip fibrosis was excised, excess upper lateral cartilage was trimmed, and anterior septal resection was performed to correct the pollybeak deformity. A septal cartilage graft was harvested, ensuring a residual 15 mm L-strut was preserved for structural integrity. The harvested rib cartilage was then carefully sculpted (Figure 2B) into multiple lamellae. Bilateral extended spreader grafts were sutured in place. A columellar strut was introduced between the spreader grafts and sutured to them (Figure 5), providing strong tip support and preventing future tip deviation.

The intermediate crura of the alar cartilages were found to be interrupted. The medial crura were shortened to decrease tip projection and were sutured to the columellar strut. Bilateral underlay septal cartilage grafts were placed to strengthen the lateral crura. The medial crura were sutured to the lateral crura bilaterally. A dome equalizing suture with a 5/0 Prolene suture was performed. This tip modification strengthens the tip, decreases projection, and enhances rotation, all while being covered with thick fibrotic skin.

The capsular fragment was sutured together over a 1 cc syringe in a tube-like fashion (Figure 2C) using Vicryl Rapide 4/0. The remaining rib cartilage was diced into very small fragments (Figure 2A) and introduced into the capsular tube, which was then sealed with Vicryl 4/0 Rapide sutures (Figure 2D). The DCIC graft was inserted over the nasal bones and stabilized with a transcutaneous Prolene 5/0 suture over a tulle gras gauze (Figure 6A). This technique provides dorsal augmentation and straightens the nasal dorsum (Figure 6).

Bilateral alar contour grafts were placed to reduce alar rim notching. The columellar skin was closed using nylon 6/0, and the mucosa was sutured with Vicryl Rapide 5/0. Packing remained in place for 48 hours, and the nasal splint, columellar sutures, and Prolene suture were removed after eight days.

OUTCOME AND FOLLOW-UP

At 12 months follow-up, the patient has tolerated the surgery very well, showing no signs of complications in the nasal or chest region. There were no breathing difficulties, nasal irregularities, or chest-related symptoms, further reinforcing the suitability of the DCIC technique.

DISCUSSION

We present a case of the DCIC technique, in which the DCIF technique was modified by using periprosthetic capsule material from a previous breast augmentation mastopexy instead of fascia from the rectus abdominis or temporalis[8].

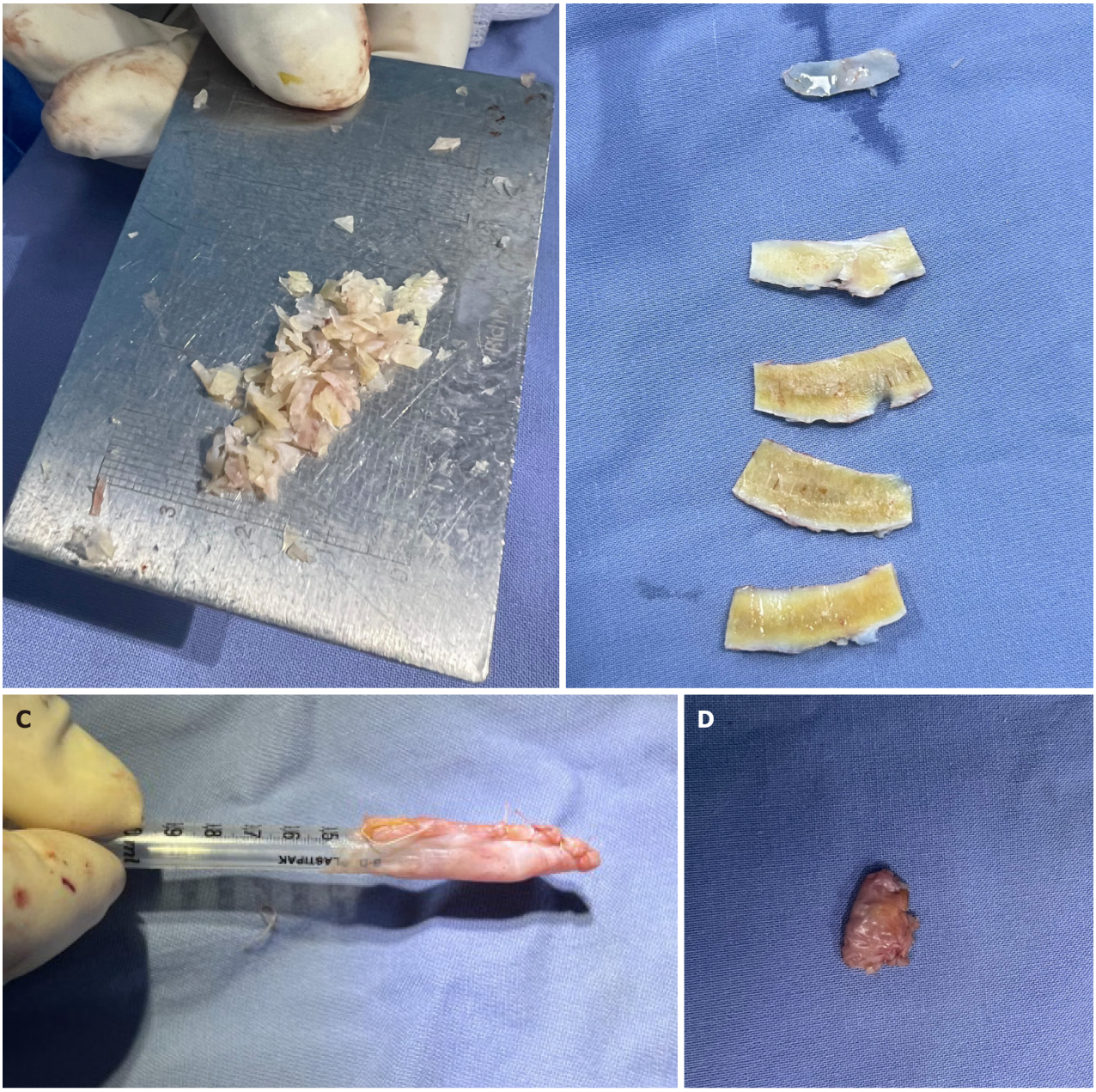

Figure 2 Preparation of cartilage and capsule. A: Diced cartilage; B: Rib cartilage sculpted in lamellaes; C: Part of capsule prepared; D: Capsule wrapping diced cartilage.

This patient, who had undergone breast augmentation mastopexy three years prior, required revisional surgery due to lateral displacement of the implants and breast asymmetry. This circumstance provided an opportunity to use the capsular material as a novel graft wrapper[9].

The use of alternative materials, such as deep temporalis fascia and rectus abdominis aponeurosis, has been explored in other rhinoplasty techniques. These materials serve similar purposes in providing a structural and aesthetic framework for nasal grafts. However, the innovative use of breast capsular material in this context not only repurposes biological waste but also reduces scarring by minimizing the need for additional donor site harvesting.

Using this autologous material, which is naturally biocompatible, offers a unique approach to enhancing graft integration and minimizing foreign body reactions.

At the 12-month follow-up, the patient had tolerated the surgery very well, showing no signs of complications in the nasal or chest regions. There were no breathing difficulties, nasal irregularities, or chest-related symptoms, further reinforcing the suitability of the DCIC technique. Additionally, a comparison between DCIC and traditional methods (DCIF and Turkish Delight) showed a comparable healing time to DCIF but faster healing than the traditional Turkish Delight method, likely due to the biocompatibility of the periprosthetic capsule. The reduced warping, visibility, and palpability in DCIC compared to DCIF suggests superior patient outcomes in dorsum contouring and structural support. The well-vascularized nature of this tissue might enhance graft integration, promoting quicker healing and better overall outcomes. Using DCIC eliminates the risk of graft warping, provides a smoother dorsum contour, minimizes visibility and palpability, and eliminates the need for additional donor site harvesting. The capsule's biocompatibility and the

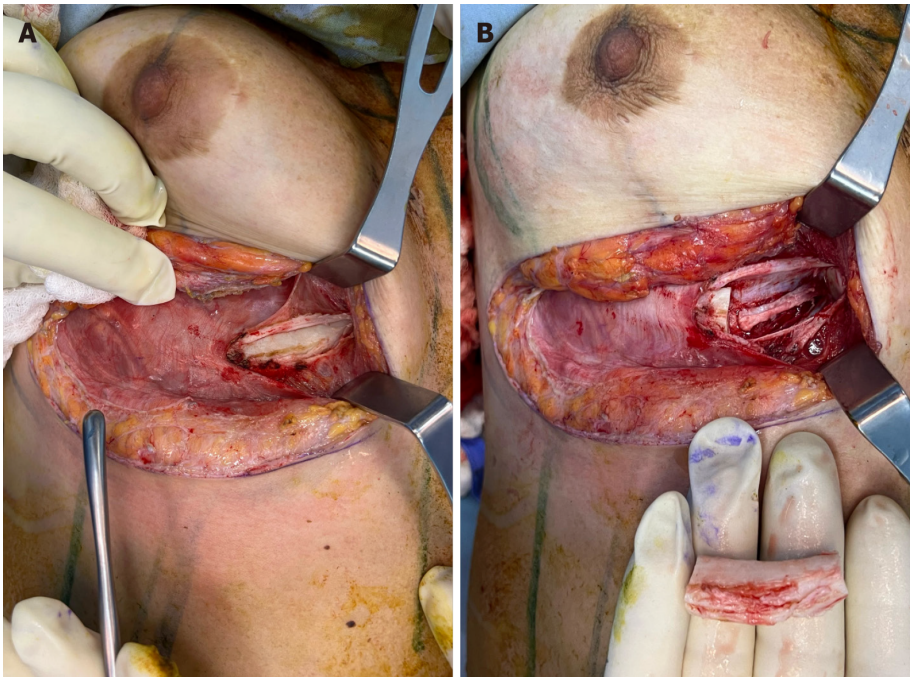

Figure 3 Approach to the fifth rib cartilage *via* inframammary fold incision. A: Before removal of right 5th rib cartilage; B: After removal of right 5th rib cartilage.

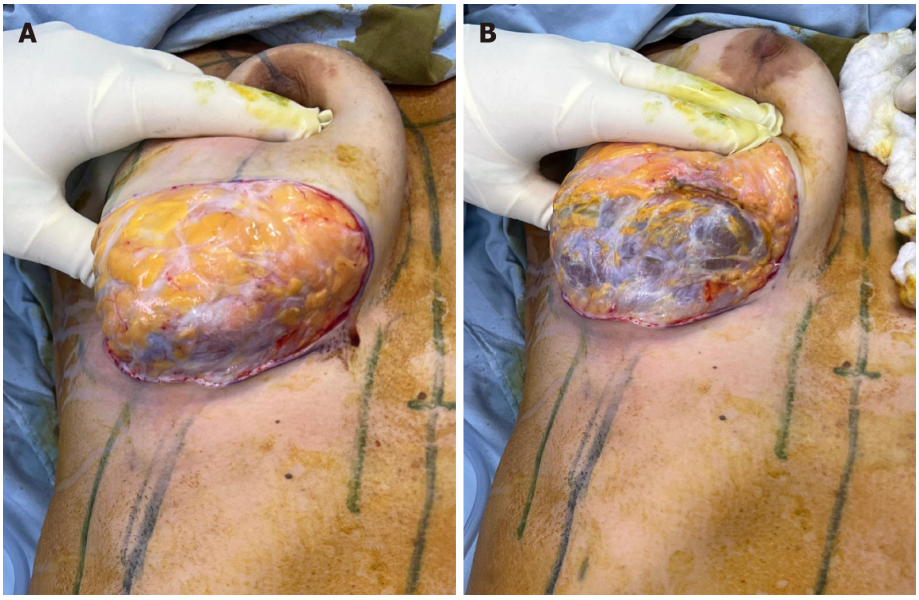

Figure 4 Exposure of breast implant capsule. A: Exposure of the breast implant capsule with surrounding fibrotic tissue; B: Removal of the breast implant capsule, revealing its internal structure.

absence of reactive inner tissue further minimize the risk of complications, such as inflammation and infection.

However, it is important to note that the application of this technique is limited to specific cases, particularly those involving patients undergoing concurrent revision breast implant surgery and rhinoplasty, as demonstrated in our case. The DCIC technique adds a new tool to our surgical armamentarium, applicable in selected cases.

Potential complications include graft rejection, though this risk remains minimal due to the autologous nature of the capsule. Infection rates appear to be lower compared to synthetic materials, and material resorption is limited due to the stability of encapsulated cartilage. Fibrosis is comparable to fascia-based techniques but without additional donor site morbidity.

However, it is essential to recognize that this study presents a single case report of an innovative technique. Larger, prospective studies comparing DCIC to traditional methods are needed to establish its efficacy and potentially refine and develop the technique further.

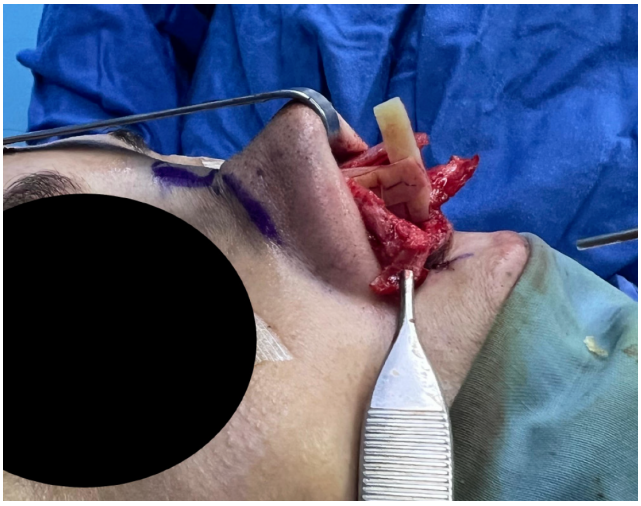

Figure 5 Columellar strut fixed to the extended spreader grafts.

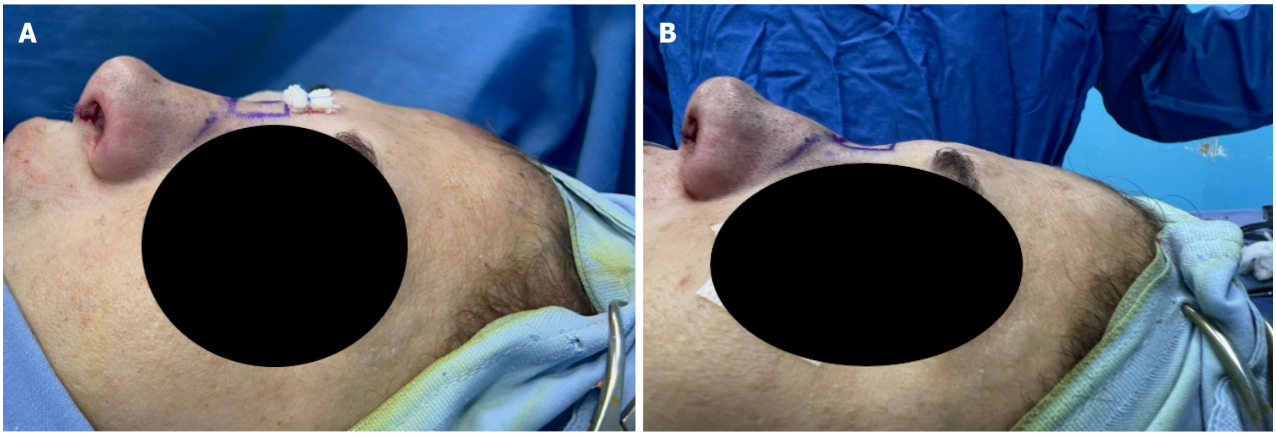

Figure 6 Before and after introducing capsular-wrapped diced cartilage. A: After introducing the capsular-wrapped diced cartilage; B: Before introducing capsular-wrapped diced cartilage.

CONCLUSION

This case highlights the innovative adaptation of the Turkish Delight technique through the DCIC method, which utilizes periprosthetic capsular material. Our findings suggest that using autologous materials, such as the breast capsule, offers significant advantages in biocompatibility and graft integration, with no complications observed at six months postoperatively. A comprehensive meta-analysis indicates that the most common long-term complications of diced cartilage grafts in rhinoplasty include infection (4.5%) and visible irregularity (5.3%), with a 5.3% revision surgery rate[10]. The DCIC technique, which utilizes readily available autologous material, could potentially reduce these complication rates and improve long-term outcomes in rhinoplasty. This adaptation underscores the importance of innovation in surgical practices, particularly in cosmetic surgery, where patient-specific characteristics and previous surgical histories can be transformed into opportunities for improved outcomes.

FOOTNOTES

Author contributions: Stephan H generated the idea of the study and treated the patient; Rihani H and Dagher E performed the research and designed the study; El Choueiri J analyzed the data and revised the manuscript; all authors contributed to writing the manuscript.

Informed consent statement: Informed consent has been obtained from the patient for this paper.

Conflict-of-interest statement: The authors declare absence of any conflict of interest.

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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S-Editor: Lin C
L-Editor: Filipodia A
P-Editor: Guo X

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World Journal of Clinical Cases

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World J Clin Cases 2025 July 6; 13(19): 102484

DOI: 10.12998/wjcc.v13.i19.102484

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Innovative approaches to managing chronic multimorbidity: A multidisciplinary perspective

Haewon Byeon

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade B, Grade C, Grade C

Novelty: Grade A, Grade B, Grade C, Grade C

Creativity or Innovation: Grade B, Grade B, Grade C, Grade C

Scientific Significance: Grade B, Grade B, Grade C, Grade C

P-Reviewer: Arumugam VA; Liaqat N; Wu ZX

Received: October 21, 2024

Revised: February 13, 2025

Accepted: February 25, 2025

Published online: July 6, 2025

Processing time: 150 Days and 3 Hours

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Abstract

The rising prevalence of chronic multimorbidity poses substantial challenges to healthcare systems, necessitating the development of innovative management strategies to optimize patient care and system efficiency. The study by Fontalba-Navas *et al* investigates the implementation of a novel high complexity unit (HCU) specifically designed to improve the management of patients with chronic complex conditions. By adopting a multidisciplinary approach, the HCU aims to provide comprehensive, patient-centered care that enhances health outcomes and alleviates the strain on traditional hospital services. Utilizing a longitudinal analysis of data from the Basic Minimum Data Set, this study compares hospitalization metrics among the HCU, Internal Medicine, and other departments within a regional hospital throughout 2022. The findings reveal that the HCU's integrated care model significantly reduces readmission rates and boosts patient satisfaction compared to conventional care practices. The study highlights the HCU's potential as a replicable model for managing chronic multimorbidity, emphasizing its effectiveness in minimizing unnecessary hospitalizations and enhancing the overall quality of patient care. This innovative approach not only addresses the complexities associated with chronic multimorbid conditions but also offers a sustainable framework for healthcare systems confronting similar challenges.

Key Words: Chronic multimorbidity; High complexity unit; Multidisciplinary approach; Patient-centered care; Integrated care model; Hospitalization metrics

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Core Tip: Fontalba-Navas *et al*'s study analyzes a high complexity unit (HCU) designed to tackle chronic multimorbidity through a multidisciplinary, patient-centered approach. The HCU's integrated care model significantly improves health outcomes, reduces readmission rates, and enhances patient satisfaction, as evidenced by longitudinal data from the Basic Minimum Data Set. This innovative framework alleviates the strain on traditional healthcare services by minimizing unnecessary hospitalizations and improving care quality. The HCU serves as a replicable model for healthcare systems facing similar challenges, offering a sustainable strategy for managing the rising prevalence of chronic multimorbidities and optimizing healthcare delivery.

Citation: Byeon H. Innovative approaches to managing chronic multimorbidity: A multidisciplinary perspective. *World J Clin Cases* 2025; 13(19): 102484
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/102484.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.102484

TO THE EDITOR

Chronic diseases pose a significant challenge to global healthcare systems, affecting millions and straining resources due to their persistent and often debilitating nature[1]. Recent studies have shown that chronic diseases are responsible for over 70% of all deaths worldwide, highlighting their impact on global health[2]. Conditions such as diabetes, hypertension, chronic obstructive pulmonary disease, and heart failure are increasingly prevalent, exacerbated by aging populations and lifestyle-related risk factors[3]. The World Health Organization projects that the prevalence of these conditions will continue to rise, further complicating healthcare delivery and burdening economic resources[4]. Addressing these diseases is of paramount importance for both medical professionals and public health policymakers.

Patients with complex chronic conditions frequently experience multiple comorbidities, which complicate their management and result in increased healthcare utilization. Comorbidity, the presence of multiple simultaneous chronic conditions, requires a comprehensive and coordinated approach to care. This complexity often leads to fragmented healthcare delivery, increased risk of medication interactions, and frequent hospital admissions. Effective management of these patients necessitates a shift towards a patient-centered model of care[5,6]. This involves engaging patients actively in their treatment plans, promoting self-care education, and ensuring cohesive communication across healthcare providers[7]. Such an approach is crucial for reducing hospital readmissions and improving overall patient outcomes.

In this context, the recent study by Fontalba-Navas *et al*[8] introduces the high complexity unit (HCU) as an innovative model designed to meet the intricate needs of patients with complex chronic diseases. The HCU focused on providing comprehensive, multidisciplinary care aimed at preventing unnecessary hospitalizations and mitigating the adverse effects associated with extended hospital stays[8]. By prioritizing personalized care strategies and fostering strong coordination among healthcare professionals, the HCU sought to enhance patient and caregiver experiences[8].

The HCU is distinguished by its emphasis on individualized care, low staff-to-patient ratios, and integration of multidisciplinary expertise. It prioritizes the continuity of care, particularly during the transition from hospital to home, and incorporates comprehensive evaluations to track patient progress. This model not only addresses the clinical needs of patients but also supports caregivers through targeted interventions and resource management.

Managing complex chronic patients effectively remains a daunting task for modern health systems, demanding substantial resources and meticulous coordination of care. The HCU represents a transformative approach, offering a specialized framework that prioritizes personalized treatment and seamless care transitions. This editorial explores the operational procedures within the HCU and underscores the importance of a stratified, multidisciplinary strategy in achieving optimal patient outcomes and satisfaction.

Theoretical background: A patient-centered approach to treating chronically ill patients

The management of chronic diseases has increasingly shifted towards a patient-centered approach[7], recognizing the importance of individualized care that respects and responds to the unique preferences, needs, and values of each patient. This paradigm is particularly crucial in the context of chronic conditions, where long-term management and patient engagement are essential for effective care.

Patient-centered care emphasizes the active involvement of patients in their own healthcare decisions, promoting shared decision-making between patients and healthcare providers[8]. This approach not only enhances patient satisfaction but also improves adherence to treatment plans, as patients are more likely to commit to therapies they have helped design and understand. Previous research[9,10] has shown that when patients are actively engaged in their care, they experience better health outcomes, reduced hospitalizations, and improved quality of life.

In the realm of chronic disease management, patient-centered care involves a comprehensive assessment of individual patient needs, including medical, psychological, and social aspects[11]. This holistic view allows healthcare providers to tailor interventions that address the entire spectrum of factors affecting a patient's health. Such strategies may include personalized medication plans, lifestyle modifications, and psychosocial support, all coordinated through a multidisciplinary team approach[12].

Furthermore, patient-centered care encourages the use of technology to enhance communication and information sharing. Tools such as electronic health records, patient portals, and telemedicine platforms facilitate continuous

interaction between patients and providers, ensuring timely updates and adjustments to care plans[13]. These technologies empower patients by providing them with easy access to their health information and the ability to engage with their care teams remotely.

The implementation of patient-centered care models, like those in HCU, demonstrates the potential for transforming chronic disease management. By focusing on the unique needs of each patient and fostering a collaborative care environment, these models not only improve clinical outcomes but also enhance the overall healthcare experience for patients and their families[14]. As healthcare systems continue to evolve, the integration of patient-centered practices will be pivotal in addressing the growing burden of chronic diseases.

Effects on HCU in chronic patients

HCU have emerged as an innovative response to the intricate challenges posed by chronic patients with multifaceted health needs[15]. These specialized units are designed to provide comprehensive, multidisciplinary care tailored specifically to individuals with complex chronic conditions, who often require intensive, coordinated management strategies.

The primary objective of HCUs is to mitigate the burden of chronic diseases by preventing unnecessary hospitalizations, minimizing the risk of complications, and enhancing overall patient outcomes[16]. By integrating a broad spectrum of healthcare professionals, including physicians, nurses, social workers, and allied health specialists, HCUs facilitate a holistic approach to patient care. This multidisciplinary collaboration ensures that all aspects of a patient's health—medical, psychological, and social—are addressed in a cohesive manner.

Previous research[17] has demonstrated that HCUs significantly improve clinical outcomes for chronic patients. These units reduce hospital readmission rates by implementing proactive management strategies and individualized care plans that are continuously monitored and adjusted as necessary[18]. The presence of dedicated care teams within HCUs allows for rapid identification and response to changes in a patient's condition, thereby preventing the escalation of health issues that could lead to acute care interventions.

Moreover, HCUs emphasize the importance of continuity of care, particularly during transitions between hospital and home[19]. This seamless transition is facilitated through comprehensive discharge planning and follow-up care, which are integral components of the HCU model. Patients and their caregivers are educated and supported throughout the process, ensuring that they are well-prepared to manage chronic conditions independently.

The impact of HCUs extends beyond clinical outcomes, contributing to improved patient satisfaction and quality of life. By fostering a patient-centered environment that prioritizes individualized attention and respect for patient preferences, HCUs empower patients to take an active role in their healthcare journey[20]. Additionally, the supportive framework of HCUs alleviates the caregiving burden, providing families with the resources and guidance needed to navigate complex healthcare landscapes.

As healthcare systems continue to grapple with the rising prevalence of chronic diseases, the role of HCUs becomes increasingly vital. These units exemplify how strategic resource allocation and a focus on coordinated care can transform the management of chronic patients, ultimately leading to more sustainable and effective healthcare delivery models. A review of previous studies[21-31] on the effectiveness of high-complexity units for chronic patients is presented in Table 1.

Key findings

The study conducted by Fontalba-Navas *et al*[8] provides an in-depth analysis of the HCU and its effectiveness in managing patients with complex chronic conditions. Utilizing a descriptive longitudinal approach, the research compares hospitalization variables among the HCU, the Internal Medicine Service, and other services at Antequera Hospital. Firstly, the HCU demonstrated a substantial reduction in avoidable hospital stays, with 310.56 days recorded compared to 3568.6 days by the Internal Medicine Service, underscoring the unit's efficiency in preventing unnecessary admissions. Secondly, patients in the HCU had an average of 13.72 diagnoses each, exceeding the 10.47 in Internal Medicine and 7.51 in the general hospital, highlighting the unit's capacity to handle more complex and multipathological cases. Thirdly, the HCU averaged 1.89 procedures per patient, a strategic reduction compared to 2.78 in Internal Medicine and 2.39 in the hospital overall, reflecting a more focused and patient-centered selection of interventions. This approach contributes to more efficient resource utilization. Additionally, the HCU's efficiency is further illustrated by its average length of stay adjusted for case mix (7.86 days) and operation (8.15 days), indicating an optimized management adapted to patient complexity. The adjusted mean length of stay was 1.10, demonstrating efficiency despite higher patient complexity. Furthermore, through a comprehensive evaluation involving 170 semi-structured interviews, the study found high levels of patient satisfaction with the care provided by the HCU. The uniform positive feedback across various demographics highlights the effectiveness of the HCU's patient-centered care model. Lastly, the comparison of management indicators, as detailed in Figure 1 and Figure 2, illustrates the HCU's superior performance in several key areas, confirming its effectiveness in managing complex chronic patients through a multidisciplinary approach (Figures 1 and 2).

Clinical implications

The study's findings highlight the transformative potential of implementing a comprehensive, patient-centered care framework within HCU, particularly for the management of patients with chronic, multimorbid conditions. This model of care, which actively involves patients in the decision-making process and emphasizes self-care education, is crucial in addressing the challenges posed by an aging population and the increasing prevalence of lifestyle-related health issues.

Firstly, the HCU model demonstrates its effectiveness in reducing the risks associated with polypharmacy and adverse drug interactions. By ensuring coordinated and integrated care across various specialties, HCUs mitigate the complexities of managing multiple medications, which is a common issue among patients with chronic conditions. This integrated

Table 1 Effectiveness of high complexity units for chronic patients

Ref.	Focus area	Key findings
Berkman *et al*[21]	Heart failure	Reduction in hospital readmissions; improved symptom management
Collado *et al*[22]	COPD	Better control of exacerbations; enhanced medication adherence
Evans *et al*[23]	Chronic kidney disease	Lower mortality rates in HCUs
Huth *et al*[24]	Diabetes	No significant difference in mortality between HCUs and standard care
Osunkwo *et al*[25]	Patient satisfaction	Higher satisfaction scores due to personalized care
Murphy Salem *et al*[26]	Mental health	Increased sense of security; improved mental health outcomes
Salem *et al*[26]	Physical health	Better outcomes due to coordinated care and monitoring
Osunkwo *et al*[25]	Mental health	Reduced anxiety and depression levels
Collado *et al*[22]	Cost implications	Higher initial costs; long-term savings through reduced readmissions
Berkman *et al*[21]	Cost-benefit analysis	HCUs are cost-effective for complex chronic patients
Paoloni-Giacobino *et al*[27]	Efficiency and workflow	Streamlined care delivery; reduced unnecessary tests and procedures
Thompson *et al*[28]	Resource allocation	Improved resource utilization; optimized healthcare delivery
Suárez-Avellaneda *et al*[29]	SLE in ICUs	Importance of evaluating disease severity for management and outcomes
Onofri *et al*[30]	Cardiogenic shock economic impact	Significant costs with a focus on critical care unit stays
Onofri *et al*[30]	Telemedicine in CMC	Effective tool for maintaining continuity of care during the pandemic
Leeksma *et al*[31]	Genomic arrays in CLL	Personalized care potential through risk stratification

COPD: Chronic obstructive pulmonary disease; HCU: High complexity units; ICU: Intensive care units; SLE: Systemic lupus erythematosus; CMC: Chronic multimorbidity; CLL: Chronic lymphocytic leukemia.

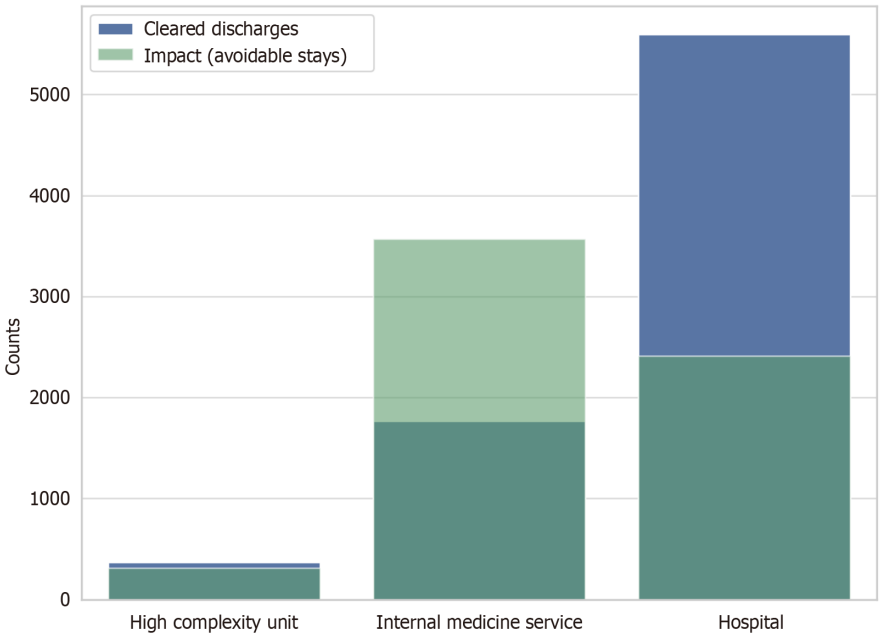

Figure 1 Cleared discharges and impact (avoidable stays).

approach not only enhances medication safety but also optimizes therapeutic outcomes by tailoring treatment plans to meet individual patient needs[11-13].

Secondly, the patient-centered approach of the HCU fosters improved clinical outcomes by actively engaging patients in their care. This engagement promotes adherence to treatment regimens and encourages patients to take an active role in managing their health, leading to better health behaviors and outcomes. Moreover, the emphasis on patient education

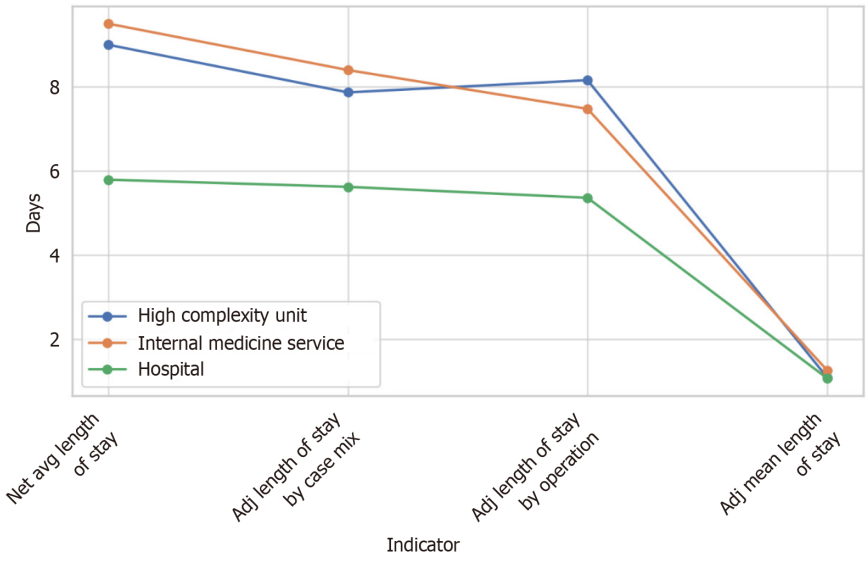

Figure 2 Length of stay indicators.

empowers individuals to make informed decisions about their care, thereby enhancing their autonomy and satisfaction with the healthcare process[14,15].

Furthermore, HCUs provide a structured environment that supports the seamless integration of multidisciplinary care teams. This collaboration is essential in addressing the multifaceted needs of chronic patients, who often require input from various healthcare professionals. By fostering communication and coordination among these teams, HCUs ensure that care delivery is both comprehensive and cohesive, reducing the likelihood of fragmented care and improving overall patient experiences.

Additionally, the strategic focus on continuity of care within HCUs addresses the critical transition from hospital to home, a vulnerable period for many chronic patients. By implementing detailed discharge planning and follow-up care, HCUs minimize the risk of hospital readmissions and ensure that patients continue to receive the necessary support and resources post-discharge. This continuity is vital in maintaining the progress achieved during hospitalization and in preventing the exacerbation of chronic conditions[16].

Lastly, the HCU model serves as an exemplary framework for healthcare systems aiming to enhance the management of chronic diseases. Its success in improving patient outcomes and reducing healthcare burdens underscores the importance of adopting similar patient-centered, integrated care models across diverse healthcare settings. By doing so, healthcare providers can better meet the growing demands of chronic disease management, ultimately improving the quality of care for patients with complex health needs[17].

Limitations of the study

Despite providing valuable insights into the management of complex chronic conditions through HCU, this study is subject to several limitations that should be acknowledged to contextualize its findings accurately. Firstly, the study's descriptive longitudinal design inherently limits the ability to establish causal relationships between the interventions implemented by the HCU and the observed outcomes. While the study effectively illustrates associations and trends, the lack of a control group or randomization means that definitive conclusions about causality cannot be drawn. Future research employing experimental designs, such as randomized controlled trials, would be beneficial in confirming these causal links.

Secondly, the study's focus on a specific population within a single healthcare setting poses challenges to the generalizability of its findings. The demographic and clinical characteristics of the patient population at Antequera Hospital may not reflect those of other regions or healthcare systems, particularly where healthcare infrastructures and patient demographics differ significantly. As such, the applicability of the results to broader, more diverse populations may be limited.

Thirdly, the study did not account for certain confounding variables that could influence the outcomes. Factors such as socioeconomic status, lifestyle habits, and genetic predispositions were not controlled for, which may have affected the results. Including these variables in future analyses could enhance the robustness of the findings and provide a more comprehensive understanding of the factors influencing patient outcomes in HCUs.

Fourthly, while the study highlights the effectiveness of the HCU model in reducing hospital stays and improving patient satisfaction, it relies heavily on subjective measures of patient satisfaction obtained through semi-structured interviews. Although valuable, these subjective assessments may be subject to bias, such as recall or social desirability bias. Incorporating objective measures of patient outcomes, such as clinical biomarkers or health-related quality of life indices, would provide a more balanced evaluation of the HCU's impact.

Lastly, the study's reliance on retrospective data collection may have introduced inaccuracies or omissions in the data recorded, potentially affecting the study's conclusions. Prospective data collection methods, which allow for real-time

data capture and monitoring, could improve data accuracy and reliability in future research efforts. Addressing these limitations in subsequent studies would help validate the current findings and expand our understanding of how HCUs can be optimized to enhance chronic disease management across various healthcare settings.

Future directions

The exploration of HCU in managing chronic multimorbid patients presents a promising frontier for future research. To further elucidate their potential, several research directions should be pursued. Expanding the demographic scope of future studies is essential to enhance the applicability and generalizability of the HCU model. By including diverse populations across various geographic, socioeconomic, and cultural backgrounds, researchers can identify how different demographic factors influence the effectiveness of HCUs. This expansion will help tailor the HCU model to meet the unique needs of disparate patient populations, ensuring its adaptability and efficacy in varied healthcare settings.

Incorporating longitudinal study designs to explore the causal pathways and long-term impacts of HCU interventions will provide valuable insights into the progression of chronic diseases and the sustained effects of interventions over time. Such an approach would enable researchers to assess not only immediate outcomes but also the durability of benefits conferred by the HCU model, thereby offering a more comprehensive evaluation of its effectiveness in chronic disease management.

Integrating advanced data analytics and machine learning techniques[32] could significantly enhance the predictive capabilities of HCUs. By analyzing large datasets, researchers can identify patterns and predictors of patient outcomes, enabling more personalized and proactive care strategies[33]. These technological advancements could facilitate the development of decision-support tools that aid healthcare providers in optimizing treatment plans for individual patients based on their unique clinical profiles.

Additionally, exploring the integration of digital health technologies within HCUs is crucial. The use of telemedicine, remote monitoring, and mobile health applications can extend the reach of HCUs beyond the hospital setting, providing continuous support and management for chronic patients in their homes. Research into the effectiveness and feasibility of these technologies in enhancing patient engagement and adherence to care plans would be invaluable in shaping the future landscape of HCU-based care.

Finally, evaluating the cost-effectiveness of the HCU model is crucial in demonstrating its value to healthcare policy-makers and stakeholders. By conducting economic analyses that compare the costs and benefits of HCU interventions with traditional care models, researchers can provide evidence of the financial sustainability of HCUs. This information is vital for securing funding and support for the widespread implementation of HCUs within healthcare systems. By pursuing these research directions, the healthcare community can advance its understanding of HCUs, refine their implementation, and ultimately improve the quality of care for patients with complex chronic conditions across the globe.

CONCLUSION

The study advances our understanding of managing chronic multimorbid patients by demonstrating the efficacy of a multidisciplinary approach in the HCU. This model not only improves clinical outcomes but also optimizes resource utilization, providing a viable solution to the challenges posed by complex chronic conditions. Future studies should continue to refine this model to ensure its adaptability and effectiveness in diverse healthcare contexts.

FOOTNOTES

Author contributions: Byeon H contributed to this paper; involved in data interpretation; and writing the article.

Supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, No. NRF- RS-2023-00237287.

Conflict-of-interest statement: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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S-Editor: Liu H
L-Editor: A
P-Editor: Zhang L

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