ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 June 6; 11(16): 3664-3931

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

PUBLICATION DATE
June 6, 2023

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World J Clin Cases 2023 June 6; 11(16): 3664-3679

DOI: 10.12998/wjcc.v11.i16.3664

ISSN 2307-8960 (online)

REVIEW

Kikuchi-Fujimoto disease: A comprehensive review

Vikram K Mahajan, Vikas Sharma, Neeraj Sharma, Ritu Rani

Specialty type: Dermatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Dauyey K, Kazakhstan; Hasan A, Egypt

Received: December 27, 2022
Peer-review started: December 27, 2022
First decision: March 24, 2023
Revised: March 29, 2023
Accepted: April 27, 2023
Article in press: April 27, 2023
Published online: June 6, 2023

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Abstract

Kikuchi-Fujimoto disease, a rare form of necrotizing lymphadenitis, is an uncommon, benign, self-limiting disorder of obscure etiology. It affects mostly young adults of both genders. Clinically, it presents with fever and lymphadenopathy of a firm to rubbery consistency frequently involving cervical lymph nodes while weight loss, splenomegaly, leucopenia, and elevated erythrocyte sedimentation rate feature in severely affected patients. Cutaneous involvement occurs in about 30%-40% of cases as facial erythema and nonspecific erythematous papules, plaques, acneiform or morbilliform lesions of great histologic heterogeneity. Both Kikuchi-Fujimoto disease and systemic lupus erythematosus share an obscure and complex relationship as systemic lupus erythematosus may occasionally precede, develop subsequently, or sometimes be associated concurrently with Kikuchi-Fujimoto disease. It is often mistaken for non-Hodgkin lymphoma while lupus lymphadenitis, cat-scratch disease, Sweet's syndrome, Still's disease, drug eruptions, infectious mononucleosis, and viral or tubercular lymphadenitis are other common differentials. Fine needle aspiration cytology mostly has features of nonspecific reactive lymphadenitis and immunohistochemistry studies usually show variable features of uncertain diagnostic value. Since its diagnosis is exclusively from histopathology, it needs to be evaluated more carefully; an early lymph node biopsy will obviate the need for unnecessary investigations and therapeutic trials. Its treatment with systemic corticosteroids, hydroxychloroquine, or antimicrobial agents mostly remains empirical. The article reviews clinicoepidemiological, diagnostic, and management aspects of KFD from the perspective of practicing clinicians.

Key Words: Cervical lymphadenopathy; Histiocytic necrotizing lymphadenitis; Kikuchi's disease; Lymphadenopathy; Lymphoma; Systemic lupus erythematosus

Core Tip: Kikuchi-Fujimoto disease or Kikuchi disease described originally in young Japanese women is a rare benign cause of fever and lymphadenopathy usually involving cervical lymph nodes. The disease has been reported worldwide in both genders across ethnic and age groups. Histopathologically, histiocytic necrotizing lymphadenitis is characteristic and needs differentiation from more serious conditions such as malignant lymphoma in acute or subacute form. Its long-term prognosis is favorable albeit long-term follow-up is recommended because of a rare but increased risk of developing systemic lupus erythematosus/other autoimmune disorders. Patients with a severe or recurrent disease need treatment with nonsteroidal anti-inflammatory drugs, systemic corticosteroids, and/or other immunomodulators.

Citation: Mahajan VK, Sharma V, Sharma N, Rani R. Kikuchi-Fujimoto disease: A comprehensive review. *World J Clin Cases* 2023; 11(16): 3664-3679
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3664.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3664

INTRODUCTION

Kikuchi-Fujimoto disease (KFD; *syn*: Kikuchi's disease, histiocytic necrotizing lymphadenitis), a rare self-limiting disorder of uncertain etiology, presents with prolonged lymphadenopathy with or without systemic features. The exact role of microbial infection and other non-infectious triggers in its etiopathogenesis remains obscure. Most patients present with firm to rubbery cervical lymphadenopathy and intermittent fever while weight loss, splenomegaly, leucopenia, and elevated erythrocyte sedimentation rate occur in severely affected patients. Cutaneous involvement occurs in about 30% to 40% of cases[1,2]. Its diagnosis is mainly retrospective from characteristic histopathology of a diseased lymph node whereas treatment mostly remains empirical. Interestingly, both KFD and systemic lupus erythematosus (SLE) share a complex and as-yet unelucidated relationship as SLE may occasionally precede, develop subsequently, or sometimes be associated concurrently with KFD[3]. KFD is a clinical entity often misdiagnosed as malignant lymphoma in acute or subacute form or missed altogether owing to its rarity, similarity to other common conditions, and lack of awareness among clinicians. Herein we revisit the clinicoepidemiological, diagnostic, and management aspects of KFD from the perspective of practicing clinicians.

EPIDEMIOLOGY

Kikuchi[4] and Fujimoto *et al*[5] in the year 1972 independently described two separate cases from Japan one presenting with 'lymphadenitis showing focal reticulum cell hyperplasia, nuclear debris, and phagocytosis' and another having 'subacute necrotizing cervical lymphadenitis', hence the nomenclature 'Kikuchi-Fujimoto disease'. Since then several cases of KFD have been reported worldwide both in children and adults in all racial and ethnic groups across countries including populations of western and Asian origin, particularly with a higher prevalence among Japanese[6-10]. While most reports have appeared from Asia, its prevalence varies widely across ethnic groups. Seventy-five percent were White individuals in a study of 88 patients with KFD in a study from the United States[6]. Only 0.5% of 920 Lymph nodes had histopathology characteristics of KFD in a study from Saudi Arabia[11]. KFD-associated adenitis was present in only 5.7% in a report from Taiwan compared to 35% of 147 Korean patients with cervical lymphadenitis[2,12]. However, the exact prevalence of KFD remains understudied perhaps for want of clinical suspicion and validated diagnostic criteria. Although initial reports suggested a female preponderance, it affects mostly young adults of both genders with variable frequency. It has been reported in patients aged between 6 and 80 years with a mean age of 30 years at presentation but the majority of affected individuals were younger than 40 years of age across studies[6,13-16]. The women were affected more often than men in three separate reports with a male to female ratio of 1:4, 1:1.6, and 1:1.3, respectively[6,17,18]. However, in a series of 20 Korean patients aged less than 18 years both genders were affected equally[19]. Among children, boys were affected slightly more frequently than girls compared to patients in the older age group in other reports[20,21]. A large review of 733 patients diagnosed worldwide since 1972 the male:female ratio was 1.4:1.8 for 19% of pediatric patients but a higher propensity for male gender was in children younger than 12 years of age[22,23].

ETIOLOGY

The clinicopathologic features of KFD favor a T-cell and histiocytes-mediated immune response to an

infectious or a non-infectious trigger. Increased levels of IFN-α and its stimulators including 2',5'-oligoadenylate synthetase, and tubuloreticular structures in the cytoplasm of stimulated lymphocytes, histiocytes, and vascular endothelium favor a viral etiology whereas a favorable therapeutic response to minocycline, ciprofloxacin, and ofloxacin in few studies suggest a pathogenic role of other non-viral microorganisms sensitive to these antimicrobial agents[8,22-25]. Nonetheless, several microbial agents including Epstein-Barr virus (EBV), human herpesvirus (HHV) 6 and 8, human immunodeficiency virus (HIV), parvovirus B19, paramyxoviruses, parainfluenza virus, *Yersinia enterocolitica*, and *Toxoplasma*, *Streptococcus pneumoniae* have been implicated as inciting factors[26-31]. Although EBV had been the most observed trigger, immunohistochemistry detected EBV-encoded protein in only one of the 10 patients showing EBV by in-situ hybridization[23,26,27,30]. A minivirus resembling circovirus, the causative agent for swine necrotizing lymphadenitis, too has been isolated in three Korean patients[32]. Although the exact relationship remains obscure, a postviral hyperimmune reaction too is a potential trigger for KFD[33,34]. B-cell lymphoma, rupture of silicone breast implant, infections due to cat-scratch disease, and *Mycobacterium szulgai* are other proposed triggers for KFD[8,35,36].

KFD has been infrequently reported following vaccination for influenza, Japanese encephalitis, and HPV[37,38]. Recently, KFD has been linked to coronavirus disease 2019 infection and SARS CoV2 vaccination[39-48]. However, whether the association is causal or epiphenomenon remains uncertain as most patients recovered rapidly and completely. One of the two patients developed KFD disease 10 d after vaccination while hemophagocytic reticulosis complicated KFD after the vaccination in another[45, 46].

It has been suggested that KFD most likely develops due to an autoimmune mechanism disease as cases had reportedly developed clinicopathological features similar to Sjögren's syndrome and systemic lupus erythematosus/mixed connective tissue disease[49,50]. Since KFD shares age and gender predisposition as well as histologic features with SLE, it has been also proposed that KFD perhaps represents a self-limiting SLE-like autoimmune disorder caused by virus-infected transformed lymphocytes[51]. The hypothesis of autoimmune pathogenesis is further supported by an association of KFD with an increased risk of its evolution into an autoimmune syndrome, particularly in females or the concurrent presence of other autoimmune disorders such as Hashimoto thyroiditis, primary Sjögren's syndrome, antiphospholipid syndrome, and leukocytoclastic vasculitis as observed in 53% of thirteen women in a follow-up study of twenty patients with KFD[52-55].

The reports implicating allogeneic hematopoietic stem cell transplantation and bariatric surgery for triggering KFD remain anecdotal[56,57].

PATHOGENESIS

No genetic transmission or inheritance of a definite pattern has been identified despite being reported uncommonly to affect twins and even human leukocyte antigen (HLA)-identical non-twin siblings[58-61]. Some of these familial cases were from the common living environment and developed symptoms almost simultaneously and demonstrated serological evidence for the same infection. However, one of the two HLA-identical sisters but not twins from Saudi Arabia developed KFD after a gap of 10 years with no identifiable infectious trigger[58,59]. Stasiuket al[58] reported a similar case of two Aboriginal sisters from northern Ontario reflecting a genetic predisposition among affected individuals. KFD and HLA class 2 alleles have been linked suggesting a possible positive relationship between DPA1*01 and DPB1*0202 alleles which are much more frequent in Japan than in Europe and the United States[62]. This perhaps accounts for a higher prevalence of KFD in the Asian population.

Up-regulation of cell-cycle-associated genes and apoptosis-associated genes including caspase, and down-regulation of apoptosis-inhibitory genes such as *BCL2* too have been observed in KFD-associated lymph nodes and not in nonspecific lymphadenitis[63]. The apoptotic cell death induced by the Fas-Fas ligand system mediated by cytotoxic CD8+ cells is the principal mechanism of cellular destruction in KFD[64-66]. The apoptosis is enhanced by histiocytes as evident from the morphology of apoptotic cells on transmission electron microscopy characterized by nuclear chromatin condensation, fragmentation along the nuclear membrane with intact organelles, and histiocytes phagocytosing karyorrhectic debris (apoptotic bodies). To summarise, primarily the activation of T lymphocytes and histiocytes occurs and the activated T cells enter the apoptotic cycle manifesting with areas of necrosis in lymph nodes, and the cellular debris is then cleaned up by the histiocytes. Also the cytokine and chemokine pathways of interferon (IFN)-γ, interleukin (IL)-18, MIG, and IFN-γ-induced protein 10 have been suggested to play a significant role in the apoptosis associated with KFD[67]. The serum levels of IFN-γ and IL-6 were elevated but not of IFN-α, tumor necrosis factor (TNF), or IL-2 in these patients during the acute phase of illness which returned to normal during convalescence[68,69]. This further reinforces the possible role of IFN-γ and IL-6 in the pathogenesis of KFD. In general, the shared and common HLA and cytokines involved in the molecular pathogenesis of this disease suggests that like other HLA-linked disorders, KFD is a two-step disease requiring a predisposing HLA and a secondary trigger such as an infection in individuals with a genetic predisposition for the exuberant T-cell mediated immune/inflammatory response[70]. However, the exact molecular pathogenesis of KFD remains complex and needs further

elucidation.

CLINICAL FEATURES

KFD usually manifests as an acute or subacute illness with fever and painful posterior cervical lymphadenopathy generally in a previously well individual and evolving over 2-3 wk[71]. Lymph nodes of firm to rubbery consistency are usually small ranging from 0.5 to 4 cm in size[18,70,72]. The most common signs and symptoms were lymphadenopathy (100%), fever (35%), erythematous rash (10%), arthritis (7%), fatigue, (7%), and hepatosplenomegaly in 3% of patients in a series of 244 individuals with KFD[73]. The association of splenomegaly too has been reported as an uncommon feature of KFD[74]. Typically, the fever is of low grade and intermittent which persists for about one week, rarely lasting for up to one month (median duration 9 d), and is a primary symptom in 30%-50% of patients[6]. Patients with higher fever (≥ 39.0 °C), larger lymph nodes, and leucopenia can have a more prolonged clinical course[75]. However, the diagnosis of KFD is unlikely to be considered without lymph node biopsy in patients with pyrexia of unknown origin. Other sporadic symptoms and signs include rigors, myalgia, arthralgia, and chest and abdominal pain[6]. Nausea, vomiting, diarrhea, night sweats, and weight loss have been reported more often in patients with extranodal disease[76].

Lymph node involvement

The lymph node involvement is the commonest presenting feature. The lymph nodes are usually enlarged only moderately varying in size from 1 to 2 cm in diameter but sometimes they are much bigger up to 7 cm in diameter[77]. The enlarged lymph nodes are typically discrete, mobile, firm, smooth, and often associated with dull or acute pain. In the majority, the lymph node involvement is limited to unilateral cervical lymphadenitis particularly localized to posterior cervical lymph nodes but there may rarely be bilateral cervical adenopathy[6,77]. Generalized lymphadenopathy involving axillary, epitrochlear, mediastinal, mesenteric, inguinal, intraparotid, iliac, retrocrural, celiac, peripancreatic, and retroperitoneal nodes occurs in about 1% to 22% of patients[71]. Extracervical disease especially with bilateral cervical adenopathy and leukopenia in a review of 60 patients (mean age of 21years) with confirmed KFD manifested with abdominal in 52%, pelvic in 47%, inguinal in 41%, and axillary lymph nodes in 30% of patients, respectively[78]. Mediastinum lymphadenopathy can occur more often while the involvement of mesenteric lymphadenitis is rare and often mimic appendicitis[79-82]. However, nodal enlargement may be minimal or remain limited to mediastinal or retroperitoneal nodes only[83,84].

Cutaneous manifestations

The involvement of skin in 30%-40% of KFD patients is the most commonly affected extranodal organ[1,2]. Facial erythema, SLE-like malar rash, and other nonspecific lesions including macules, patches, papules, nodules, or plaques, occasionally pruritic, and histologically resembling KFD occur typically and are observed more frequently in children than adults[2,21,85,86]. More sick patients may develop transient skin rashes resembling rubella or drug-induced eruptions[87,88]. Other cutaneous manifestations include pruritus, lichen planus, polymorphous light eruptions, scattered indurated lesions, leukocytoclastic vasculitis, ulcers, scales, and alopecia[2,26,85,89]. Mucosal involvement in the form of oropharyngeal redness, oral ulceration, and conjunctival injection/papillary conjunctivitis may occur[8,90].

Systemic manifestations

Multiple systemic complications may occur. Weight loss is common in adult patients and leukocytosis is perhaps more frequent than leukopenia[20,86]. An association of KFD with various other inflammatory disorders such as hemophagocytic syndrome, arthritis, myocarditis, and hepatic dysfunction has been indicated[86,90-96]. Macrophage activation syndrome, a secondary form of hemophagocytic lymphohistiocytosis (HLH), has been recognized in some older patients hospitalized under intensive care with KFD and HLH who required systemic corticosteroids or had ended fatally[97].

Involvement of the central nervous system presenting as aseptic meningitis, meningoencephalitis, acute cerebellar symptoms with tremors and ataxia, and optic neuritis has been reported frequently[92,97-102]. Aseptic meningitis mostly at the time of the lymphadenopathy is the commonest neurological complication seen in some of these cases and may be associated with very high levels of intracranial pressure, low cerebrospinal fluid (CSF)-serum glucose, and recurrent subdural effusions requiring intervention[103,104]. While recurrent meningitis occurs more often in males, encephalopathy in children may occur after 10 d to 3 mo which is characterized by very high CSF protein levels and extensive magnetic resonance imaging changes requiring early treatment.

DIAGNOSIS

Distinguishing KFD from malignant lymphoma and SLE remains a major diagnostic challenge owing to similar histopathologic appearances. Patients with KFD especially in its proliferative phase have been often misdiagnosed as having non-Hodgkin or Hodgkin lymphoma leading to extensive investigations and, in some cases, aggressive treatment with cytotoxic agents owing more so to unfamiliarity with this uncommon entity[6]. Parotid gland tumor, lupus lymphadenitis, Kawasaki's disease, cat-scratch disease, Sweet's syndrome, sarcoidosis, lymphogranuloma venereum, drug eruptions, infectious mononucleosis, and viral or tubercular lymphadenitis are other more common differentials[6,8,105-107]. Mesenteric lymphadenopathy presenting as acute appendicitis too has been described[69].

The diagnosis of KFD is mostly retrospective and based exclusively on lymph node histopathology and excisional biopsy has been recommended frequently in the past. However, fine needle aspiration (FNA) histology with features varying from nonspecific reactive lymphadenitis to those of KFD can be a useful diagnostic tool with an overall accuracy of about 56% in expert hands; nonetheless, it provides clues to exclude other common causes of lymphadenopathy[108]. Ultrasound-guided FNA using smears and cell block preparations designed to preserve lymph node architecture is considered a better alternative[109-111]. However, ultrasound-guided core needle biopsy with a diagnostic accuracy of 95.6% as compared with FNA is now the suggested diagnostic modality of choice[112]. Extracellular debris and intracellular apoptotic debris embedded in the cytoplasm of crescentic and phagocytic macrophages are characteristic of KFD[113,114]. Nevertheless, lymph node biopsy should be preferred for an early diagnosis, to avoid unnecessary investigative work up, and to exclude more serious conditions such as lymphoma requiring early and intensive therapeutic intervention.

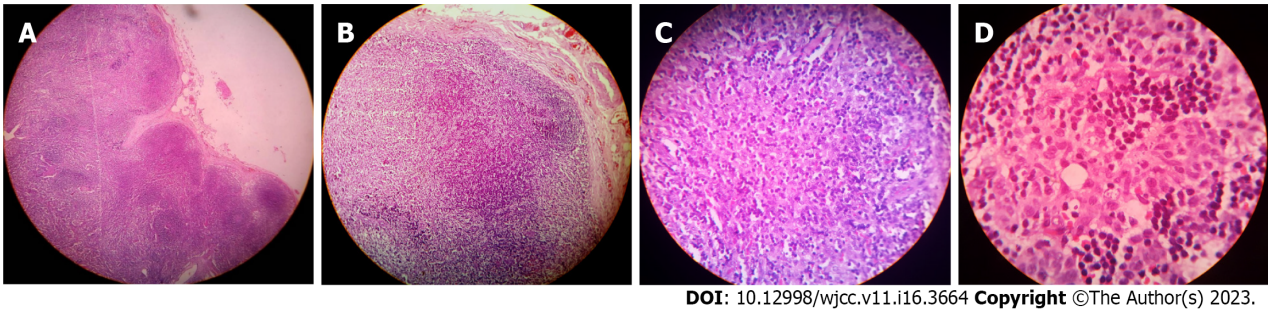
Histopathology

The cut surface of the involved lymph nodes may show yellowish necrotic foci on gross examination. Histological examination (Figure 1) usually shows single or multiple foci of focal or complete loss of follicular architecture often with necrosis of the cortical and paracortical areas and extensive infiltrate consisting of small lymphocytes, immunoblasts, histiocytes, and plasmacytoid T-cells[8]. Perinodal inflammation is common and the capsule may be infiltrated. The necrotizing process is often localized to areas of eosinophilic fibrinoid material with fragments of nuclear debris distributed irregularly. However, obvious coagulative necrosis is not essentially diagnostic of KFD.

The histologic appearance changes as the disease progresses and can be classified into three histologic subtypes; an early phase of "proliferative type" in more than 30%, a late phase of "necrotizing type" in 50% being the commonest, and the end phase of "xanthomatous type" the least common form seen in < 20% cases[77]. The presence of follicular hyperplasia and paracortical expansion by lymphocytes, T and B cell blasts, plasmacytoid monocytes, and histiocytes with numerous background apoptoses is the hallmark of the early "proliferative phase" of KFD. The numerous blast cells may evoke the possibility of lymphoma or EBV/HHV infection. While preservation of the nodal architecture, polyclonal infiltrate, absence of monoclonal T-cell receptor rearrangement, and negative viral serology will exclude these possibilities, its oligoclonal pattern and spontaneous regression favor a more benign immune reaction [115]. The "necrotizing phase" with an absence of a neutrophilic infiltrate is predominately associated with progressive dominance of histiocytes often with crescentic nuclei and phagocytosed debris as the major cell type. Histiocytes with predominantly CD8+ T lymphocytes and CD68+ plasmacytoid monocytes are visualized on immunohistochemical staining[63]. The absence of neutrophils in the necrotizing phase differentiates KFD from SLE and drug-induced lymphadenopathy. The "xanthomatous type" seems to be a distinct histologic variant or perhaps indicates a healing phase characterized by the predominance of foamy histiocytes, and necrosis may or may not be present[116,117].

Systemic lupus erythematosus, tubercular or viral lymphadenitis, and Hodgkin and non-Hodgkin lymphoma are common histological differentials. The absence of Reed-Sternberg cells, the presence of numerous histiocytes, and relatively low mitotic rates favor the diagnosis of KFD rather than lymphoma [118]. The histology of the lymph node in KFD can be differentiated easily from most known infectious causes of fever and lymphadenopathy but its differentiation from lymphadenopathy in SLE may be particularly difficult. However, positive results for immunohistochemistry taken together with clinicopathologic features may be of diagnostic help[2,6,13,119].

In contrast, the histologic features of skin lesions in KFD are mostly nonspecific and highly variable featuring epidermal changes mainly of interface dermatitis, necrotic keratinocytes, non-neutrophilic karyorrhectic debris, basal vacuolar change, papillary dermal edema, and a lymphocytic infiltrate[2,120]. Vacuolar interface changes in 75%, necrotic keratinocytes in 68%, karyorrhexis in 100%, superficial and deep lymphohistiocytic infiltration in 100% and 56%, respectively, and panniculitis in 60% were major histologic features noted in a retrospective review of skin biopsies from sixteen patients with KFD [121]. Atwater *et al*[2] proposed that diagnosis of KFD can be reasonably made in an appropriate clinical setting if the biopsy specimen meets the following criteria: (1) A dermal (lympho)-histiocytic infiltrate; (2) epidermal changes with an emphasis on necrotic keratinocytes; (3) non-neutrophilic karyorrhectic debris; (4) basal vacuolar change; and (5) papillary dermal edema. However, confirmation is needed by immunohistochemical staining with CD68 for the presence of histiocytes.



DOI: 10.12998/wjcc.v11.i16.3664

Figure 1 Histopatholgy of a lymph node in Kikuchi-Fujimoto disease. A: Scanner power view of a lymph node in Kikuchi-Fujimoto disease: The pale foci located in between the benign germinal centers are due to the collection of histiocytes(Stain, H&E; × 4); B: Focal areas of the effaced architecture of the lymph node by necrotic foci. Necrosis and pink debris among histiocytes and lymphocytes are typically seen while well-formed granulomas are absent (Stain, H&E; × 10); C: Seen here are focal areas of necrosis without neutrophils and sheets of histiocytes with pale nuclei with a violaceous hue and pink cytoplasm (Stain, H&E; × 40); D: Histiocytes with round-to-sickle-shaped nuclei and typical pink necrotizing nodules mainly composed of histiocytic debris. Neutrophils or suppurative abscesses, a hallmark of suppurative granulomas, are conspicuously absent (Stain, H&E; × 100).

Immunohistochemistry

Hassan *et al*[122] observed positive immunostaining by antibodies Mac 387, KP1 (CD 68), and Ki M1P, and the majority of the cells were a mixture of CD8+ and CD68+ in the affected foci (Figure 2).

Additionally, a variable number of T-cells immunostained by antibody MT1 (CD 43) or UCHL1 and (CD 45RO) and CD8+ T cells stained positive with antibody CD8/144 in all lesions. They opined that immunohistochemistry can be useful in differentiating KFD from other chronic cervical lymphadenopathies. KFD can be distinguished from necrotizing lymphadenitis due to other causes with digital quantification of CD123 immunohistochemical staining[123]. There are fewer surrounding mononuclear cells and neutrophils are usually present in HHV-associated lymphadenitis. Contrasting with KFD, necrosis in Hodgkin lymphoma usually includes neutrophils and CD15, CD30, and CD45 positive Reed-Sternberg cells, the large atypical cell variants. The plasmacytoid dendritic cells infiltrate the lymph nodes more frequently in KFD irrespective of its duration than in either reactive lymphadenitis or T or B cell lymphoma and can be useful cytologic indicators in the diagnosis of KFD[124]. The presence of abundant CD8+ cytotoxic T cells around necrotic areas can help in differentiating necrotic lymph nodes from head and neck cancer or metastatic disease from SLE and reactive lymphoid hyperplasia[125,126]. CD68+ and CD163+ histiocytes and CD3+ T lymphocytes are predominant infiltrating cells in skin lesions whereas, neutrophil-predominant inflammation with superficial dermal edema features in skin lesions with Sweet syndrome-like morphology[121,127].

Laboratory investigations

No specific laboratory investigations are recommended for the diagnosis of KFD but these are advocated to exclude other causes of (cervical) lymphadenopathy. Although atypical lymphocytes in up to 25% and leukopenia in up to 43% have been observed, the blood counts are usually normal in a majority of the patients with KFD[6,12,17,73]. Thrombocytopenia, pancytopenia, and anemia of chronic disease in those with severe disease are other reported hematological abnormalities[26,73,128]. The erythrocyte sedimentation rate and C reactive protein can be normal but were elevated (> 60 mm/h) in 70% of patients in one series[83]. Mildly abnormal liver function tests and elevated serum lactate dehydrogenase are other nonspecific findings[96].

Increased macrophages without atypical cells are frequently seen in bone marrow cytology whereas, increased numbers of mature hemophagocytic histiocytes in the bone marrow may cause diagnostic confusion with virus-associated hemophagocytic syndrome[17,77]. However, bone marrow studies are rarely recommended for the diagnosis of KFD.

Serodiagnostic studies

Serology for EBV, HHV, cytomegalovirus, HIV, toxoplasmosis, *Y. enterocolitica*, cat scratch disease, and other infectious agents is often performed in a suspected case of KFD to exclude other differentials of fever and lymphadenopathy. Antinuclear antibodies (ANA) and other investigations for SLE, and rheumatoid factor are, although not always, negative and help distinguish the two. However, patients initially diagnosed with KFD may have concurrent or developed SLE subsequently, it is generally recommended to perform an ANA test in patients suspected of KFD with features suggestive of SLE and to exclude this diagnosis[6,129]. There may be a transient rise in anti-deoxyribonucleic acid and anti-ribonuclear protein antibody levels[17]. Screening for the presence of adult-onset Still's disease in patients with suspected KFD is also recommended because of reports of their concurrent occurrence [130].

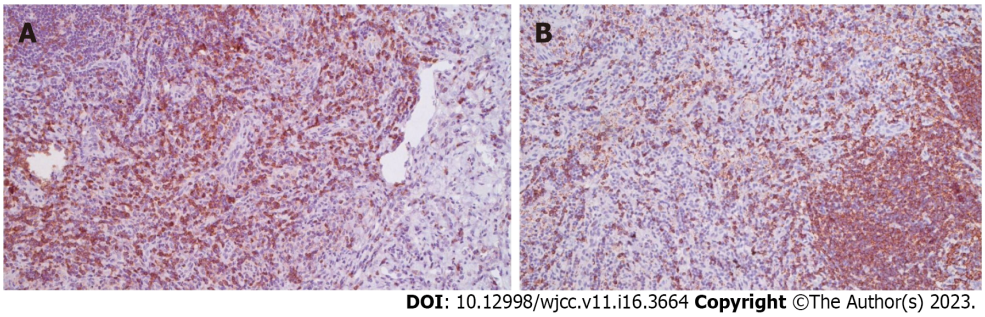


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Figure 2 Immunohistochemical staining of lymph node inKikuchi-Fujimoto disease. A: Kikuchi-Fujimoto disease: CD8 immunostaining of lymph node biopsy showing predominantly CD8+ T (cytotoxic) cells highlighting lymphoid cells and large immunoblasts (× 10); B: Kikuchi-Fujimoto disease: Immunohistochemistry of lymph node biopsy showing CD68+ histiocytes in the necrotic areas (× 10).

Imaging studies

No specific radiographic finding has been established to make a diagnosis of KFD. However, a chest X-ray should be obtained in a routine workup of a patient with fever and cervical lymphadenopathy for any evidence of pulmonary tuberculosis or malignancy. Ultrasonography of the neck for lymph nodes can be performed but results need careful interpretation as in a series of 29 lymph nodes evaluated by sonography 66% showed features suggestive of malignancy whereas tubercular lymphadenitis remains another common differential[119,131]. Features such as posterior neck involvement, echogenic hilum, absence of internal calcification and necrosis (rarely present in partial necrosis), normal vascular pattern (hilar vascular structures are central or branch radially from the hilum in both longitudinal and transverse planes) on power Doppler ultrasound are considered typical of KFD[119]. In Doppler ultrasonography, the lymph nodes are smaller, less rounded, and mostly have an echogenic hilum and abnormal posterior cervical region but necrosis and internal calcifications are less likely in KFD as compared to tuberculous adenitis[119]. Computed tomography (CT) of the neck may be helpful before biopsy and the features may be similar to lupus lymphadenitis and malignant lymphoma. It exhibits unilateral, uniform homogeneous enlargement and post-contrast enhancement of cervical lymph nodes preferably affecting levels II-V in most patients with KFD[132]. Perinodal infiltration is typically seen in about 81% and homogenous nodal contrast enhancement occurs in 83% of affected lymph nodes[132]. The pattern of necrosis, when present, suggests tuberculosis while the absence of necrotic lymphadenopathy and nodal cortical attenuation and its ratio to adjacent muscle on CT imaging differentiates KFD from tuberculous lymphadenopathy and nodal reactive hyperplasia[133]. Magnetic resonance imaging findings of 52 enlarged cervical lymph nodes predominantly showed unilateral distribution at level II-V in a study[134]. Areas of hypointensity in peripheral distribution and clear margins representing necrosis in paracortical areas, and occasional focal non-enhancing areas suggestive of necrosis within the enlarged lymph nodes were observed in T2-weighted images in the same study. Positron emission tomography scanning has been used to assess disease severity and most patients are found to have multiple hypermetabolic lymph nodes but only a few were enlarged[135,136]. Radiating vessels from the central hilum to the periphery of the lymph node and normal or scant hilar vascularity within the whole lesion in 92% of patients with KFD on color Doppler imaging indicates its benign nature[137]. Lee *et al*[138] performed real-time elastography in two patients with KFD to measure the elasticity score of affected cervical lymph nodes. Based on a scale of 1 to 4 devised by Ying *et al*[139] the elasticity score of 1 in both patients was consistent with the benign nature of KFD. However, all these investigative modalities need further evaluation for their diagnostic accuracy compared to histopathology, the gold standard in diagnosis.

SYSTEMIC COMPLICATIONS

Although considered benign and self-limiting, systemic complications in KFD may develop prompting urgent intervention. These include cardiac tamponade, pleural effusions, pulmonary infiltrates and nodules (interstitial lung disease), symmetrical polyarthritis, thyroiditis and parotid enlargement, autoimmune hepatitis, acute renal failure, bilateral papillary conjunctivitis and panuveitis, ocular vasculitis and subretinal macular infiltrates, polymyositis, hemophagocytosis, limb paresis because of brachial plexus neuritis, peripheral neuropathy, and antiphospholipid syndrome with multiorgan failure[91,92,140-154]. Still's disease, cryptogenic organizing pneumonia, hemophagocytic syndrome, and B cell lymphoma have been described occasionally in association with KFD[35,155-160].

KFD AND SYSTEMIC LUPUS ERYTHEMATOSUS

KFD shares gender and age predisposition as well as histologic features with SLE. SLE may occasionally precede, sometimes be associated with KFD, or develop subsequently. In a review of 55 patients with KFD in the context of definite connective tissue disorder fifty were associated with SLE; 22 (40%) patients had simultaneous onset, 19 (35%) patients predated the onset, and 14 (25%) patients developed KFD after the onset of SLE[3]. KFD may also complicate preexisting SLE as described by Tarabichi *et al* [161] requiring intensive therapeutic intervention. Their patient of SLE, a 20-year-old girl, had been doing well with hydroxychloroquine (HCQS 200 mg/d)/analgesics. But, after two months she developed KFD affecting multiple cervical/extra cervical lymph nodes and hepatomegaly and needed high doses of systemic methylprednisolone (250 mg/d, given as pulse therapy for 5 d) and 40 mg/d thereafter in addition to HCQS (200 mg twice daily) for adequate control.

Many reports of KFD cases also support the idea that the two diseases share common immunopathological and clinical features such as the disappearance of the lesions without any specific treatment whereas, the possibility of recurrence suggests the involvement of immune mechanisms and that KFD could be a common aspect of SLE[151,162,163]. One ultrastructural study proposed that KFD perhaps reflects a self-limiting, SLE-like autoimmune condition triggered by virus-infected transformed lymphocytes[51]. The histological findings of focal necrosis with immunoblastic infiltration in lupus lymphadenitis are indistinguishable from KFD. The absence of neutrophils is characteristic of both KFD and lupus lymphadenitis[8]. The tubuloreticular structures in the lymphocytes and endothelial cells in patients with SLE have similarities to those seen in KFD whereas a similar tubuloreticular structure in human lymph nodes is not seen except in cases of SLE. However, the detection of this peculiar structure of unknown origin in an ultrastructural study of necrotizing lymphadenitis suggests a direct relationship between SLE and KFD[51]. In addition, the key distinguishing histologic feature of SLE lymphadenitis is the presence of hematoxylin bodies, an amorphous aggregate of basophilic material [163].

Skin lesions in KFD may also clinically and histologically resemble those seen in SLE or subacute lupus erythematosus[164]. Skin biopsy of KFD lesions reveals a pattern of interface dermatitis in KFD that evolved into SLE suggesting that it could be a histopathological marker of evolution into SLE and might predict clinical outcomes in KFD[125]. An association of KFD with hemophagocytic syndrome also suggests a common pathogenesis[148].

According to Tabata *et al*[126], CD30 immunostaining may help in differentiating KFD from SLE as CD30+ cells significantly are more numerous in KFD than in SLE and most of these were located around necrotic areas in their study of 30 patients with KFD and six patients with SLE. These CD30+ cells were CD8+ activated cytotoxic T cells around necrotic areas and characteristic of KFD and occurred predominantly in females having only mild symptoms and normal laboratory data[126]. The relationship between KFD and SLE remains complex and uncertain requiring long-term follow-up because of late evolution of KFD to SLE or other autoimmune diseases after several months to years[49,120,165].

KFD IN PREGNANT WOMEN AND CHILDREN

Although KFD affects women younger than 40 years of age more often, there is a paucity of data on its impact on gestation and pregnancy outcomes. The treatment with antibiotics, steroids, or both had no adverse impacts on the mother, fetus, or the course of pregnancy in two patients with KFD manifesting during pregnancy[166,167]. Another patient with KFD had a miscarriage reportedly with evolving SLE [168].

The presenting clinical features in children are similar to those in adults, although fever, rash, and bilateral cervical lymphadenopathy are more frequent in children younger than 18 years than in adults [72,169-171]. Generalized lymphadenopathy was less common while fever and rash were more common in children as compared to adults[170]. The presentation may be atypical in children < 6 years old. Recurrent disease seen in approximately 3% of pediatric patients is uncommon and occurs more often in boys compared to adults where recurrences have been more frequent in women[21,73].

TREATMENT

No specific treatment has been established as signs and symptoms usually resolve spontaneously within 1 to 4 mo without serious sequelae[172]. Fever usually subsides after removal of the affected lymph node suggesting the possible therapeutic benefit of excisional biopsy by removal of the focus for the inflammatory process in addition to being diagnostic[173]. Pharmacotherapy is usually targeted to reduce morbidity and prevent complications. Nonsteroidal anti-inflammatory drugs (NSAIDs) usually suffice to alleviate fever and lymph node tenderness in mild cases. Patients with prolonged fever, severe or symptoms lasting for more than 2 wk, and recurrent disease have been treated with immunomodulators, systemic corticosteroids (prednisolone 1-2 mg/kg body weight) alone or in combination, high-

dose corticosteroids and intravenous immune globulin (IVIg) especially in patients presenting with extranodal or generalized severe disease or hemophagocytic syndrome with good therapeutic outcome [174-176]. There have been reports of recurrent or steroid-resistant KFD treated successfully with hydroxychloroquine monotherapy or in combination with systemic corticosteroids[177,178]. Rezai *et al* [177] treated a patient of KFD with systemic symptoms with chloroquine and achieved a rapid response in four days. One patient unresponsive to steroid therapy reportedly responded well to the IL-1 inhibitor, anakinra[179]. The anecdotal efficacy of ciprofloxacin, minocycline, and ofloxacin in remitting KFD needs further evaluation[8,24,25].

PROGNOSIS

In general, the prognosis in KFD is good as it is self-limiting in a majority of the patients and the symptoms may spontaneously subside in 1-6 mo, although recurrences can occur in 3% to 4% cases[128, 180-182]. In a series with a median of 32 mo of follow-up 92% of patients were alive and well[6]. Recurrences respond well to treatment similar to the first occurrence. Nevertheless, affected patients should be followed up for some years as unpredictably they may develop SLE, and sometimes recurrences of KFD can continue for many years. For instance, in a Korean case series recurrence was seen in 11.3% and 2.7% of patients who developed autoimmune diseases after an initial diagnosis of KFD[183]. Similarly, four episodes of lymphadenopathy over 18 years occurred in a patient and another had two episodes separated by 6 years[128,180]. In another Korean series of 102 patients (mean age 26.7 years) followed up between 2001 and 2006, late recurrence happened in 13% of patients and early relapse occurred in 8% of patients while 3% of patients developed SLE[181]. These recurrent cases had fever and fatigue with extranodal involvement and remained symptomatic for a longer period than non-recurrent cases. A positive fluorescent antinuclear antibody test was found to be associated with a significantly higher risk of recurrent disease. An EBV seropositive and ANA negative KFD presenting initially with severe disease relapsed frequently despite being treated with multiple courses of systemic corticosteroids and hydroxychloroquine[184]. With a reported fatality rate of 2.1% and severe and fatal cases having been generally associated with hemophagocytic syndrome or connective tissue disease, a long-term follow-up remains essential[3,73,185].

CONCLUSION

Kikuchi-Fujimoto disease is an uncommon, idiopathic, benign lymphadenopathy primarily affecting both genders at a young age between 20 and 40 years worldwide across ethnicities. The acute or subacute onset of adenopathy is usually associated with fever, body aches, night sweats, and weight loss (B symptoms). Its exact etiology remains obscure. The results of studies looking for viral etiology have been inconsistent. Molecular pathways implicated in its pathobiology are also not well understood. Concomitant autoimmune disorders have been reported or they may also be diagnosed more frequently following the resolution of KFD. Despite differing opinions, SLE is perhaps the commonest disorder linked to KFD and has been suggested to be its *forme fruste*. However, further research is necessary to reach a definitive conclusion.

Although modern hematopathological methods have made misdiagnosis less likely, a diagnosis of malignant lymphoma for KFD is still reported. Since the diagnosis is exclusively based on histopathology, an early excision biopsy of the affected lymph node will be diagnostic in doubtful cases. However, using high-throughput nucleotide sequencing of lymph node tissue to identify exomes and transcriptomes, candidate single nucleotide polymorphisms for markers of KFD have been identified and the altered gene expression found may help in better understanding of the disease, diagnosis, and treatment[186]. The proposed diagnostic criteria using a scoring system based on temperature, maximum lymph node size, and serum B2 microglobulin described for children avoiding lymph node biopsy had 100% sensitivity and specificity in a study[187]. However, further evaluation with multicenter studies involving larger numbers of patients across all age groups remains highly desirable.

Treatment guidelines for KFD have not been established and recommendations are mostly based on case reports, small case series, and the opinion of the experts. Treatment with systemic corticosteroids, NSAIDs, hydroxychloroquine or other immunomodulators, used alone or in combination, in a few patients with severe symptoms or recurrent disease remains the mainstay in therapeutics. Anecdotal therapeutic efficacy and place of chloroquine, anakinra, IVIg, and antimicrobial agents in the treatment ladder need to be evaluated further.

FOOTNOTES

Author contributions: Mahajan VK planned, obtained, compiled, analyzed and interpreted the data, prepared the

draft, and critically evaluated the manuscript for important intellectual content; Sharma V, Sharma N, and Rani R helped in planning, compiling, and preparing the draft; all authors were involved in the revision of the manuscript and agreed to the final content.

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

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S-Editor: Gong ZM
L-Editor: A
P-Editor: Zhao S

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3680-3693

DOI: 10.12998/wjcc.v11.i16.3680

ISSN 2307-8960 (online)

REVIEW

Current diagnostic tools and treatment modalities for rectal prolapse

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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 scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Bustamante-Lopez LA, Brazil; Kumar S, India; Mehrvarz S, Iran

Received: January 31, 2023
Peer-review started: January 31, 2023
First decision: March 14, 2023
Revised: March 31, 2023
Accepted: April 25, 2023
Article in press: April 25, 2023
Published online: June 6, 2023

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Abstract

Rectal prolapse is a circumferential, full-thickness protrusion of the rectum through the anus. It is a rare condition, and only affects 0.5% of the general population. Multiple treatment modalities have been described, which have changed significantly over time. Particularly in the last decade, laparoscopic and robotic surgical approaches with different mobilization techniques, combined with medical therapies, have been widely implemented. Because patients have presented with a wide range of complaints (ranging from abdominal discomfort to incomplete bowel evacuation, mucus discharge, constipation, diarrhea, and fecal incontinence), understanding the extent of complaints and ruling out differential diagnoses are essential for choosing a tailored surgical procedure. It is crucial to assess these additional symptoms and their severities using preoperative scoring systems. Additionally, radiological and physiological evaluations may explain some vague symptoms and reveal concomitant pelvic disorders. However, there is no consensus on or standardization of the optimal extent of dissection, type of procedure, and materials used for rectal fixation; this makes providing maximum benefits to patients with minimal complications difficult. Even recent publications and systematic reviews have not recommended the most appropriate treatment options. This review explains the appropriate diagnostic tools for different conditions and summarizes the current treatment approaches based on existing literature and expert opinions.

Key Words: Rectal prolapse; Constipation; Fecal incontinence; Diagnosis; Minimally invasive surgical procedures; Colorectal surgery

Core Tip: Patients with rectal prolapse should be subjected to detailed history taking, thorough physical examinations, and assessments with appropriate scoring systems before deciding to proceed with surgical intervention. The aim of surgery is an anatomical correction to obtain optimal functional outcomes. Magnetic resonance defecography is beneficial for understanding both functional and anatomical pathologies. To date, robotic and laparoscopic ventral mesh rectopexies are the most commonly performed surgeries and achieve better functional and anatomical outcomes than other surgical alternatives.

Citation: Oruc M, Erol T. Current diagnostic tools and treatment modalities for rectal prolapse. *World J Clin Cases* 2023; 11(16): 3680-3693
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3680.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3680

INTRODUCTION

Rectal prolapse and rectal intussusception are pelvic floor dysfunction-associated anatomical disorders that are characterized by a complete or partial descent of the rectum. External rectal prolapse is defined as a full-thickness protrusion of the rectum through the anal canal. However, in case of intussusception, the protrusion is limited and does not extend through the anal canal. Most patients with rectal prolapse present with obvious manifestations and can be diagnosed based on a physical examination. Conversely, for a small proportion of patients with intussusception, diagnosis can be challenging (even after making them squat or sit).

Patients also present with additional functional disorders that are accompanied by anatomical abnormalities. It is crucial to assess these additional symptoms and their severity using preoperative scoring systems[1]. Radiological and physiological evaluations may explain some unclear symptoms and also reveal concomitant pelvic disorders[2].

Optimal treatment options for rectal prolapse remain controversial; even recent publications and systematic reviews have not recommended the most appropriate treatment option[3]. According to the practice guidelines proposed by the American Society of Colorectal Surgeons, the goal of a rectal prolapse surgery is to correct the prolapse without causing bowel dysfunction and improve the associated functional abnormalities[4].

This review focuses on the current diagnostic methods, additional treatment modalities, and controversial issues regarding surgical techniques for rectal prolapse.

EPIDEMIOLOGY

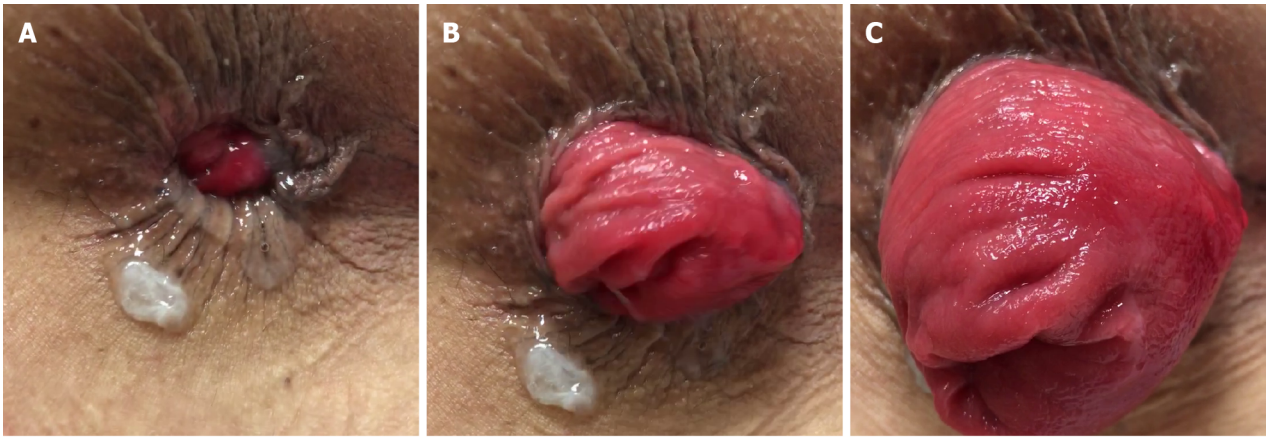
Rectal prolapse has an annual incidence of 2.5% (per 100000 people); their incidence increases after the fifth decade of life[5]. The condition is more common among women, inmates, and patients with mental disorders[6-8]. The most common symptoms are constipation, incontinence, incomplete evacuation, rectal bleeding, pain, and tenesmus[9]. Although the spectrum of symptoms varies with the type of rectal prolapse, 50%-75% and 25%-50% of the patients complain of fecal incontinence and constipation, respectively[10,11].

Although the disease progression is not understood clearly, chronic straining and constipation are the main predisposing factors. The presence of a deep Douglas pouch, redundant sigmoid colon, insufficient rectosacral fixation, and pelvic floor weakness may also contribute to disease progression [12]. Sustained recto-anal inhibition and the dilatator effect of the prolapsed segment may explain the low resting anal pressure and incontinence seen in most patients[13]. Furthermore, the initial increase in external sphincter tonus may be the first factor that initiates outlet obstruction, constipation, and a straining chain.

TYPES OF PROLAPSE

External rectal prolapse

External rectal prolapse is defined as a full-thickness protrusion of the rectum through the anal canal (Figure 1). A full-thickness rectal prolapse has concentric folds of prolapsed tissue, whereas prolapsed hemorrhoids and rectal mucosa have radial invaginations. Diagnoses can be made merely on the basis of history and physical examination findings. No specific test is necessary for diagnosis, except in patients with fecal incontinence. Patients can generally describe the extent of tissue prolapse and whether it reduces spontaneously or requires manual reduction. Most patients report rectal bleeding



DOI: 10.12998/wjcc.v11.i16.3680

Figure 1 Progression of external prolapse out of the anal canal. A-C: Prolapse becomes more evident with straining.

and pain that can be attributed to solitary rectal ulcers or irritation of the rectal mucosa[14]. Internal rectal prolapse (IRP) is not a precursor of and rarely progresses to external rectal prolapse[15,16].

Internal rectal prolapse (rectal intussusception)

IRP is characterized by the circular in-folding of the rectal wall into the lumen during straining. Typically appearing 6-8 cm above the anal canal, it has widely varying manifestations. For instance, it can be minimal (such as a 3 mm folding of the wall) or can comprise a circular invagination of all three layers of the rectal wall. In severe cases, IRP may fill the rectal ampulla, which can then obstruct the lumen and hinder stool passage[17]. It is difficult to visualize during a physical examination, and thus, difficult to diagnose[18].

The most common symptoms of IRP are constipation and obstructive defecation (85%), followed by fecal incontinence (56%)[19]. Fecal incontinence is more severe in patients with higher-grade IRP[13].

Differential diagnosis

Other conditions similar to rectal prolapse include prolapsing hemorrhoids and a mass prolapsing out of the rectum (Figure 2). Concentric folds of the rectum cannot be observed in prolapsing hemorrhoids because the remaining muscular wall of the rectum remains in place. Occasionally, early prolapse may not be completely circumferential but can still be distinguished from hemorrhoids, because it lacks grooves between the columns of prolapsing tissue[14].

CLINICAL MANIFESTATIONS

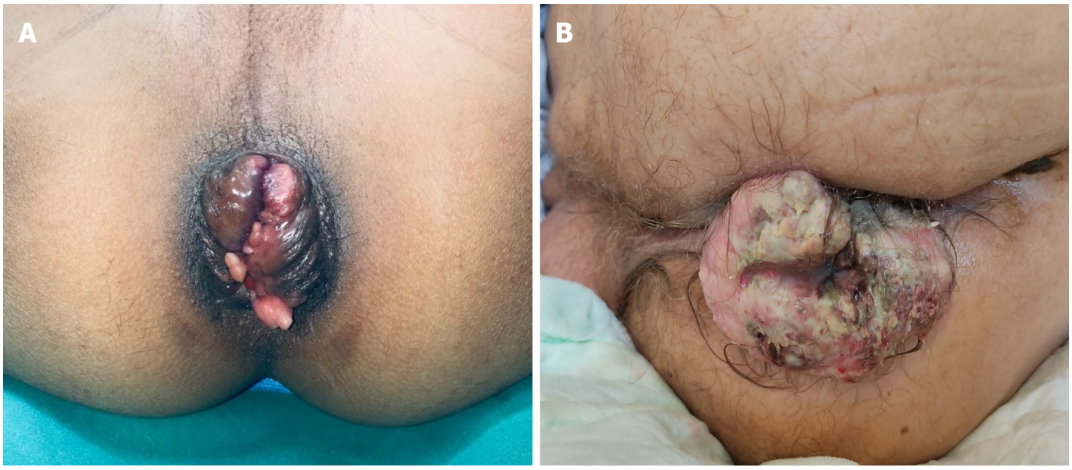
Constipation

Constipation assessment is a critical component of examination. Constipation may result from rectal intussusception, which leads to narrowing of the bowel lumen; the subsequent blockage then deteriorates with excessive straining and colonic dysmotility[10,11]. Patients with extreme constipation suggestive of colonic inertia also require a workup for this condition. Different scoring systems, such as the Wexner Constipation Score or the Rome 4 Criteria, are used to evaluate such patients[20,21].

A redundant colon may also be a predisposing factor for constipation and rectal prolapse. Constipation and excess straining likely contribute to prolapse development, but can also be exacerbated by the prolapse itself[14]. Differentiating impaired rectal emptying from slow-transit constipation may be difficult, and transit studies (such as the Sitz Marker Study) are useful for differential diagnosis.

Fecal incontinence

Fecal incontinence generally develops late in the clinical course of rectal prolapse. Several factors may contribute to the emergence of fecal incontinence; main factors comprise a patulous anus, continuous recto-anal inhibitory reflex with impaired recto-anal excitatory reflex, pudendal neuropathy, and external prolapse. Any kind of fecal incontinence (urge, passive, and mixed) may present with varying degrees of severity; in some cases, constipation may accompany incontinence[22]. Fecal incontinence is aggravated by recurrent prolapse, which creates stretch injuries in the sphincters[23]. Patient prognosis would improve if rectal prolapse is treated early. Although rectal prolapse repair does not directly correct sphincter dysfunction, it improves the symptoms of incontinence[24].



DOI: 10.12998/wjcc.v11.i16.3680

Figure 2 Differential diagnoses of rectal prolapse. A: Prolapsing hemorrhoids; B: Anal canal mass.

Fecal incontinence severity can be measured using different scoring systems, such as the Wexner/Cleveland Clinic Fecal Incontinence Score (CCFIS) and Fecal Incontinence Severity Index (FISI). The Wexner/CCFIS, which is the most well-known and most cited score, contains a five-item scale; each item is graded 0–4, and the total score is 20[1]. The FISI score qualifies the type and quantity of incontinence with regard to the number of episodes and generates a summary score in combination[25]. The FISI score is highly correlated with symptom severity and the Fecal Incontinence Quality of Life score. The Rapid Assessment Fecal Incontinence Score is a new scoring system that has been recently updated and validated; however, further research is required to assess its external validity[26].

DIAGNOSTİC MODALITIES

Fluoroscopic defecography

The use of fluoroscopic defecography (FD) has gradually decreased over the years; however, compared with existing modalities, FD has a higher detection rate of pelvic floor anomalies and allows imaging in a more natural position[2]. A 2017 systematic review and meta-analysis revealed that compared with magnetic resonance defecography, traditional FD has higher detection rates for rectocele, rectal prolapse, rectoanal intussusception, and perineal descent, but not for enterocele[27]. However, fluoroscopy has the following disadvantages: Inability to demonstrate the intrapelvic interaction of the pelvic organs[28], radiation exposure, inability to visualize the pelvic soft tissue, and low sensitivity [29]. Moreover, evacuation proctography may reveal retro rectal intussusception in asymptomatic individuals; Palit *et al*[30] revealed that proctography revealed IRP in 20% of the healthy volunteers that they analyzed[30].

The Oxford radiological rectal prolapse grading system is used to categorize rectal prolapse[31]; it categorizes rectal prolapse into five levels: High rectal (Grade I - level above the rectocele), low rectal (Grade II - level of the rectocele but above the anal canal), high anal (Grade III - descending to the top of the anal canal), low anal (Grade IV - descending into the anal canal), and external (Grade V - protrusion from the anal canal).

Dynamic magnetic resonance defecography

Dynamic magnetic resonance defecography (DMRD) allows the evaluation of concomitant pelvic floor disorders and enables clear demonstration of the pelvic anatomy. It provides information on both structural and functional abnormalities; this is extremely important, especially for patients who have undergone prior pelvic or perineal surgery[18]. DMRD can differentiate among mucosal, full-thickness rectorectal, and rectoanal intussusception. A small amount of rectal prolapse is normal and found in approximately 80% of the population[32]. DMRD also reveals associated anterior pelvic support defects, such as cystocele, rectocele, enterocele, and vaginal vault prolapse. In patients with multicompartment pelvic organ prolapse, urodynamic and urogynecological examinations should be performed before deciding whether concomitant surgical intervention is necessary[33]. The pelvic organ prolapse quantification system has been used for pelvic organ prolapse classification; it has a high correlation with DMRD findings[34]. Defecography may influence clinical decision-making and surgical approaches in 28%-41% of the cases[35,36].

DMRD must be used to evaluate the squeeze (Kegel), strain (Valsalva), and defecation (evacuation) phases for optimal reporting. For accurate visualization and grading of anterior and middle compartment prolapse, patients should be made to perform the Kegel exercise and evacuation first and the Valsalva maneuver thereafter[37]. The defecation phase should be repeated thrice for a proper diagnosis. Furthermore, radiologists must determine whether defecation has been achieved. Studies have revealed no significant differences in defecography findings between the supine and sitting positions[38,39].

The 2019 recommendations of the European Society for Radiology outline the H-line, M-line, and organ prolapse system, which allows for consistent grading of various pelvic floor disorders[40]. The H-line is measured from the inferior pubic bone to the posterior anorectal junction; the M-line is drawn perpendicularly, connecting the pubococcygeal line to the posterior H-line. A pubococcygeal line is drawn from the inferior pubic bone to the final coccygeal point (Figure 3).

Patients with postoperative recurrence should also be evaluated using DMRD. DMRD can identify synthetic materials, especially polyvinylidene fluoride meshes, and evaluate their position, integrity, and associated complications (such as scarring, infections, fistula formation, and recurrent prolapse)[41,42].

Anal manometry

Anal manometry provides valuable information about anal sphincter function, including the resting and squeeze pressures, length of the functional anal canal, recto-anal inhibitory reflex activity during rectal distension, rectal sensation, rectal compliance, and defecation function[2].

Manometric results indicative of anal hypotonia are frequently reported, and these include impaired maximal voluntary contraction in patients with rectal prolapse[43]; however, these findings rarely influence surgical planning, especially for external rectal prolapse[14]. Even then, anal manometry helps predict the postoperative patient prognosis. Patients with decreased anal pressures and slowed nerve conduction are more likely to have postoperative incontinence[44]. Glasgow *et al*[45] found that patients with a maximum squeeze pressure of > 60 mmHg had better postoperative continence, but the correlation between manometric findings and incontinence severity in them was low[45]. Therefore, postoperative functional evaluation using anal manometry may achieve more accurate findings. Manometry is more useful for addressing inconsistent data regarding pelvic floor function and evaluating continuous defecatory problems after surgery[2].

In patients with internal rectal prolapse, anorectal manometry and endoanal sonography confirm sphincter hypotonia and sphincter rupture, explain the origin of continence disorders, and identify dyssynergic defecation (anismus; a rare condition that requires physical therapy)[46].

Endoanal ultrasonography

Endoanal ultrasonography allows precise imaging of the sphincter complex, accurate recognition of occult anal sphincter defects[47], and mapping of the extent of sphincter injury. If a patient has a history of vaginal delivery, proctological/perianal surgery, or fecal continence impairment, sphincter integrity should be investigated using endoanal ultrasonography[23]. However, in patients with external rectal prolapse with no previous trauma, endoanal ultrasound is not necessary for the preoperative workup.

Colonoscopy and other diagnostic tools

Before rectal prolapse surgery, neoplasms and inflammatory bowel disease should be ruled out. Furthermore, 10%-15% of the patients have solitary rectal ulcers, which are generally indicative of surgical treatment[14]. Abdominal and pelvic computed tomography is optional and useful for ruling out malignancy and other diseases.

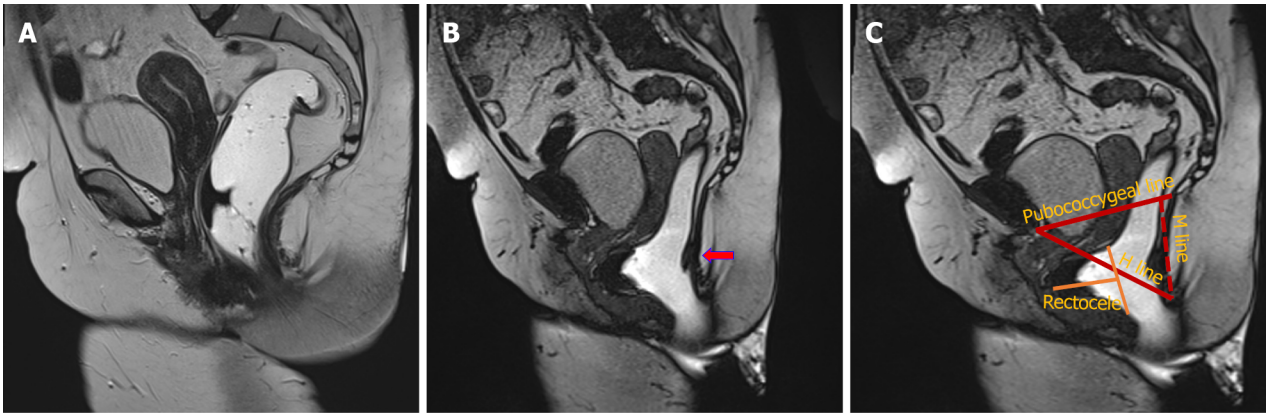
TREATMENT OPTIONS

Non-surgical therapies

Patients with internal rectal prolapse of Oxford grades I–III without incontinence, those with internal prolapse of Oxford grade IV with a high surgical risk, and those with minimally symptomatic external prolapse are candidates for conservative therapies[46]. Nonoperative management includes defecation training, use of stool softeners, and dietary changes. Patients should consume 30–40 g of fiber daily and perform at least 100 min of aerobic exercise weekly. Biofeedback therapy, which involves real-time training of pelvic muscle contraction and anal sphincter relaxation in coordination with rectal emptying, may also be beneficial. These treatments do not cure rectal prolapse, but may be useful for improving the quality of life. Surgery should be considered if conservative therapies fail after 2–3 mo[48].

Surgical treatment

Surgical treatment is indicated for internal prolapse of Oxford grades III–IV and symptomatic external rectal prolapse[48]. To date, many different surgical techniques have been described in literature; many



DOI: 10.12998/wjcc.v11.i16.3680

Figure 3 Dynamic magnetic resonance defecography images. A: Magnetic resonance imaging during rest; B: The red arrow indicates slight rectal intussusception and advanced pelvic prolapse present during straining; C: Pubococcygeal, M and H lines. The yellow line reveals severe rectocele accompanying pelvic prolapse.

of these have been completely abandoned or are rarely used in modern surgical treatment[4].

Surgical treatment options are generally divided into two categories, namely abdominal and perineal approaches. Choice of the optimum approach is usually dictated by the patient's general condition (age, comorbidities, and bowel function) and the surgeon's experience and preference[49]. Each approach has its own advantages and disadvantages.

Abdominal vs perineal approach

Generally, frail older patients with comorbidities are better candidates for perineal operations because these procedures can be performed under locoregional anesthesia with lower perioperative morbidity and shorter hospital stays. Although some retrospective, low-powered studies suggest that, compared with abdominal procedures, these procedures have higher recurrence rates and worse functional outcomes[50], a recent Cochrane review found no difference between the two procedures[51]. Furthermore, the PROSPER trial did not find any differences in recurrence between abdominal and perineal approaches, especially since patients for whom a perineal procedure was elected were older and had worse physical status and bowel function than patients for whom an abdominal procedure was elected in this study[5]. A meta-analysis performed by Pellino *et al*[52] claimed that the recurrence rate might be higher with perineal approaches, which may be related to the fact that the patients are old and the follow-up periods are long; therefore, a clear result cannot be established[52].

Perineal approaches

Among perineal interventions, the Delorme procedure (resection of the mucosa and plication of the rectal wall) is generally preferred for short-segment prolapse (< 5 cm long) and the Altemeier procedure (perineal proctosigmoidectomy; Figure 4) is reserved for long-segment prolapse; both technique achieve similar results in terms of reccurence[53]. Moreover, different randomized trials have suggested that these approaches have significant improvement from baseline quality of life[5,54].

Addition of levatorplasty

Levatorplasty theoretically improves postoperative incontinence by restoring the anorectal anatomy, and can be performed if the surgeon prefers a perineal procedure; however, its benefit remains unclear [55]. Some studies have revealed significant improvements in incontinence scores and decreased recurrence rates with levatorplasty[56,57]. Furthermore, levatorplasty enables tension-free overlap repair and repair of any undetected sphincter damage in the upper part of the sphincter complex[7].

Stapled transanal rectal resection (STARR): Stapled transanal rectal resection is another transperineal approach that may be a good alternative, especially for patients with obesity who experience obstructive defecation, associated rectocele, rectal intussusception, and satisfactory sphincter performance[58]. As this reduces rectal compliance, patients with anal incontinence are not good candidates for this technique. The most frequent complication is urgency, and serious complications, such as staple line disruption, pelvic cellulitis, rectovaginal fistula, peritonitis, and stricture, have also been reported. However, the STARR procedure is safe and efficient in treating ODS symptoms and enhancing patients' quality of life[59].

Natural orifice transanal endoscopic rectopexy: This technique was introduced in 2019 as an alternative to the abdominal and perineal methods for complete rectal prolapse[60]. In this procedure, the colon is

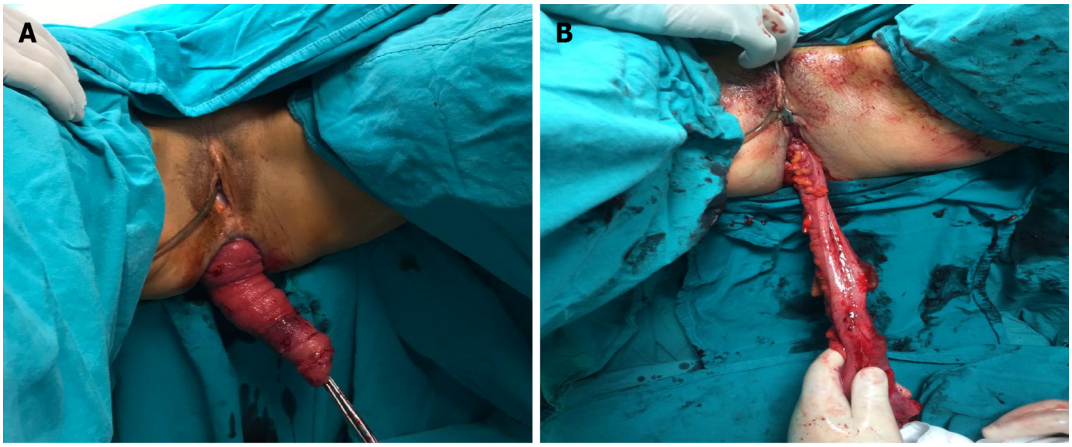


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Figure 4 A patient with external rectal prolapse who underwent an alternative procedure. A: External rectal prolapse; B: Altemeier procedure.

fixed to the abdomen and promontory using custom endoscopic devices without mesh. Although this method is unlikely to offer the same level of long-term durability as other approaches, it may be an effective choice for patients with frailty, particularly when mesh avoidance is preferred[61].

Abdominal approaches

Abdominal procedures are generally preferred for patients fit to withstand surgery without age concerns[4] because of lower recurrence rates and better functional outcomes. Patients with severe endometriosis, history of severe adhesions, and peritonitis are unsuited for abdominal approaches.

Although the outcomes of open, laparoscopic, and robotic repairs are similar, minimally invasive approaches are more common because of faster recovery, lower morbidity, decreased postoperative pain, and lesser blood loss[62,63].

Abdominal surgeries vary according to the dissection plane and fixation technique. All of these different procedures aim to prevent prolapse by fixing the rectum and provide better functional outcomes.

Dissection plane

The plane of rectal dissection is a controversial issue in rectal prolapse surgery. A pooled analysis of 532 patients was performed to determine the influence of the extent of rectal mobilization on the rate of recurrent rectal prolapse after abdominal rectopexy; both univariate and multivariate analyses suggested that circumferential mobilization was associated with a lower long-term recurrence rate[64]. However, during posterior and lateral mobilization, there is a risk of autonomic nerve plexus injury and worsening of preexisting constipation and the obstructive defecation syndrome. Speakman *et al*[65] found that division of the lateral ligaments was a risk factor for postoperative constipation and that the rectal electrical sensory thresholds were increased in patients who underwent ligament division[65].

The risk of sigmoidocele and enterocele development also increases with lateral dissection[7]. Several studies have suggested that avoiding complete rectal mobilization improves postoperative constipation and protects from *de novo* constipation with a similar rate of recurrence[66,67].

During posterior mesh rectopexy (Wells procedure), anterior dissection is avoided, and the dissection is performed through the lateral and posterior aspects. After attaching either a polyester or polypropylene mesh to the presacral fascia, it is loosely wrapped around the rectum (270˚)[68]. An overall improvement in continence (74%-100%) was reported with this technique, with conflicting results regarding constipation and *de novo* constipation in 5%-44% of the patients[12]. Other studies also revealed new-onset constipation after posterior mesh rectopexy in more than 50% of the patients[51,69].

In lateral mesh rectopexy (Orr–Loygue procedure), the rectum is mobilized circumferentially and the mesh is fixed to the anterolateral rectal wall and sacral promontory[57]. A significant reduction in incontinence scores was reported after 1 year[57]. However, as for posterior rectopexy, worsening of constipation has been reported in up to 27% of the patients[70].

In resection rectopexy (Frykman–Goldberg procedure), after complete rectal mobilization and sigmoid resection, the distal rectum is fixed to the presacral fascia using sutures[71]. As fixation performed by sutures this is the most preferred technique in the United States because of potential mesh complications and lawsuits[72,73]. This procedure is preferred in cases of proven slow-transit constipation, redundant sigmoid colon, and preexisting diverticular disease[18,74]. A Cochrane review conducted in 2015 suggested that bowel resection was associated with lower rates of constipation than rectopexy alone[51]. Smedberg *et al*[54] compared four surgical approaches (resection, suture, Altemeier,

and Delorme) in a randomized clinical trial and found none to be superior; however, a 20% recurrence rate was observed. Laparoscopic resection rectopexy has higher complication rates than laparoscopic ventral mesh rectopexy (LVMR); however, it offers a better improvement in incontinence[75].

In suture rectopexy, the rectum is circumferentially mobilized, two or three sutures are placed on either side, and the lateral ligaments are fixed to the presacral fascia using non-absorbable sutures[76]. A systematic review suggested higher recurrence rates but lower operative times with suture rectopexy than with ventral mesh rectopexy[77]. As expected, owing to extensive mobilization of the rectum, a longer gastrointestinal transit time and worse functional outcomes in terms of constipation were reported in a randomized study[78].

Although a relatively new technique, ventral mesh rectopexy is the most common procedure for rectal prolapse in Europe[63]. D' Hoore first described this technique in 2004; no rectal mobilization or lateral dissection is performed in the original technique, and the lateral ligaments are preserved[56]. The mesh is placed on the anterior rectal wall, and fixation to the sacral promontory is performed using sutures, staplers, or even surgical glue[79]. Reinforcement of the rectovaginal septum, correction of the enterocele, correction of genital prolapse by adding sacrocolpopexy, and preservation of the hypogastric and parasympathetic nerves are possible by this technique. Therefore, ventral mesh rectopexy may be the optimal treatment modality for patients with incontinence and concomitant anterior compartment disorders. Owing to the lower rate of postoperative constipation, lower recurrence rate, and avoidance of colonic anastomosis[74], it appears to be superior to the other abdominal techniques explained above in terms of functional outcomes[80].

Laparoscopic versus robotic approach

The laparoscopic and robotic approaches do not differ in terms of rates of conversion to open surgery [81]. However, in deep and narrow pelvises or in patients with morbid obesity, the robotic approach has eliminated the limitations of the laparoscopic approach; it enables meticulous dissection in deep and narrow spaces[82,83] (Figure 5).

Moreover, robots can ease the learning curve, a study revealed that almost 100 cases of the laparoscopic approach and only 20 cases of the robotic approach were required to gain proficiency[84].

A meta-analysis of eight studies suggested that robotic surgery is associated with significantly fewer complications than laparoscopic surgery[85]; furthermore, the recurrence rates do not differ significantly between the two (0%-20% *vs* 0%-26.7%)[86,87].

Robotic surgery is considered more expensive than other techniques; however, after adjusting for the cost of an improved health-related quality of life, the expenditure is almost comparable with that of laparoscopic surgery[88]. Although reinforcement of the rectovaginal septum is reportedly similar between the robotic and laparoscopic approaches, an improved quality of life has been attributed to a more precise mesh fixation[63].

Mesh type

Another contentious aspect of rectal prolapse surgery is the mesh type. Meshes can be divided into three categories: First generation (synthetic non-absorbable meshes made of polypropylene or expanded polytetrafluoroethylene), second generation (combinations of more than one synthetic material (such as polypropylene, polyester, or expanded polytetrafluoroethylene) and/or other materials (such as titanium, omega-3 fatty acids, poliglecaprone-25, and polyvinylidene fluoride), and third generation (biological prostheses). Compared with first-generation meshes, second-generation meshes are less susceptible to infection, adhesion, and recurrence. Furthermore, biological meshes provide a matrix for native cells to populate, which fills the hernia defect with connective tissue[89].

In 2008, the National Institute of Clinical Excellence conducted a review that revealed erosion rates of 0%, 7%, and 14% for biological meshes (xenografts), synthetic meshes, combined biological and synthetic meshes, respectively[90]. Even then, the European Society of Coloproctology guidelines on the use of mesh for rectal prolapse repair suggested that both mesh types were suitable for repair; however, this suggestion was based on low-quality data. The superiority of one mesh type over the other has not yet been demonstrated[91]. Biological grafts can be used in high-risk patients (diabetics; smokers; and those with previous pelvic radiation, inflammatory bowel disease, and intraoperative findings of a rectal or vaginal leak)[92,93], even though current data have not indicated any particular benefits.

POSTOPERATIVE EVALUATION AND ADDRESSING RECURRENCE

After surgery, patients should be advised against lifting, engaging in sexual intercourse, and consuming laxatives for at least 6 weeks postoperatively. The functional outcomes may not improve promptly and may not resolve completely; patients should be informed of these possibilities. Pelvic floor physical therapy can be continued for patients who present with obstructive defecation or incontinence preoperatively[94].

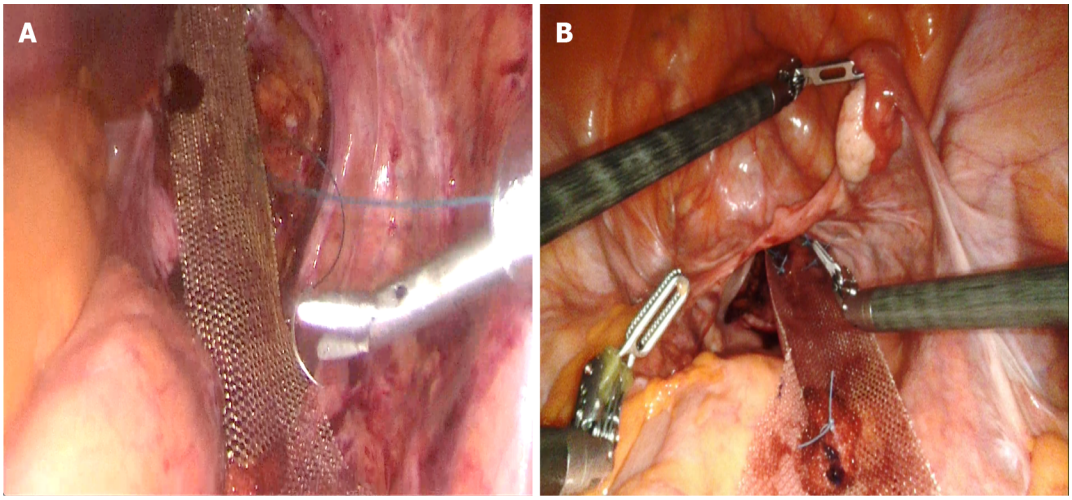

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Figure 5 Laparoscopic and robotic ventral mesh rectopexy. A: Laparoscopic mesh placement before peritoneal closure; B: Robotic mesh placement before peritoneal closure.

Both patient-related (sex, body mass index, and prior history of prolapse repair)[95] and technical (inadequate anterior rectal dissection, inadequate fixation of the mesh to the anterior rectal wall or sacral promontory, and the mesh type)[84,96] factors may affect recurrence rates. In perineal approaches, stapled anastomosis, shorter specimen lengths, and severe pre-existing constipation are associated with an increased risk of recurrence[97]. Furthermore, Fu *et al*[98] found that a prolonged pudendal nerve terminal motor latency, which indicates denervation of the external anal sphincter, is predictive of recurrence.

Patients presenting with recurrence should undergo magnetic resonance imaging (MRI)-based evaluations for identifying the potential etiology. Most importantly, patients should wait for at least 6 months before undergoing a reoperation[94].

In patients with early recurrence of full-thickness rectal prolapse, the European Society of Coloproctology guidelines recommend reoperation to reattach the mesh to the sacral promontory. In case of erosion, location of the mesh erosion is important for treatment. Depending on the extent of the erosion, surgical removal of the mesh can be considered if a technically feasible, and diverting stoma should be considered. Reintervention presents a significant technical challenge and should only be performed at experienced centers[91].

A systematic literature review failed to develop an algorithm for treatment of recurrent rectal prolapse[99]. Steele *et al*[100] reported significantly more recurrences after a perineal procedure than after an abdominal procedure for recurrent external rectal prolapse[100]. Repetition of a perineal proctosigmoidectomy is possible for recurrence after a resection procedure but must be utilized with great caution because of the possibility of leaving an ischemic segment between anastomoses unless the previous anastomosis is resected[101,102]. In addition, the recurrence rate following redo perineal proctosigmoidectomy is higher than that after the primary procedure[103].

Studies have suggested that the efficacy of repeating LVMR for recurrent prolapse following a failed perineal or abdominal procedure is similar to that of primary LVMR[98,104]. Conversely, a prospective cohort study on 109 patients who underwent ventral rectopexy revealed 1-year, 3-year, and 5-year prolapse recurrence rates of 1.4%, 6.9%, and 9.7% for primary repairs and 13.9%, 25%, and 25% for recurrent prolapse repairs respectively. The time to recurrence was shorter in patients who underwent Ventral Rectopexy for recurrent prolapse[105]. Further studies are required to understand the effectiveness of LVMR in patients with a recurrence.

CONCLUSION

Management of rectal prolapse is complex. To select the appropriate surgical intervention, factors such as the patient's medical history, clinical symptoms, surgeon's experience, and hospital equipment must be considered. Precise preoperative planning would help choose the best option for the patient, including validated scoring systems and imaging modalities. Although robotic rectopexy is anticipated to eventually be deemed the gold standard, intriguing methods such as the NOTES technique continue to be developed. Close postoperative follow-up is crucial to monitor improvements in the quality of life, incomplete resolution of symptoms, or recurrence. More randomized controlled studies are still required to determine the best surgical treatment; however, close follow-up of quality of life and

functional outcomes and proper management of patients will help achieve better results, regardless of the method chosen.

ACKNOWLEDGEMENTS

Dr. Ali Konan for permission to use photographs in Figure 3.

FOOTNOTES

Author contributions: Oruc M designed the report, drafted the manuscript, and reviewed the literature; Erol T designed the report, drafted the manuscript, supervised manuscript writing, and provided surgical examples.

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

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Fan JR

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3694-3705

DOI: 10.12998/wjcc.v11.i16.3694

ISSN 2307-8960 (online)

MINIREVIEWS

Application of laparoscopic surgery in gallbladder carcinoma

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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 scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Chowdhury D, United Kingdom; Hori T, Japan; Tenreiro N, Portugal

Received: December 10, 2022
Peer-review started: December 10, 2022
First decision: February 7, 2023
Revised: March 4, 2023
Accepted: April 19, 2023
Article in press: April 19, 2023
Published online: June 6, 2023

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Abstract

Gallbladder carcinoma (GC) is a rare type of cancer of the digestive system, with an incidence that varies by region. Surgery plays a primary role in the comprehensive treatment of GC and is the only known cure. Compared with traditional open surgery, laparoscopic surgery has the advantages of convenient operation and magnified field of view. Laparoscopic surgery has been successful in many fields, including gastrointestinal medicine and gynecology. The gallbladder was one of the first organs to be treated by laparoscopic surgery, and laparoscopic cholecystectomy has become the gold standard surgical treatment for benign gallbladder diseases. However, the safety and feasibility of laparoscopic surgery for patients with GC remain controversial. Over the past several decades, research has focused on laparoscopic surgery for GC. The disadvantages of laparoscopic surgery include a high incidence of gallbladder perforation, possible port site metastasis, and potential tumor seeding. The advantages of laparoscopic surgery include less intraoperative blood loss, shorter postoperative hospital stay, and fewer complications. Nevertheless, studies have provided contrasting conclusions over time. In general, recent research has tended to support laparoscopic surgery. However, the application of laparoscopic surgery in GC is still in the exploratory stage. Here, we provide an overview of previous studies, with the aim of introducing the application of laparoscopy in GC.

Key Words: Gallbladder carcinoma; Laparoscopic surgery; Open surgery; Gallbladder perforation; Port site metastases; Prognosis

Core Tip: Gallbladder carcinoma (GC) is a rare cancer of the digestive system. Surgery is the main treatment strategy for this disease. The gallbladder was one of the first organs to undergo laparoscopic surgery. However, the safety and feasibility of laparoscopic surgery in patients with GC remain controversial. The disadvantages and advantages of laparoscopic surgery have been reported by different studies. In general, recent studies have tended to support laparoscopic surgery by experienced surgeons in selected patients. Clinical research with high-level evidence is required to validate the existing conclusions.

Citation: Wu X, Li BL, Zheng CJ. Application of laparoscopic surgery in gallbladder carcinoma. *World J Clin Cases* 2023; 11(16): 3694-3705
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3694.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3694

INTRODUCTION

Since the second half of the last century, noncommunicable diseases have replaced infectious diseases as the main global health concern[1]. Specifically, over 75% of premature deaths among individuals aged 30–70 years are caused by noncommunicable diseases[1]; cardiovascular disease and cancer are the main culprits. Based on current trends, cancer is expected to surpass cardiovascular diseases and become the leading cause of premature death during this century[2]. More than 80% of all countries have formulated cancer control plans; however, detailed evidence-based programs that are tailored to resource levels remain lacking[3]. Digestive system tumors, such as gastric and colon cancer, account for a high proportion of the global cancer incidence and mortality rates[4,5]. Gallbladder carcinoma (GC) is a relatively rare gastrointestinal tumor. According to the 2018 global cancer estimates of incidence and mortality, its morbidity and mortality rates account for 1.2% and 1.7% of all tumors, ranking 22nd[5]. In the 2020 edition, the incidence and mortality rates account for 0.6% and 0.9% of all tumors, ranking 25th[4]. Furthermore, the incidence of GC varies greatly by country and region[6]. For example, in China, where the incidence is high, an estimated 30–50 thousand new cases and 25–40 thousand deaths occur annually[7,8], while in the United States, where the incidence is low, an estimated 4–10 thousand new cases and 2–4 thousand deaths occur each year[8,9]. The therapeutic outcome of GC remains unsatisfactory, with a median survival time of approximately 25 mo after curative resection[10,11]. Surgery is the only potential cure for GC[6,11], and selecting a reasonable surgical extent and approach for individual patients is crucial. Moreover, laparoscopic technology has developed rapidly since its application in the field of surgery[12-15], and favorable outcomes of laparoscopic surgery for GC have been achieved[16-18]. However, the safety and feasibility of laparoscopic surgery for patients with GC remain controversial[19]. The present paper aims to review the changes in tumor staging of GC, the application of laparoscopic techniques in surgery, and the advantages and disadvantages of laparoscopic surgery for GC, in order to analyze the safety and effectiveness of laparoscopic surgery for patients with GC.

TUMOR STAGING OF GC

Tumor staging is vital to determine the subsequent treatment and prognosis. The American Joint Committee on Cancer (AJCC) cancer staging system is the most commonly used and widely accepted tumor staging system. The AJCC staging system stages GC according to the depth of tumor invasion, lymph node status, and distant metastases[20]. Specifically, T staging is based mainly on the depth of invasion of the gallbladder wall, as well as the direct invasion of the liver and other surrounding organs (Table 1). N staging is based primarily on the number of positive lymph nodes (Table 2), and M staging is based on the presence or absence of distant metastases. However, GC staging differs significantly between the 7th and 8th editions of the AJCC staging system. The changes are based on the biological behavior and prognosis of different tumor stages. Identifying the stage of the tumor and the content of the stage change is crucial for the selection of appropriate treatment, especially when deciding whether the tumor is suitable for laparoscopic surgery.

Two main changes were made from the AJCC 7th edition to the AJCC 8th edition of GC tumor staging. First, the T2 stage has been further classified according to the tumor location as T2a (peritoneal side) and T2b (hepatic side). T2b exhibits a worse prognosis than T2a[21]. Second, N staging is no longer based on the location of lymph node metastases, but rather on the number of lymph node metastases, which is correlated with the prognosis[22]. These changes have practical implications for laparoscopic surgery in patients with GC. For example, no-touch radical excision is more feasible for T2a tumors than T2b tumors. Moreover, at least six lymph nodes must be resected and evaluated[23,24], including in laparoscopic surgery.

Table 1 Definition of T-stage for gallbladder carcinoma

T category	T criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor invades the lamina propria or muscular layer
T1a	Tumor invades the lamina propria
T1b	Tumor invades the muscular layer
T2	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) or tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T2a	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)
T2b	Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

According to the AJCC 2018 TNM classification, 8th edition.

Table 2 Definition of N-stage for gallbladder carcinoma

N category	N criteria
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to one to three regional lymph nodes
N2	Metastases to four or more regional lymph nodes

According to the AJCC 2018 TNM classification, 8th edition.

APPLICATION OF LAPAROSCOPIC TECHNIQUE IN SURGERY

The advent of laparoscopy has revolutionized surgery. Compared with traditional open surgery, laparoscopic surgery has the advantages of convenient operation and magnified field of view. It allows surgeons to see the details of the interior of the abdominal cavity, providing better operating conditions. Surgeons can perform a variety of complex operations by manipulating various movements of the sticks, avoiding blood stains on the gloves and direct contact of hands and organs. Additionally, for patients, the long scar on the abdomen from open surgery is replaced by a few small holes, which facilitates physical and psychological recovery. Laparoscopic techniques have been successful in most aspects of surgery. For example, for laparoscopic gastrectomy, numerous clinical studies have reported no differences from open surgery in postoperative complications, mortality, and oncological outcomes [25-28]. Laparoscopic gastrectomy leads to less blood loss, shorter hospital stays, and faster return of bowel function, at the expense of longer operation time. Due to the short- and long-term advantages, laparoscopic gastrectomy has been recommended in many national guidelines[29]. Moreover, laparoscopic liver resection has demonstrated better surgical outcomes, such as duration of hospitalization and postoperative complication rates, with similar overall survival and disease-free survival time, compared with open liver resection[30]. Due to the widespread application of laparoscopic liver resection, the International Laparoscopic Liver Society was formed in 2016 by a group of experts[31]. Single-incision and robot-assisted technology are also available for minimally invasive liver surgery[32, 33]. Additionally, laparoscopic techniques have achieved great success in the treatment of adrenal, prostate, and rectal diseases, among others[34-36]. For some established laparoscopic procedures, such as cholecystectomy, different methods and port numbers have been reported[37]. Laparoscopic surgery has also been combined with endoscopic techniques to treat concomitant gallstones and common bile duct stones, early gastric cancer, gastrointestinal stromal tumors, and other diseases[38-40]. Compared with its relatively established application in gastrointestinal surgery, the application of laparoscopic surgery in GC is still in the exploratory stage.

LAPAROSCOPIC SURGERY FOR GC

The gallbladder was one of the first organs to undergo laparoscopic surgery. Mühe performed the first laparoscopic cholecystectomy (LC) in 1985, and Dubois began to regularly perform LC by 1988[41]. Thereon, the application of laparoscopic techniques in benign diseases of the gallbladder developed quickly, and LC has become the gold standard treatment for gallstones, gallbladder polyps, and other benign diseases. However, the application of laparoscopy in GC is far inferior to that in gastrointestinal tumors. The limitations include the clarity of the endoscopic field of view, the convenience of operation, and most importantly, the principles of no-touch surgery. Nevertheless, research over the past several decades has focused on laparoscopic surgery for GC.

Research before 2000

Since the application of LC, the safety of this operation has gained attention. The two major risks of laparoscopy for GC include gallbladder perforation and port site metastasis. As the gallbladder serves as a temporary storage site for bile, intraoperative perforation must be avoided. Sarli *et al*[42] performed a matched cohort analysis involving 1127 patients who underwent LC. Intraoperative gallbladder perforation occurred in more than 10% of patients (131/1127), and the only risk factor associated with gallbladder perforation was the surgeon's experience. Moreover, a study in Italy of 350 consecutive patients who underwent LC at the authors' hospital revealed that chronic cholecystitis, gallbladder hydrops, and a history of previous laparotomies were risk factors for gallbladder perforation during surgery[43]. Specifically, the probability of intraoperative gallbladder perforation was 3.5% among patients with no risk factors and up to 25% among those with all risk factors. Accidental bile spillage induced by gallbladder perforation during surgery may result in tumor implantation and metastasis, which is one of the greatest concerns of laparoscopic surgery for GC. With the widespread application of laparoscopic technology in gastroenterology and gynecology, whether laparoscopic surgery could result in tumor seeding in patients with GC and other abdominal tumors has been studied. A questionnaire study from Germany, Switzerland, and Austria including 117840 patients that underwent LC (including 409 cases of incidental GC) and 412 patients that underwent laparoscopic colorectal procedures found that 109 patients experienced tumor recurrence[44]. Thus, laparoscopic surgery for cancer exhibited a higher rate of abdominal wall metastasis than that of open surgery, and the use of plastic retrieval bags and an intact tumor specimen did not eliminate the possibility of port site recurrence. Furthermore, Z'graggen *et al*[45] studied 37 patients with preoperatively unknown gallbladder adenocarcinoma and found that these patients had a high rate of port site recurrence, which increased in cases of gallbladder perforation. Additionally, a national, multicenter study from Sweden involving data from 30 hospitals, including 11976 LCs, found that, of 447 patients with GC, 270 had their gallbladder removed, 55 underwent laparoscopic surgery, and 9 exhibited port site metastasis[46]. The researchers inferred that port site metastases are common and recommended open surgery in cases of suspected GC. In addition to gallbladder perforation and port site metastasis, pneumoperitoneum is also expected to be associated with poor prognosis[44]. For these reasons, many researchers have proposed that laparoscopic surgery is more appropriate for patients with early-stage GC. In addition, Wibbenmeyer *et al*[47] identified 9 patients with GC out of 928 patients who underwent cholecystectomy and reported that this procedure was suitable for patients with GC confined to the mucosa. Overall, early studies on laparoscopic surgery for GC focused primarily on the risks of laparoscopic technology.

Research from 2000 to 2010

After a period of application, the focus of research on laparoscopic surgery for GC shifted from the risks of surgery to the changes in the treatment of GC. However, intraoperative gallbladder perforation remained an issue. A Japanese survey of 498 patients with GC revealed that approximately 20% of patients who underwent LC experienced gallbladder perforation during surgery, and their survival rate was significantly lower than that of patients without gallbladder perforation[48]. Recommendations have also been made for unsuspected GC after LC. Steinert *et al*[49] reviewed the studies regarding GC and LC and recommended a radical procedure and additional port site excision after a postoperative diagnosis of stage ≥ T2 GC. A study from Japan identified 9 patients with unsuspected GC from a cohort of 1663 patients who underwent LC[50]. Five of the nine patients experienced tumor recurrence and died 4–37 mo after the initial operation. As a result, the authors emphasized the importance of preventing bile spillage. The widespread popularization of LC has also promoted the diagnosis and treatment of early-stage GC. Kokudo *et al*[51] retrospectively studied 152 patients with GC and found that the preoperative diagnostic accuracy for T and N staging was 52.6% and 24.5%, respectively. These low rates of preoperative diagnosis hinder the selection of appropriate treatment options. Shih *et al*[52] compared 53 patients with incidentally diagnosed GC and 54 patients with preoperatively diagnosed lesions. They found that LC could result in the early discovery of GC, likely improving patient prognosis. Moreover, Darabos and Stare[53] reviewed 3158 patients who underwent LC and 3083 who underwent classic cholecystectomies. They reported that more early-stage GC could be diagnosed and treated due to the increased use of LC, highlighting the importance of LC for early-stage GC. Thus,

advances in laparoscopic equipment and surgical techniques have played a distinct role in promoting the development of laparoscopic surgery for GC.

Research from 2010 to 2020

Research from 2010–2020 evaluated the relationship between bile spillage caused by intraoperative perforation and the prognosis of GC. In a Korean study, 12 patients with GC with intraoperative bile spillage were compared with 16 patients without bile spillage[54]. Both disease-free survival (71.4 *vs* 20.9 mo) and overall survival (72.6 *vs* 25.8 mo) were significantly shorter in the bile spillage group. The authors demonstrated that bile spillage was associated with incomplete resection and systemic recurrence, and they recommended that open surgery should be considered when GC is suspected. With the widespread use of retrieval bags, studies evaluated whether the routine use of retrieval bags would reduce the occurrence of port-site complications. A meta-analysis was performed to investigate the role of retrieval bags in LC, but no significant benefit in reducing the infection rate was found[55]. Despite concerns of the risks of laparoscopic surgery, a growing number of studies began to suggest its advantages[56-59]. For example, Goetze and Paolucci[60] used the German Registry system and analyzed 837 patients with incidental GC. They divided the patients into three groups: A laparoscopic approach group, an open surgery group, and an initially laparoscopic approach but converted to open surgery group. The laparoscopic approach was associated with significantly better 5-year survival rates and had similar accidental intraoperative perforation rates and recurrence rates to those of open surgery. Moreover, Yoon *et al*[61] performed a 10-year prospective cohort study, including 45 patients with GC (Tis, n = 2; T1a, n = 10; T1b, n = 8; T2, n = 25). The disease-specific survival rate was 92.3%, and the authors considered the long-term prognosis to be favorable and recommended laparoscopic surgery for selected patients. Furthermore, Jang *et al*[62] studied 197 patients with stage T1 GC and reported that the 5-year disease-specific survival rates were similar in patients who underwent LC and open cholecystectomy, as well as in patients underwent extended and simple cholecystectomy. Due to the advantages of a shorter hospital stay, less blood loss, and better cosmetic outcomes, they recommended LC to be performed by highly experienced surgeons as standard treatment for stage T1 GC. Moreover, Itano *et al*[63] studied 19 patients with suspected stage T2 GC and reported that the laparoscopic surgery group had lower intraoperative blood loss (104 *vs* 584 mL), shorter postoperative hospital stays (9.1 *vs* 21.6 d), and similar operative time (309 *vs* 324 min) and numbers of harvested lymph nodes (12.6 *vs* 10.2) compared with the open surgery group. They also reported no cases of recurrence after a mean follow-up time of 37 mo. Hence, the authors recommended laparoscopic surgery as the preferred strategy for suspected stage T2 GC. In a retrospective study from India, 24 patients who underwent radical LC were compared with 46 patients who underwent radical open cholecystectomy[64]. Compared with the open group, the laparoscopic group had longer operating time (270 *vs* 240 min), lower blood loss (200 *vs* 275 mL), and similar mortality and lymph node yield. Thus, these authors also recommended radical LC for selected patients with GC. Shirobe and Maruyama[65] reported a study on 11 patients with GC who underwent radical LC with lymph node dissection. The 5-year survival rates of patients with stages T1b and T2 GC were 100% and 83.3%, respectively. Therefore, the authors recommended exclusive laparoscopic surgery for patients with stages T1b and T2 GC. Due to the advances in laparoscopic technology, even reoperation for incidental GC can be completed laparoscopically[66,67]. Moreover, laparoscopic resection of the hepatoduodenal ligament and IVb-V segments could be performed appropriately and safely at experienced centers. Although controversy remains, laparoscopic surgery has become more common for GC due to its rapid development and proven efficacy for other types of abdominal tumors.

Research from 2020 and beyond

In recent years, more studies have been conducted on laparoscopic surgery for GC. Because of the development of high-definition display equipment, the refinement of surgical equipment, and the technical progress of surgeons, current research supports the application of laparoscopic surgery for GC. Kim *et al*[68] performed a propensity analysis to compare the outcomes of pure extended LC and open extended cholecystectomy. They found that extended LC resulted in shorter postoperative hospital stays (7 *vs* 12 d) and similar complication rates and disease-free survival rates compared with open surgery. Moreover, Navarro *et al*[69] performed a propensity score-matched analysis of patients with stage T2 GC. They compared 43 patients who underwent radical LC with 43 who underwent open radical cholecystectomy and found that the LC group had a shorter hospital stay, lesser blood loss, fewer complications, and similar 5-year overall and disease-free survival rates compared with open surgery group. Similarly, Wang *et al*[18] retrospectively reviewed 106 patients with incidental GC after LC. All patients underwent reoperation, and radical laparoscopic reoperation resulted in better 1-year (95.56% *vs* 86.89%) and 5-year (44.44% *vs* 29.51%) survival rates, lesser blood loss (100 ± 25.4 *vs* 200 ± 45.6 mL), shorter hospital stays (3.5 ± 1.9 *vs* 5.6 ± 2.7 d), and lower complication rates (6.7% *vs* 13.1%) compared with open surgery. In addition, a study from China included 50 patients with GC and found that laparoscopic surgery was associated with a shorter postoperative hospital stay (6.2 ± 2.4 *vs* 8.6 ± 2.3 d) and lesser intraoperative blood loss (242 ± 108.5 *vs* 401 ± 130.3 mL)[70]. Moreover, Bakos *et al*[71] reported a study of 47 patients with GC and found that LC could diagnose GC at an early stage in some patients[71]. Cho *et al*[72] performed a propensity score-matched analysis to evaluate the effects of

laparoscopic surgery on patients with stage T2 GC. Compared with the open surgery group, the laparoscopic surgery group showed significant advantages in terms of operation time (316.8 ± 80.3 *vs* 218.9 ± 145.0 min) and postoperative hospital stay (14.4 ± 6.0 *vs* 8.4 ± 5.9 d). However, the 3-year overall and disease-free survival rates were similar between the laparoscopic and open surgery groups. Hamad *et al* [73] used the National Cancer Database to investigate the impact of different operative approaches on lymph node evaluation and yield. They identified 2014 patients and found that patients who underwent open and minimally invasive surgery had similar lymph node evaluation and yield rates. Due to the difficulty in diagnosing GC by only imaging tests before surgery, Tokumitsu *et al*[74] reported and recommended their novel approach using whole-layer LC and gallbladder bed dissection, which could serve as an optimal treatment strategy. Imamura *et al*[75] evaluated 13 patients who underwent whole-layer LC and 18 who underwent laparoscopic gallbladder bed resection, and reported that their surgical strategy was curative and safe.

Systematic reviews have also provided evidence supporting the use of laparoscopic surgery for GC. Liu *et al*[76] systematically reviewed 24 studies of minimally invasive surgery for GC and found that minimally invasive surgery for GC could be performed safely in selected patients by experienced surgeons. Feng *et al*[77] performed a systematic review and meta-analysis of 15 studies with a total of 1068 patients and found no significant differences in the 1-, 3-, and 5-year overall survival rates, intraoperative blood loss, operation time, number of harvested lymph nodes, or complication rates between laparoscopic and open surgery. However, the length of hospitalization was shorter in the laparoscopic group. This review revealed that laparoscopic surgery is as safe and feasible as open surgery in patients with early-stage GC.

With the advancement of laparoscopic technology, some complex operations can now be performed laparoscopically. For example, a patient with synchronous GC and extrahepatic cholangiocarcinoma underwent successful laparoscopic hepatopancreaticoduodenectomy[78]. Additionally, a patient with postoperatively diagnosed GC underwent successful laparoscopic bile duct resection with lymph node dissection and was discharged on postoperative day 4[17]. Nevertheless, although great care is taken to protect the port site, port site metastasis still occurs on occasion[79,80]. Moreover, the use of retrieval bags has been recommended as the gold standard[80]. While recent studies focus on the advantages of laparoscopic surgery for GC, it remains controversial. Finally, most existing studies have focused on early and mid-stage GC, recommending that laparoscopic surgery be performed by experienced surgeons.

CURRENT SITUATION AND DEVELOPING TREND

Although laparoscopic technique has been widely used in patients with GC and many studies have obtained positive results, it is not recommended by current guidelines. The Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) published their clinical practice guidelines for the management of biliary tract cancers in 2007, and updated them twice in 2015 and 2020[19,81]. As the only guidelines that provide the management of all biliary tract malignant diseases, the JSHBPS recommends open cholecystectomy as a rule for patients with suspected GC. They suggested that laparoscopic surgery could be performed as a clinical study with informed consent. Meanwhile, in the guideline for the diagnosis and treatment of GC (2019 edition), Branch of Biliary Surgery, Chinese Surgical Society and Chinese Committee of Biliary Surgeons do not recommend laparoscopic surgery for patients with GC [82]. Accumulation of evidence is awaited for the application of laparoscopic surgery in GC. In Table 3, we summarize the data of several existing studies in recent years. More studies are expected in the next few years.

The application of laparoscopic surgery in GC is in line with the concept of minimally invasive and Enhanced Recovery After Surgery (ERAS). Robotic surgery can be seen as an upgrade and advancement of laparoscopic surgery. It has also been used in patients with GC. Sucandy *et al*[83] reported a study of 15 consecutive patients with GC who underwent robotic surgery. No intraoperative complications were observed, and the median hospital stay was 3 d. Byun *et al*[84] reported 16 patients who underwent robotic extended cholecystectomy for suspected stage T2 or above GC. The mean operation time was 198 min, and the median hospital stay was 7 d. Robotic surgery has many advantages over open and laparoscopic surgery, especially regarding ergonomics[85]. Its role in the treatment of GC should be complementary to laparoscopic techniques. ERAS is a multidisciplinary and comprehensive patient management model[86-90]. This model aims to reduce the perioperative stress response, decrease complications, and shorten the length of hospitalization and has been proven effective for many types of surgery[91-93]. However, ERAS study on patients with GC is rare[94]. Laparoscopic surgery for GC can reduce trauma, accelerate patient recovery, and shorten hospital stay, which satisfies the requirements of ERAS. The development trend of laparoscopic surgery in GC is bound to include robotic surgery and ERAS management.

Table 3 Data of several existing studies in recent years

No.	1	2	3	4	5
Year	2019	2021	2020	2021	2022
Ref.	Feng *et al*[59]	Regmi *et al*[70]	Navarro *et al*[69]	Kim *et al*[68]	Cho *et al*[72]
Country	China	China	Korea	Korea	Korea
Number of patients (*n*)					
Laparoscopy	41	20	43	17	19
Laparotomy	61	30	43	17	19
Operation time (min)					
Laparoscopy	137 ± 92	258.3 ± 72.5	139.1 ± 97.1	175 (160-180)	218.9 ± 145.0
Laparotomy	168 ± 51	227.0 ± 59.8	211.2 ± 91.4	156 (120-191)	316.8 ± 80.3
P value	0.058	0.101	0.001	0.370	0.016
Blood loss (mL)					
Laparoscopy	358 ± 390	242 ± 108.5	71.6 ± 178.8	300 (300-500)	-
Laparotomy	386 ± 391	401 ± 130.3	208.1 ± 242.2	300 (200-900)	-
P value	0.732	< 0.01	0.004	0.846	-
Postoperative hospital stays (d)					
Laparoscopy	5 ± 3	6.2 ± 2.4	6.1 ± 9.8	7.0 (7.0-9.0)	8.4 ± 5.9[1]
Laparotomy	11 ± 5	8.6 ± 2.3	12.6 ± 5.5	12.0 (10.0-14.0)	14.4 ± 6.0[1]
P value	< 0.001	< 0.01	0.0001	0.009	0.004
Perforation (*n*)					
Laparoscopy	8	-	-	-	0
Laparotomy	3	-	-	-	0
P value	0.069	-	-	-	-
Recurrence and metastasis (*n*)					
Laparoscopy	12	2	-	3	-
Laparotomy	10	4	-	2	-
P value	0.121	0.722	-	0.446	-
3-yr survival rates					
Laparoscopy	-	-	-	71.5%[2]	88.9%
Laparotomy	-	-	-	82.4%[2]	86.3%
P value	-	-	-	0.94	0.660
5-yr survival rates					
Laparoscopy	51.9%	-	64.0%	-	-
Laparotomy	55.7%	-	80.4%	-	-
P value	0.453	-	0.214	-	-

[1]Hospital stays.
[2]Disease-free survival.

CONCLUSION

Laparoscopic surgery for GC is feasible, and a considerable amount of research has been conducted on the safety of this surgical strategy. While gallbladder perforation and port site metastasis are major concerns of laparoscopic surgery, many clinical studies have confirmed the advantages of laparoscopic surgery over open surgery in terms of operation time, intraoperative bleeding, and hospital stay, as well

as their similarity regarding therapeutic efficacy. However, compared with its applications for gastrointestinal tumors, the application of laparoscopic surgery for GC is underdeveloped. Prospective, multicenter, randomized, and controlled clinical trials are required to further confirm the safety and feasibility of laparoscopic surgery for GC. Currently, laparoscopic surgery for GC should be conducted within reason, according to the tumor stage and experience of the surgeons.

FOOTNOTES

Author contributions: All authors helped to perform the research; Wu X performed manuscript writing and data analysis; Li BL contributed to manuscript conception and design; Zheng CJ contributed to manuscript conception, design, and writing.

Supported by Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences, No. 2022-I2M-C&T-A-004; and National High Level Hospital Clinical Research Funding, No. 2022-PUMCH-B-005.

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

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S-Editor: Fan JR
L-Editor: Wang TQ
P-Editor: Wu RR

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3706-3713

DOI: 10.12998/wjcc.v11.i16.3706

ISSN 2307-8960 (online)

MINIREVIEWS

Current research of idiopathic normal pressure hydrocephalus: Pathogenesis, diagnosis and treatment

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Specialty type: Neurosciences

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

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Gokce E, Turkey; Wijaya JH, Indonesia

Received: December 27, 2022
Peer-review started: December 27, 2022
First decision: January 20, 2023
Revised: February 18, 2023
Accepted: May 4, 2023
Article in press: May 4, 2023
Published online: June 6, 2023

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Abstract

Idiopathic normal pressure hydrocephalus (iNPH) is caused by impaired cerebrospinal fluid absorption in the elderly; it is a surgically treatable form of dementia. Gait disturbance, dementia, and urinary incontinence are the triad of signs for iNPH. In addition to these clinical findings, imaging studies show characteristic ventricular enlargement. High Evans Index and 'disproportionately enlarged subarachnoid hydrocephalus' are other well-known imaging findings of iNPH. If the tap test shows improved symptoms, shunt surgery is performed. The disease was first described by Hakim and Adams in 1965, followed by the publication of the first, second, and third editions of the guidelines in 2004, 2012, and 2020, respectively. Recent studies signal the glymphatic system and classical cerebrospinal fluid (CSF) absorption from the dural lymphatics as aetiological mechanisms of CSF retention. Research is also underway on imaging test and biomarker developments for more precise diagnosis, shunting technique options with fewer sequelae and complications, and the influence of genetics. Particularly, the newly introduced 'suspected iNPH' in the third edition of the guidelines may be useful for earlier diagnosis. However, less well-studied areas remain, such as pharmacotherapy in non-operative indications and neurological findings other than the triadic signs. This review briefly presents previous research on these and future issues.

Key Words: Review; Idiopathic normal pressure hydrocephalus; Treatable dementia; Shunt surgery; Drug therapy

Core Tip: Idiopathic normal pressure hydrocephalus (iNPH) presents with gait disturbance, dementia, and urinary incontinence. Improvement in these symptoms by tap testing, and imaging studies showing characteristic ventricular enlargement, are important for the diagnosis. iNPH is a dementia that is treatable by shunt surgery. This review describes recent pathophysiology, diagnosis, and treatment in iNPH.

Citation: Ishida T, Murayama T, Kobayashi S. Current research of idiopathic normal pressure hydrocephalus: Pathogenesis, diagnosis and treatment. *World J Clin Cases* 2023; 11(16): 3706-3713
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3706.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3706

INTRODUCTION

The initial documentation of idiopathic normal pressure hydrocephalus (iNPH) was made by Hakim and Adams[1] in 1965. In 2004, the first global guidelines for iNPH were published[2]. The guidelines placed the tap test at the centre of the diagnostic algorithm. A second edition of the guidelines was published in 2008[3]. These guidelines emphasised the importance of clinical features such as gait disturbance, urinary incontinence, and cognitive impairment, as well as 'disproportionately enlarged subarachnoid hydrocephalus' (DESH).

PATHOPHYSIOLOGY

Classically, the third circulation theory (bulk flow theory) has been considered the established theory for classical cerebrospinal fluid (CSF) production and absorption. In this theory, CSF is produced from blood in the choroid plexus within the ventricles, and the CSF has a steady flow. CSF flows from the uppermost lateral ventricles and drains through the foramen of Monroe, the third ventricle, the middle cerebral aqueduct, and the fourth ventricle, into the subarachnoid space. In the subarachnoid space, CSF further flows from the posterior cranial fossa through the basilar, sylvian, and cerebral hemispheric fissures to the higher arcuate region in the vicinity of the superior sagittal arteriovenous system. However, more recently, involvement of the glymphatic system and a mechanism of CSF absorption from the dural lymphatics has been considered more appropriate[4,5]. According to these theories, CSF is produced from the interstitial fluid produced by brain cells *via* the glymphatic system. Some CSF drains into the ventricles and has a steady flow, as in the classical theory. However, the majority of CSF is absorbed from the intradural lymphatics by anomalous flow. Future research is needed on the relationship between these new theories and clinical ventricular enlargement mechanisms.

GENETICS

Future research is needed to identify the relationship between these new theories and clinical ventricular enlargement mechanisms. iNPH has been classified as secondary hydrocephalus, with it being secondary to subarachnoid haemorrhage and other conditions, and the actual cause of iNPH may be unknown. Although there have been reports of sibling cases, there are no reports of familial or hereditary hydrocephalus. However, familial normal pressure hydrocephalus (fNPH) has recently been reported, with affected families being reported from Japan in 2011[6], Canada in 2012[7], and Greece in 2014[8]. There is also a family history of shunting in 5% of patients with iNPH in Finland[9]. Thus, fNPH may exist in clinically important numbers. In addition, the gene encoding the protein 'Scm-like with four MBT domains protein1 (SFMBT1)' has been reported as a risk gene for iNPH, and the cilia- and flagella-associated protein 43 (CFAP43) as a causative gene for fNPH in the field of genetic medicine[10,11]. SFMBT1 localises to cells constituting the subarachnoid space, cerebral arteries, veins, and ventricular walls. CFAP43 affects proteins related to villus structure and function. Therefore, research on fNPH may also help in understanding the pathogenesis of iNPH and developing treatment.

KEY POINTS OF THE THIRD EDITION OF THE GUIDELINES

Traditionally, the diagnosis of iNPH was classified into three levels: possible, probable, and definite. However, "suspected iNPH" was added in the third edition of the guidelines. Suspected iNPH is defined by two conditions: (1) An age of 60 years or older; and (2) enlarged ventricles (Evans Index >

0.3) on head imaging. Clinical symptoms such as dementia, gait disturbance, and dysuria are not required. This classification is expected to lead to earlier diagnosis of iNPH and earlier treatment[12]. In the study of asymptomatic iNPH, there is also the concept of asymptomatic ventriculomegaly with features of iNPH on MRI (AVIM)[13]. AVIM characterizes the supplementary observation of constriction in the subarachnoid space and cortical sulci at the peak convexity of the cerebrum, which is added to the classification of suspected iNPH. AVIM may also represent a preclinical stage of iNPH.

IMAGING

In the diagnosis of iNPH, head imaging findings are as important as abnormal neurological findings such as dementia, gait disturbance, and dysuria. It is important to recognize that solely relying on imaging results should not exclude iNPH. Techniques such as diffusion tensor imaging (DTI) and single photon emission computed tomography should also be considered, and fluorodeoxyglucose positron emission tomography imaging are also useful in the diagnosis of iNPH. However, they are omitted from this discussion owing to word count limitations.

Differentiating iNPH from Alzheimer's disease

In the diagnostic process, it's essential to distinguish between Alzheimer's dementia and iNPH, though this can be difficult in real-world situations. Interestingly, iNPH is viewed as a distinct disease in Europe and Japan, while in the United States, it's classified as an Alzheimer's disease subtype[14].

zEI and ventricle ratio 200

In cases of iNPH, the Evans Index typically exceeds 0.3 (Figure 1A). Frequently, the subarachnoid space expands within the sylvian fissure and in a downward direction, accompanied by narrowing in the elevated curvature area[15-18]. DESH is also an important imaging finding, as discussed in 'Changes in iNPH guidelines' (Figure 1B). DESH and cerebral atrophy due to Alzheimer's disease can be differentiated with high sensitivity and specificity[16-18]. DESH can be assessed visually, but previous studies have examined atrophic changes in more detail using voxel-based morphometry[18]. In addition to DESH, other evaluation criteria of interest include the Z-Evans Index (zEI) and brain/ventricle ratio (BVR) (Figure 1C). The (classic) Evans Index is a useful indicator of lateral ventricular enlargement in the horizontal section direction. However, in practice, iNPH patients often have lateral ventricles that show high-convexity tightness visible in the z-axis rather than in the horizontal section. The zEI is defined as the maximum z-axis length of the cranium from the maximum z-axis length of the frontal horn. This index is useful for detecting ventricular enlargement in the z-axis direction rather than in the horizontal sectional direction[19]. Yamada suggested that zEI may be associated with tap-test positivity. BVR is defined as the width of the anterior horn of the lateral ventricle/intracranial width immediately above the lateral ventricle[20]. A BVR < 1.0 in coronal sections on anterior commissure points, or a BVR < 1.5 in coronal sections on posterior commissure points, is considered an indicator of DESH findings [20].

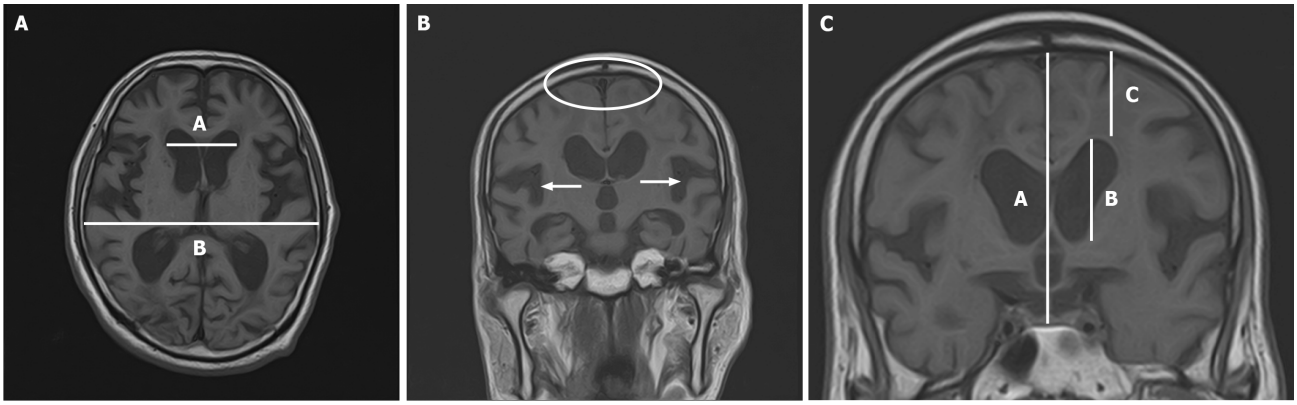
Rad scale

The radiological scale (Rad scale) has a total score of 12 points and is used to assess iNPH over the following seven items: (1) Widening of the ventricular/intracranial cavity width ratio (Evans Index > 3.0); (2) widening of the sylvian fissure; (3) narrowing of the high circumflex and median subarachnoid space, (4) steepening of the cerebral corpuscle angle; (5) focal widening of the cerebral sulci (a pooling phenomenon of cerebrospinal fluid); (6) widening of the lateral subventricular angle; and (7) periventricular hyperintensity[21]. The Rad scale correlates with the severity of iNPH[22]. The Rad scale is also useful for distinguishing subjects with iNPH from healthy elderly people, and for the differential diagnosis between iNPH and cerebrovascular dementia, progressive supranuclear palsy, and multiple system atrophy[23].

BIOMARKERS

Proteins and neuropeptides in cerebrospinal fluid have been studied as biomarkers for iNPH. Previous studies reported comparisons of total tau, phosphorylated tau, and amyloid-β42 between iNPH and Alzheimer's disease[24-31]. In addition, leucine-rich α2-glycoprotein (LRG), protein tyrosine phosphatase receptor type Q (PTPRQ), and neurofilament light chain (NfL) are biomarkers that have recently received attention[32-34]. These are useful markers not only for diagnosis, but also for predicting the effect of shunting. In iNPH, total tau and phosphorylated tau are generally lower than in Alzheimer's disease, with higher levels predicting a poor response to shunting.

Amyloid-β42 is also lower in patients with iNPH than in healthy subjects, and low levels are an indicator of a poor response to shunting procedures. NfL-PTPRQ-LRG is higher in patients with iNPH



DOI: 10.12998/wjcc.v11.i16.3706

Figure 1 head magnetic resonance imagines. A: Axial head magnetic resonance imaging of idiopathic normal pressure hydrocephalus. Evans Index (EI) = maximum width of the frontal horns of the lateral ventricles/maximal internal diameter of the skull at the same level (A/B). EI > 0.3 is a significant finding suggestive of idiopathic normal pressure hydrocephalus; B: Coronal head magnetic resonance imaging of idiopathic normal pressure hydrocephalus. This image shows narrowing of the fornix region (white oval) and widening of the bilateral sylvian fissures (white arrows); C: Coronal magnetic resonance imaging at the anterior commissure perpendicular to the line connecting the anterior and posterior commissures. Z-Evans Index (zEI) = width of the frontal horn of the lateral ventricle/median intracranial diameter (B/A). Brain/ventricle ratio (BVR) = intracranial width immediately above the lateral ventricles/anterior horn width of the lateral ventricles (C/B). Scores of zEI > 0.42 and BVR < 1.0 are significant findings suggestive of idiopathic normal pressure hydrocephalus.

than in healthy subjects. High NfL-LRG values are indicative of poor effectiveness of shunting procedures, but the relevance of high PTPRQ is unknown. Future work in this area is likely to focus on whether these biomarkers can be combined to make them more sensitive for diagnosis and prediction of treatment response.

TREATMENTS

Shunting

Shunting procedures for iNPH include ventriculo-peritoneal (VP), lumbo-peritoneal (LP), and ventriculo-atrial (VA) shunts. Of these, VP and LP shunts are the most common, while VA shunts are less common[35]. There is no significant difference in efficacy and complications between LP and VP shunts, and the technique considered most appropriate for each case is selected[36]. LP shunts do not puncture the brain and are considered safe in elderly patients, but are not suitable for patients with scoliosis, peritonitis, severe constipation, or obesity[37].

VP shunts are often chosen when LP shunts cannot be performed for the above reasons. Although VA shunts are used in fewer cases than LP and VP shunts, as described above, it is reported that adverse events and dysfunctions are less common than with VP shunts[38,39]. Endoscopic transtentorial ventriculostomy (ETV), which differs from the above shunting techniques, should also be described. ETV is a procedure to create a short-circuit pathway to avoid an obstruction in the ventricle. Traditionally, ETV has had narrower indications than shunting. However, recent studies have shown that ETV may improve not only CSF outflow, but also the compliance of the periventricular wall parenchyma[40-42]. Thus, iNPH surgeries continue to be investigated according to their theoretical bases and actual results to determine the best method. Although the safety of the above-mentioned shunt surgeries has improved over the years, adverse events are still common. A previous study showed that re-operations due to problems such as infection are more frequently associated with adverse events than first-time shunting procedures[43].

The two main types of shunt valves currently in use are pressure-fixed and pressure-variable valves. Pressure-fixed valves have a simpler mechanism and are cheaper. However, variable-pressure valves allow pressure to be set non-invasively from outside the body after shunt placement. The 2020 Cochrane Systematic Review did not show any superiority or inferiority between these two shunt valves[44]. However, the Japanese Guidelines for Idiopathic Normal Pressure Hydrocephalus, 3rd edition, recommend the use of variable valves for safety reasons[45]. In addition, antimicrobial-impregnated catheters have recently been used in many cases to prevent shunt infection. Previous studies have shown that antimicrobial-impregnated catheters significantly reduce shunt reconstruction associated with infection[46]. Therefore, the use of antimicrobial-impregnated catheters may be beneficial in shunt surgery in infection-prone children and immunocompromised patients.

Pharmacotherapy

As mentioned in the surgery section, surgical intervention carries risks and potential complications. In

cases where a tap test doesn't demonstrate a significant enhancement in cognitive abilities, surgery is not required. If surgery is not performed, the treatment of patients with iNPH is limited to symptomatic treatment. This section describes symptomatic pharmacotherapy.

First, there are anti-dementia drugs. These anti-dementia drugs inhibit the progression of cognitive decline but do not improve cognitive function. Four anti-dementia drugs are used in Japan: donepezil, galantamine, rivastigmine, and memantine. All of these are indicated for Alzheimer's disease, while only donepezil is also indicated for dementia with Lewy bodies. Clinically, these anti-dementia drugs are often prescribed for patients with other types of dementia, including iNPH. However, there is no clear evidence on their efficacy. Therefore, below we introduce the previous case reports. Moriuchi *et al* [47] reported that donepezil was effective in four patients with iNPH with residual cognitive decline after shunting surgery. Takaya[48] reported a case report in which memantine was effective for psychiatric symptoms of iNPH. Basic experiments also suggest that memantine may reduce hydrocephalus-induced neurodegenerative disorders[49]. Goreisan is a herbal medicine that regulates water metabolism and has been reported to be effective in normal pressure hydrocephalus[50]. Nonetheless, there is a lack of established guidelines or extensive research to endorse the application of Goreisan in treating iNPH. Furthermore, low-dose acetazolamide, also a diuretic, was reported to restore periventricular leukomalacia in a small case series of patients with iNPH[51].

EPILEPSY

Lately, attention has been drawn to patients experiencing late-onset epilepsy, who frequently appear in outpatient dementia clinics[52]. Past research indicates that while uncommon, postoperative complications of iNPH can involve seizures, with a mere 0.16% incidence rate in cases[53]. Two case reports have been published on nonsurgical iNPH presenting with seizures. In the first case, hyponatraemia associated with the administration of laxatives following lower gastrointestinal endoscopy triggered an epileptic seizure[54]. In the other case, a change in diagnosis and treatment from donepezil treatment for Alzheimer's disease to levetiracetam treatment for symptomatic epileptic seizures associated with iNPH resulted in improved cognitive function[55].

CONCLUSION

Promptness and individualisation are needed in the treatment of iNPH. In particular, the fact that suspected iNPH is defined solely by age and imaging findings leads to a more rapid diagnosis. Other novel indicators such as z-EI, BVR, and Rad scale have increased the sensitivity and specificity of the diagnosis.In terms of individualisation, research on biomarkers in spinal fluid has also developed. This has enabled the effect of shunting to be predicted preoperatively. In addition, further research is needed on drug therapy in cases where surgery is not expected to improve symptoms. The development of biomarkers for less invasive samples such as urine and blood is also expected in the future.

FOOTNOTES

Author contributions: Ishida T was responsible for the conception and design of the study and writing of the manuscript; Murayama T and Kobayashi S assisted in the critical review and editing of the manuscript; All authors gave their approval for the final version to be submitted.

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

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World J Clin Cases 2023 June 6; 11(16): 3714-3724

DOI: 10.12998/wjcc.v11.i16.3714

ISSN 2307-8960 (online)

MINIREVIEWS

Helicobacter pylori plays a key role in gastric adenocarcinoma induced by spasmolytic polypeptide-expressing metaplasia

Mian-Li Li, Xin-Xin Hong, Wei-Jian Zhang, Yi-Zhong Liang, Tian-Tian Cai, Yi-Fei Xu, Hua-Feng Pan, Jian-Yuan Kang, Shao-Ju Guo, Hai-Wen Li

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Haruma K, Japan; Lei X, China

Received: January 4, 2023
Peer-review started: January 4, 2023
First decision: January 22, 2023
Revised: March 1, 2023
Accepted: April 23, 2023
Article in press: April 23, 2023
Published online: June 6, 2023

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Abstract

Heliobacter pylori (*H. pylori*), a group 1 human gastric carcinogen, is significantly associated with chronic gastritis, gastric mucosal atrophy, and gastric cancer. Approximately 20% of patients infected with *H. pylori* develop precancerous lesions, among which metaplasia is the most critical. Except for intestinal metaplasia (IM), which is characterized by goblet cells appearing in the stomach glands, one type of mucous cell metaplasia, spasmolytic polypeptide-expressing metaplasia (SPEM), has attracted much attention. Epidemiological and clinicopathological studies suggest that SPEM may be more strongly linked to gastric adenocarcinoma than IM. SPEM, characterized by abnormal expression of trefoil factor 2, mucin 6, and Griffonia simplicifolia lectin II in the deep glands of the stomach, is caused by acute injury or inflammation. Although it is generally believed that the loss of parietal cells alone is a sufficient and direct cause of SPEM, further in-depth studies have revealed the critical role of immunosignals. There is controversy regarding whether SPEM cells originate from the transdifferentiation of mature chief cells or professional progenitors. SPEM plays a functional role in the repair of gastric epithelial injury. However, chronic inflammation and immune responses caused by *H. pylori* infection can induce further progression of SPEM to IM, dysplasia, and adenocarcinoma. SPEM cells upregulate the expression of whey acidic protein 4-disulfide core domain protein 2 and CD44 variant 9, which recruit M2 macrophages to the wound. Studies have revealed that interleukin-33, the most significantly upregulated cytokine in macrophages, promotes SPEM toward more advanced metaplasia. Overall, more

effort is needed to reveal the specific mechanism of SPEM malignant progression driven by *H. pylori* infection.

Key Words: Gastric cancers; *Helicobacter pylori*; Intestinal metaplasia; Macrophages; Spasmolytic polypeptide-expressing metaplasia

Core Tip: Spasmolytic polypeptide-expressing metaplasia (SPEM), induced by *Heliobacter pylori* (*H. pylori*) infection in humans, is strongly associated with gastric adenocarcinoma. Chronic inflammation and immune responses caused by *H. pylori* infection play important roles in the malignant progression of SPEM. Recent studies suggest that CD44 variant 9 and whey acidic protein 4-disulfide core domain protein 2 expressed by SPEM leads to M2 macrophage recruitment. Furthermore, M2 macrophages upregulate the expression of interleukin 33, which eventually promotes malignant progression.

Citation: Li ML, Hong XX, Zhang WJ, Liang YZ, Cai TT, Xu YF, Pan HF, Kang JY, Guo SJ, Li HW. *Helicobacter pylori* plays a key role in gastric adenocarcinoma induced by spasmolytic polypeptide-expressing metaplasia. *World J Clin Cases* 2023; 11(16): 3714-3724
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3714.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3714

INTRODUCTION

The Working Group Meeting of the International Agency for Research on Cancer with the World Health Organization has classified *Helicobacter pylori* (*H. pylori*) as a group 1 human gastric carcinogen. *H. pylori* colonizes the gastric mucosa of more than half of the world's population[1]. Epidemiological studies in humans and experiments in rodents have shown that *H. pylori* infection, the accompanying immune response, and chronic inflammation are closely related to the occurrence and progression of gastric adenocarcinoma[2-5]. Alterations in gland cell lineages between normal and metaplasia cells, including intestinal metaplasia (IM) and spasmolytic polypeptide-expressing metaplasia (SPEM), are key processes in *H. pylori*-induced gastric cancer. Gastric cancer is one of the most common and deadly cancers worldwide, leading to the death of nearly 1 million of people every year[6]. Approximately 95% of gastric cancers are adenocarcinomas derived from the glandular epithelium of the gastric mucosa[7]. This theory (called the Correa pathway) was first proposed by Correa and Piazuelo[8] in 1975 and was updated in 1992[8]. The progression was later recognized as normal gastric mucosa → superficial gastritis (later renamed non-atrophic gastritis → multifocal atrophic gastritis without IM → IM of the complete (small intestine) type → IM of the incomplete (colonic) type → low-grade dysplasia (low-grade noninvasive neoplasia) → high-grade dysplasia (high-grade noninvasive neoplasia) → invasive adenocarcinoma[8]. Among these stages, IM is of great interest to pathologists because the intestinal mucosa containing goblet cells is found in the stomach. Follow-up studies focused on IM suggest that it is a useful biomarker for gastric cancer risk. However, recent studies have revealed the existence of a second metaplastic lineage, SPEM[9]. SPEM, characterized by abnormal expression of spasmolytic polypeptide (SP)/trefoil factor 2 (TFF2) in the deep glands of the stomach, is a type of mucous cell metaplasia caused by acute injury or inflammation. SPEM also expresses mucinous molecular markers, such as mucin 6 (MUC6) and Griffonia simplicifolia lectin II (GSII)[10]. This underappreciated type of mucous metaplasia has been described with various names, including pseudo-pyloric metaplasia, mucous metaplasia, or antralization of the corpus. Numerous studies have reported that SPEM may have a stronger link to gastric adenocarcinoma than IM, and is a neoplastic precursor of gastric adenocarcinoma in humans[3,4,11]. Epidemiological studies in the United States, Japan, and Iceland showed that SPEM, typically located in the mucosa adjacent to the carcinoma or areas of dysplasia, was associated with > 90% of resected gastric cancers and > 50% of early gastric cancers[9,11]. Additionally, a clinicopathological study in patients from Korea suggested that TFF2 expression plays a role in gastric cancer invasion[12]. Previous studies have reported that SPEM and IM often co-exist in people with atrophic gastritis caused by chronic *H. pylori* infection[13,14]. Notably, SPEM and IM are two different lineages of metaplastic cells. SPEM are cells marked by the expression of TFF2 and MUC6, while the characteristic markers of IM are TFF3, MUC2 and Caudal-related homeobox transcription factor 2(CDX2)[15]. The current mainstream view is that the progression of SPEM leads to IM. According to immunocytochemical evidence, SPEM expressing TFF3 and MUC2 has been reported; therefore, intermediates of intestinalized SPEM may exist that reflect evolution of metaplastic phenotypes[13]. However, one study also found Muscle intestine stomach expression 1(MIST1) and CDX2 double

positive SPEM cells, indicating that IM may not come from a single pathway of SPEM progression[14].

THE CHARACTERISTICS OF SPEM

SPEM is induced by the loss of parietal cells in combination with additional signals

Initially, it was believed that the loss of parietal cells (oxyntic atrophy) alone was a sufficient and direct cause of SPEM[16]. Studies examining the predisposing factors of SPEM in mice have demonstrated that SPEM develops after parietal cell loss and chronic Helicobacter infection or acute injury due to treatment with DMP-777, L-635, or high-dose tamoxifen[17-19]. SPEM caused by *H. pylori* infection is discussed separately in the following sections. Here, SPEM induced by drug treatment in a mouse model is discussed. Three drugs, DMP-777, L-635, and tamoxifen, have frequently been used to study the progression of SPEM in mice because they induce acute parietal cell loss of mucous glands, which leads to the development of TFF 2–expressing metaplasia (SPEM)[16,19-22]. DMP-777, a parietal cell-specific protonophore, can partition into the apical acid secretory membranes of parietal cells, leading to acute death after acid secretion[4,23]. DMP-777 is also a potent neutrophil elastase inhibitor, does not elicit a significant inflammatory response to the acute parietal cell loss. L-635 is an analog of DMP-777 with the same ability to specifically kill parietal cells without inhibiting the inflammatory response[4, 23]. Tamoxifen, a selective estrogen-receptor modulator, is widely used in chemotherapy and to treat osteomalacia. However, one study found that treatment of normal mice with a single > 3 mg/20 g body weight dose of tamoxifen led to > 90% apoptosis of all gastric parietal cells, and expression of mucous neck cell marker TFF2 which occurred at the base of mucous glands[19,24-26]. SPEM is induced by these drugs, causing the loss of parietal cells and altering the orderly differentiation of gastric mucosal cell lineages. However, the mechanism by which this occurs remains unclear (Table 1). In addition, SPEM was found in a rodent animal model that had received preoperative nitrite carcinogen administration and developed post-gastrectomy syndrome[27]. Parietal cells secrete several epidermal growth factor (EGF) receptor ligands, including transforming growth factor (TGF)-α, amphiregulin (AR), and heparin-binding EGF–like growth factor[28-31], which regulate differentiation and epithelial cell function. Therefore, altering the levels of these EGF receptor ligands may contribute to the emergence of SPEM. Previous studies using AR knockout and TGF-α knockout mice showed that the loss of TGF-α did not influence the induction of SPEM and loss of AR caused an acceleration and augmentation in the induction of SPEM[4,32]. Additionally, the AR-null mouse model represents the first mouse model for the spontaneous development of fundic SPEM with progression to IM and neoplasia. An increasing number of trials are underway to decipher the precise mechanism of the progression from parietal cell loss to SPEM. Additional signals, such as cytokines secreted by immune cells, are also important for the progression of SPEM. As the necessities of th2 cytokine induction in the stomach, interleukin (IL)-33 signaling pathway has been proved indispensable for the development of metaplasia after parietal cell loss. Interestingly, IL33 KO (IL33 knockout), ST2 KO (IL33 receptor knockout, ST2, knockout), and IL13 KO (IL13 knockout) mice treated with either L-635 or DMP-777 did not develop metaplasia following acute parietal cell loss. IL-33 signaling drives M2 macrophage polarization, which is associated with progression toward more advanced metaplasia[33,34]. Although the association between the immune phenotype and SPEM remains unclear, there is growing evidence that some immune factors lead to the development of SPEM. For example, interferon-γ (IFN-γ), the most abundant cytokine detected in the highly complex cytokine milieu of atrophic gastritis, contributes to the emergence of SPEM[35]. An investigation showed that IFN-γ causes gastric epithelial cells expressing the IFN-γ receptor to die and promotes the progression from gastritis caused by anti-parietal T-cells to atrophic gastritis and SPEM [33]. Overall, After the loss of parietal cells, inflammatory factors, as additional signals, are crucial for the production of SPEM. Specifically, IL13, IL33 and their receptor ST2 have been found to play an indispensable role. In addition, overexpression of IFN-γ also causes parietal cell death and induces SPEM. At present, it is not clear why parietal cell loss induces SPEM, but the absence of AR secreted by parietal cells may be the key factor (Table 2).

SPEM cells may arise from different types of cells besides mature chief cells and professional progenitors

There are two hypotheses regarding the derivation of SPEM cells: (1) These metaplastic cells arise from cryptic professional progenitors that enter an abnormal differentiation state stimulated by the environment; and (2) SPEM cells originate from transdifferentiation of mature chief cells. Increasing experimental evidence from human and rodent models supports the latter hypothesis. In 2009, Nam *et al* [4] performed lineage tracing of chief cells using Mist1CreER/+ mice, in which Mist1 was chief cell-restricted expression, to examine to origin of SPEM lineages. Initially, complete separation of TFF2 immune-stained mucous neck cells and X-gal stained Mist1-expressing chief cells were observed in the fundus. After the 10-d period after tamoxifen treatment, basal glandular cells labeled with antibodies against TFF2 were observed, which concomitantly showed β-galactosidase enzymatic activity, indicating that these SPEM cells were derived from mature, Mist1-expressing chief cells[16]. In 2017, Radyk *et al*[36] successfully induced SPEM in mice using a non-genetic approach by intraperitoneal

Table 1 Characteristics of various spasmolytic polypeptide-expressing metaplasia inducers

Inducers of SPEM	Pharmacological action	Inflammatory response	Dosage and usage	Time to onset of SPEM	Notes
DMP-777	It may cause backwash of acid into the cell leading to parietal cell death	No significant inflammatory response in reaction the acute parietal cell loss	> 200 mg/kg/d, oral gavage	7–10 d	(1) SPEM induced by these drugs may completely revert to normal mucosal cell lineages after a withdrawal period, despite the profound oxyntic atrophy and SPEM; and (2) L-635 and tamoxifen elicit parietal cell loss and induce SPEM faster than DMP-777, because of the inflammation cause by L-635 and tamoxifen
L-635	Same as DMP-777	A prominent submucosal and intramucosal inflammatory infiltrate is observed	350 mg/kg/d, oral gavage	3 d	
Tamoxifen	Same as DMP-777	Inflammatory is scant than L-635	≥ 3 mg/20 g body weight dose, oral or intra-peritoneal	3 d	

SPEM: Spasmolytic polypeptide-expressing metaplasia.

Table 2 The influence of the absence of additional signals and epidermal growth factor

Genotype	SPEM	IM	Neoplasia
AR-null mouse	Yes	Yes	Yes
TGF-α-null mouse	No	No	No
IL33 KO mouse + L635	No	No	No
ST2 KO mouse + L635	No	No	No
IL13 KO mouse + L635	No	No	No
IFN-γ overexpression mouse	Yes	No	No

SPEM: Spasmolytic polypeptide-expressing metaplasia; AR: Amphiregulin; TGF: Transforming growth factor; IL: Interleukin; IFN: Interferon; IM: Intestinal metaplasia; KO: Knockout.

injections of 5-fluorouracil, which blocked gastric cell proliferation, and tamoxifen. In this study, a similar magnitude of gastric intrinsic factor (GIF)$^+$ cell loss and GIF$^+$GSII$^+$ SPEM cell increase was observed at the gland base, indicating that SPEM developed in the absence of cell proliferation; therefore, it did not arise from stem cells. Then, histological analysis were used to investigate gastric resection specimens from 10 patients with adenocarcinoma and found normal zymogenic chief cells that were transitioning into SPEM cells only in the gland bases, rather than the proliferative stem cell zone [36]. Recent studies have shown that SPEM is derived from mature chief cells. Caldwell *et al*[37] used a GIF-green fluorescent protein (GIF-GFP) marker to trace the cell lineage of mice during the development of acute metaplasia after L-635 treatment, and performed co-immunofluorescence staining for various gastric lineage markers. These results demonstrated that SPEM cells predominantly transdifferentiated from GFP-expressing chief cells, rather than proliferating isthmal progenitor cells, thereby providing pivotal evidence for cell lineage contributions from differentiated gastric chief cells[37]. In contrast, Hata *et al*[38] identified G protein-coupled receptor 30 (GPR30), the G-protein-coupled form of the estrogen receptor, as a chief cell-specific marker of mice to trace the gland cell lineage during the development of SPEM[38]. This study found no evidence of lineage expansion from GPR30$^+$ chief cells after treatment with tamoxifen and suggested that GSII+GIF+ SPEM may not be a sign of chief cell dedifferentiation but represent a regenerative expansion of neck cells in response to chief cell depletion. Although the hypotheses regarding the origin of SPEM remain divisive, more studies are investigating the mechanism of SPEM cell differentiation, with the mainstream belief being that SPEM cells arise from transdifferentiation of mature chief cells.

SPEM plays a functional role in repairing gastric epithelial injury

The complex process of tissue repair in gastric ulcers involves re-epithelialization and regeneration[39]. Ulcer-associated cell lineages (UACL) greatly contributes to epithelial regeneration, proliferation, and differentiation into intestinal crypts of the injured gastric tissue[39,40]. Recent studies have claimed that SPEM is always localized to the base of the ulcer margin in the stomach mucosa, in a position similar to that of the UACL after severe gastric injury[41]. Data from numerous pathologists have demonstrated that SPEM also represents the major reparative lineage responsible for wound healing. Engevik *et al*[42] determined the quality of ulcer repair with advancing age in mice and found that the emergence of

SPEM within the ulcerated region in young mice coincided and disappeared when the mucosa returned to its normal compendium of cell lineages, a response that was absent in aged mice with a weaker capacity for repair injury[42]. This study suggests that SPEM might secrete the growth factors and cytokines necessary for wound repair in ulcers and is correlated with age. Therefore, further research performed by Aihara *et al*[43] revealed that TFF2 expression by SPEM has a central role in gastric injury and repair[43]. TFF2 was upregulated and sustained in mice with gastric ulcers induced by acetic acid application, and promoted gastric healing after injury through anti-apoptotic and motogenic (cell migratory) activities[44-47]. Gastric ulcer healing was strongly delayed in TFF2 knockout mice, suggesting that TFF2 is markedly involved in the initial closure of an ulcer[43]. The development of SPEM is also followed by the expression of CD44 variant isoform 9 (CD44v9), which contributes to defense against reactive oxygen species (ROS); therefore, promoting tumor growth[48-50]. CD44v9 expression emerged at the ulcer margin during gastric ulcer repair and was rarely expressed as the gastric epithelium healed. While CD44 KO mice demonstrated loss of epithelial repair ability, CD44 KO mice transplanted with CD44v9-expressing gastric organoids demonstrated epithelial repair comparable to that of the normal group[51]. These data suggested that CD44 contributes to gastric ulcer repair.

The progression from normal gastric mucosa to SPEM is dynamic and consecutive

The mature chief cell, differentiated from mucous neck cells migrating toward the bottom of the glands, expresses not only pepsinogen but also GPR30, helix-loop-helix transcription factor Mist1, and GIF[52]. Unlike chief cells, SPEM, is a type of mucous cell metaplasia characterized by the expression of TFF2, MUC6, CD44v9, and GSII[10]. Immunohistochemistry is widely used to monitor different cell locations, proliferation states, and survival stages, based on differences in expression levels and reveals the dynamic and consecutive transformation of glandular molecular expression profiles during metaplasia [53]. Dual immunofluorescence staining for TFF2 and GIF in Hp-infected Mongolian gerbils revealed that SPEM exhibits TFF2 and GIF double-staining at the bases of glands in the earlier stages. However, over the time of infection, GIF staining progressively decreased and single staining was observed with anti-TFF2[3]. Similarly, in resection and gastric tissue microarray (TMA) samples obtained from SPEM lesions from the USA and Republic of Korea, TFF2+/MIST1+ and TFF2+/MIST1- SPEM cells were observed coincidentally[14]. Lennerz described these samples as exhibiting hybrid-SPEM and established SPEM because MIST1 expression was restricted to the chief cell compartment in the normal oxyntic mucosa[14]. This suggests that the transdifferentiation of master cells is a continuous process, in which the characteristics of chief cells are gradually reduced and the cell expression profile is transformed from mature master cells to SPEM. Single-cell RNA sequencing of two SPEM phenotypes (Tff2+Muc6+Gif+ and Tff2+Muc6+Gif-) revealed that Gif+ and Gif- TFF2-expressing mucinous cells exhibit nearly indistinguishable transcriptomes[54]. Different metaplastic cells exhibit overwhelming overlap in physical location within the gastric unit, implying that Gif expression is gradually lost during the development of SPEM, and they share an ontology rather than a separation into unique subsets[54]. Therefore, it is conceivable that a pathological definition of SPEM includes cells that do not express mature chief cell transcripts, such as Gif in the murine stomach.

THE LINK BETWEEN *H. PYLORI* INFECTION AND SPEM

H. pylori infection is not only a predisposing factor for SPEM but also causes chronic inflammation and immune response which promotes SPEM development. *H. pylori* infection is the major predisposing factor for gastric cancer, as it causes parietal cell loss and induces the development of SPEM. Additionally, in the presence of ongoing inflammation, metaplasia evolves and expands[16,21,23,27,34].

The presence of SPEM promoted the colonization and spread of H. pylori

H. pylori attaches to the gastric epithelium primarily through the binding of two bacterial adhesins, BabA11 and SabA,12 to the glycosylated receptors Lewis B (Leb) and sialyl-Lewis X (sLex), respectively [55]. sLex extends deep into the metaplastic neck and gland base, and accompanies SPEM progression in the stomach. Therefore, *H. pylori* can access deeper regions along the gastric corpus units, which protects *H. pylori* from the harsher, more acidic environment near the gastric lumen[56]. This mechanism allows *H. pylori* to advance the infected area throughout the stomach by binding to the expanded sLex. Furthermore, because *H. pylori* interacts with the injured corpus epithelium and may lead to an accumulation of mutations within metaplastic cells, increased expression of sLex indicates poor prognosis in gastric adenocarcinoma[57].

Chronic inflammation and immune response caused by H. pylori infection exacerbates SPEM malignant transformation

SPEM appears to be a traumatic stress mechanism to repair the gastric mucosa in the event of acute injury. After the injury is repaired, the gastric glands return to normal. One study, using a tamoxifen-induced SPEM mouse model, showed that SPEM cells are able to re-differentiate into chief cells

following recovery from injury without chronic inflammation[58]. However, the continuous expansion of *H. pylori* infection causes chronic inflammatory infiltration, which changes the expression of SPEM and leads to the development of dysplasia or IM. SPEM development as a result of *H. pylori* infection is focused on as it is the most common situation of SPEM development in humans. Gastric epithelial cells adhere to each other through tight junctions (TJs), sealing intercellular spaces to maintain epithelial barrier function and mucosal homeostasis[59-61]. The stomach-type claudin-18 (stCLDN-18) is the predominant claudin expressed in the stomach, resisting H+ and pepsin leakage[62]. One study found that *H. pylori* infection in mice resulted in focal loss, attenuation, and disruption of CLDN18 in gastric epithelial cells and showed parietal cell loss and SPEM characteristics[10]. Further study using stCLDN-18 gene knockout mice showed that stClDN-18 deficiency causes gastric tumor emergence *via* cytokine, stemness, and Wnt signaling–activated pathways[63]. Once *H. pylori* or inflammation attenuates the expression of stCLDN18, adenocarcinoma progression occurs spontaneously[10]. This could be attributed to the SPEM development; however, the detailed mechanisms are unclear. To identify the commonalities and differences between SPEM lineages induced by three different methods, Weis *et al* [20] used three different mouse models of parietal cell loss, chronic inflammation with *Helicobacter felis* infection, acute inflammation with L-635 treatment, and without inflammation following DMP-777 treatment[20]. The RNA transcripts showed that while markers such as whey acidic protein (WAP) 4-disulfide core domain protein 2 (WFDC2, also named HE4) and clusterin (Clu) are expressed in all three phenotypic SPEM lineages, cytokines such as cystic fibrosis transmembrane conductance regulator, which is expressed only in IM in humans, are only upregulated in metaplasia associated with chronic inflammation. These data indicate that distinct heterogeneity is present in three different SPEM mice models, but inflammatory infiltration leads to the evolution of metaplasia toward a more proliferative lineage. Overall, inflammation is a key factor in the progression of SPEM to a more aggressive metaplastic phenotype. Another important factor related to *H. pylori* infection that promotes SPEM toward gastric cancer is the immune response. MicroRNAs (miRNAs) are critical post-transcriptional regulators of gene expression[64,65]. miRNA sequencing, which investigated mice infected with *H. felis*, showed that several miRNAs were highly expressed in normal chief cells but downregulated in SPEM cells, and a decrease in miR148a in chief cells induced upregulation of CD44v9, one of the transcripts expressed at an early stage of SPEM development[66]. These results suggest that miR-148a regulates early reprogramming of chief cells and the process of transdifferentiation into SPEM[66]. CD44v9 plays a critical role in wound repair and recruits macrophages, key immune cells, and secretes cytokines, chemokines, and pro-angiogenic factors that are necessary for repair. Marked infiltration of macrophages was observed around the SPEM, and were positive for the M2 marker and hemoglobin scavenger receptor CD163, suggesting M2 polarization[34,67,68]. Although M2 macrophages are linked to repair and are anti-inflammatory, they have been shown to promote neoplasia[69]. The occurrence and development of SPEM are closely related to macrophages. Firstly, L635-treated macrophage-depleted mice demonstrated a significant reduction in SPEM cell numbers, indicating that macrophage infiltration may promote the production of SPEM cells[70]. Secondly, after SPEM induction, WFDC2 secreted by SPEM cells has been confirmed to induce M2 macrophage polarization and up-regulate the secretion of IL33 by macrophages to advance SPEM[70,71]. Studies of mouse models and human metaplastic tissues indicate that M2-macrophages promote the progression of metaplasia toward a more proliferative and advanced phenotype[34]. Petersen *et al*[34,71] used RNA sequencing to analyze macrophages from the stomach corpus of mice with SPEM and identified an M2a-polarized macrophage population. Additionally, IL-33, an IL-1 family member, was the most significantly upregulated cytokine in macrophages, which drives M2 macrophage polarization associated with the progression toward more advanced metaplasia[34,71]. Another study investigating the function of IL33 and IL33 receptor ST2 showed that IL33/ST2 promoted the malignant progression of gastric cancer cells[72]. In addition, Jeong *et al*[70] observed a similar phenomenon; WFDC2, a small secretory protein highly expressed in fibrosis, lung cancer, and stomach cancer in humans, was able to induce M2 macrophage polarization and IL33 production in mice. Wfdc2-knockout mice treated with DMP-777, L-635, or high-dose tamoxifen showed remarkable resistance to SPEM development. However, M2 macrophage polarization, IL33 production, and SPEM development were observed after treatment with recombinant WFDC2[70] (Figure 1). Therefore, after the SPEM induced, WFDC2 secreted by SPEM has been confirmed to induce M2 macrophage polarization and up-regulate the secretion of IL33 by macrophages to advance SPEM[70,71]. However, whether high WFDC2 gene expression affects the poor prognosis of SPEM through the WFDC2 protein or other pathways remains controversial. We found that upregulation of WFDC2 gene expression was accompanied by WFDC2 protein reduction in SPEM murine models with chronic *H. pylori* inflammation (data not shown). Similarly, a previous report showed that serum WFDC2 Levels were not altered in patients with gastric cancer[73]. These studies suggest that *H. pylori* infection, leading to the loss of parietal cells, induces SPEM emergence and upregulation of CD44V9 and WFDC2 expression under chronic inflammation and immune responses. CD44V9 and WFDC2 recruit M2 macrophages and release IL33 to advance SPEM malignant progression, which may be the potential mechanism of gastric cancer (Figure 2).

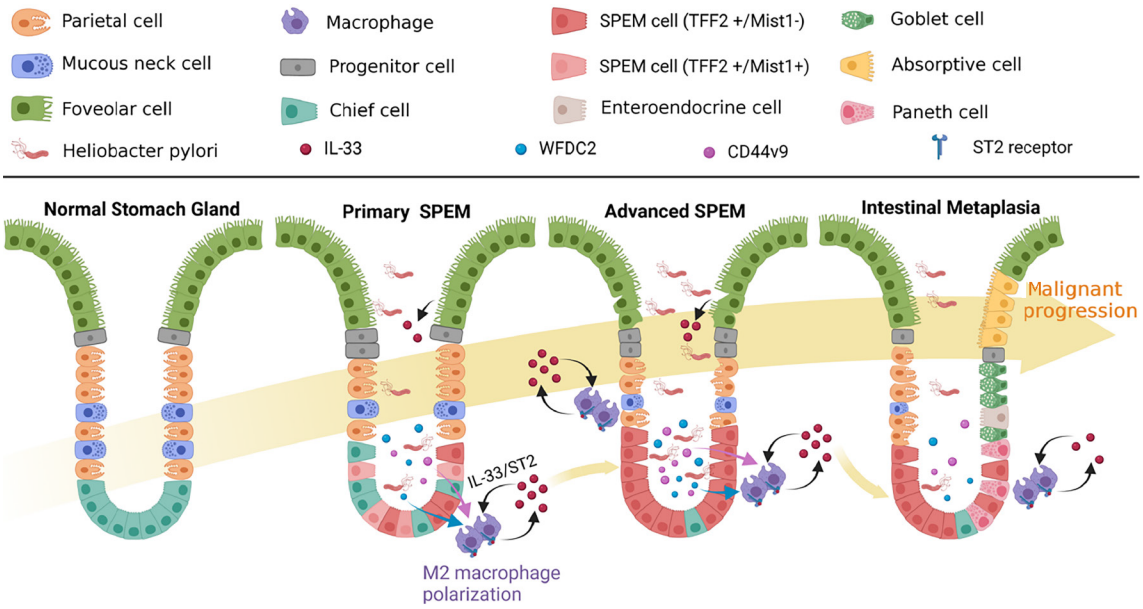

Figure 1 Alteration of glandular cells during spasmolytic polypeptide-expressing metaplasia malignant progression due to *Heliobacter pylori* infection. Under the influences of chronic inflammation, CD44 variant 9, and whey acidic protein 4-disulfide core domain protein 2 produced by spasmolytic polypeptide-expressing metaplasia (SPEM) malignant cells, M1 and M2 polarization is induced in local macrophages, after which M1 polarized macrophages will secrete interferon-γ, which is one of the important inflammatory factors that aggravate local inflammation. M2 polarization causes macrophages to secrete large amounts of interleukin-33, which aggravates the transdifferentiation of mature master cells and promotes the malignant progression of SPEM. Citation: Created with BioRender.com. (Supplementary material). SPEM: Spasmolytic polypeptide-expressing metaplasia; IL: Interleukin; WFDC: Whey acidic protein 4-disulfide core domain protein 2; CD44v9: CD44 variant isoform 9.

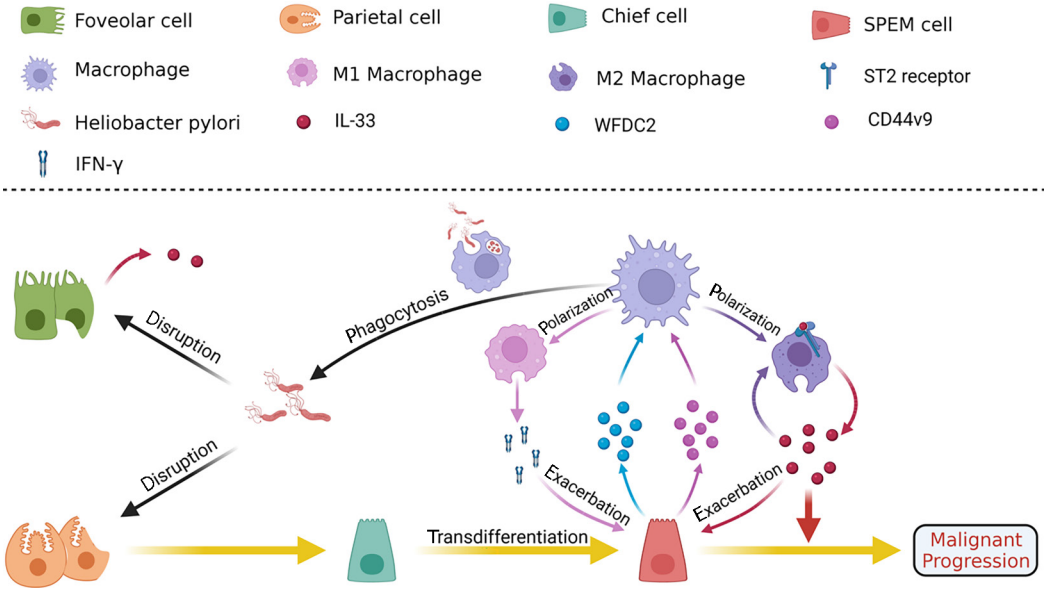

Figure 2 Influence of immune cells and cytokines on spasmolytic polypeptide-expressing metaplasia development. Parietal cells of fundic glands are gradually lost and mature chief cells transdifferentiate into spasmolytic polypeptide-expressing metaplasia (SPEM) in gland bases due to the chronic inflammation caused by *Helicobacter pylori* infection. In earlier stages, trefoil factor (TFF) 2+/MIST1+ and TFF2+/MIST1- SPEM cells appear at the bases of the same glands. As the inflammation progresses, MIST1 and TFF2 double-positive SPEM cells are gradually replaced by TFF2+/MIST1- cells, in which high expression of CD44V9 and whey acidic protein 4-disulfide core domain protein 2 and macrophage M2 polarization play important roles leading glands to intestinal metaplasia characterized by goblet and Paneth cells. Citation: Created with BioRender.com. (Supplementary material). IFN: Interferon; IL: Interleukin; WFDC: Whey acidic protein 4-disulfide core domain protein 2; CD44v9: CD44 variant isoform 9.

CONCLUSION

Alterations in gland cell lineages between normal and metaplastic cells, including in IM and SPEM, are key processes in *H. pylori*-induced gastric cancer. SPEM, induced by the loss of parietal cells, is a type of

mucous cell metaplasia characterized by abnormal expression of TFF2 in the deep glands of the stomach. It is generally believed that SPEM cells arise following transdifferentiation of mature chief cells and represent the major reparative lineage responsible for wound healing. However, the chronic inflammation and immune response caused by *H. pylori* infection exacerbates the transformation of SPEM into cancerous malignancies. The mechanism of how *H. pylori* causes parietal cell loss remains unclear, although it may be related to the disruption of CLDN18 in gastric epithelial cells. After parietal cell loss, SPEM emerges in the deep glands of the stomach. CD44V9 and WFDC2 secreted by the SPEM cells recruit macrophages and drive M2 polarization; thus, up-regulating inflammatory factors such as IL33 and IFN-γ to promote the progression of SPEM to IM and adenoma. Further studies on the specific association between SPEM and adenocarcinomas are needed.

FOOTNOTES

Author contributions: Li ML and Li HW conceptualized the and wrote the initial manuscript; Hong XX and Zhang WJ conceptualized the table and figures; Liang YZ and Cai TT performed the literature search; Xu YF and Kang JY conceptualized the structure of the text; Pan HF and Guo SJ supervised and approved the final version of the review.

Supported by the Guangdong Basic and Applied Basic Research Foundation, No. 2020A1515110947; the National Natural Science Foundation of China, No. 82104747; the Scientific Research Project of Guangdong Bureau of Traditional Chinese Medicine, No. 20231303; and the Guangdong Provincial Key Research and Development Plan, No. 2020B1111100011.

Conflict-of-interest statement: Li HW is an employee of Shenzhen Traditional Chinese Medicine Hospital.

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S-Editor: Li L
L-Editor: A
P-Editor: Wu RR

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3725-3735

DOI: 10.12998/wjcc.v11.i16.3725

ISSN 2307-8960 (online)

MINIREVIEWS

Review of deep learning and artificial intelligence models in fetal brain magnetic resonance imaging

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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 scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Hanada E, Japan; Li J, China; Reis F, Brazil; Tai MCT, Taiwan

Received: January 4, 2023
Peer-review started: January 4, 2023
First decision: January 20, 2023
Revised: January 30, 2023
Accepted: May 6, 2023
Article in press: May 6, 2023
Published online: June 6, 2023

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Abstract

Central nervous system abnormalities in fetuses are fairly common, happening in 0.1% to 0.2% of live births and in 3% to 6% of stillbirths. So initial detection and categorization of fetal Brain abnormalities are critical. Manually detecting and segmenting fetal brain magnetic resonance imaging (MRI) could be time-consuming, and susceptible to interpreter experience. Artificial intelligence (AI) algorithms and machine learning approaches have a high potential for assisting in the early detection of these problems, improving the diagnosis process and follow-up procedures. The use of AI and machine learning techniques in fetal brain MRI was the subject of this narrative review paper. Using AI, anatomic fetal brain MRI processing has investigated models to predict specific landmarks and segmentation automatically. All gestation age weeks (17-38 wk) and different AI models (mainly Convolutional Neural Network and U-Net) have been used. Some models' accuracy achieved 95% and more. AI could help preprocess and post-process fetal images and reconstruct images. Also, AI can be used for gestational age prediction (with one-week accuracy), fetal brain extraction, fetal brain segmentation, and placenta detection. Some fetal brain linear measurements, such as Cerebral and Bone Biparietal Diameter, have been suggested. Classification of brain pathology was studied using diagonal quadratic discriminates analysis, K-nearest neighbor, random forest, naive Bayes, and radial basis function neural network classifiers. Deep learning methods will become more powerful as more large-scale, labeled datasets become available. Having shared fetal brain MRI datasets is crucial because there aren not many fetal brain pictures available. Also, physicians should be aware of AI's function in fetal brain MRI, particularly neuroradiologists, general radiologists, and perinatologists.

Key Words: Artificial intelligence; Fetal brain; Magnetic resonance imaging; Neuroimaging

Core Tip: The manual detection and segmentation of fetal brain magnetic resonance imaging (MRI) may be time-consuming, and susceptible to interpreter experience. During the past decade, artificial intelligence (AI) algorithms, particularly deep learning, have made impressive progress in image recognition tasks. A machine learning approach may help detect these problems early and improve the diagnosis and follow-up process. This narrative review paper investigates the role of AI and machine learning methods in fetal brain MRI.

Citation: Vahedifard F, Adepoju JO, Supanich M, Ai HA, Liu X, Kocak M, Marathu KK, Byrd SE. Review of deep learning and artificial intelligence models in fetal brain magnetic resonance imaging. *World J Clin Cases* 2023; 11(16): 3725-3735
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3725.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3725

INTRODUCTION

Role of magnetic resonance imaging for fetal brain imaging

Although sonography is the most used imaging and monitoring technique, magnetic resonance imaging (MRI) is increasingly employed to assess the fetus. Fetal MRI for detecting brain disorders is commonly used with prenatal ultrasound when an anomaly is discovered. Fetal MRI is often requested to research further suspected brain abnormalities such as ventriculomegaly, missing corpus callosum, and posterior fossa anomalies[1]. MRI allows for a more precise and high-quality prenatal brain examination in high-risk fetuses referred from ultrasound. MR images of fetuses can also assist clinicians in detecting brain abnormalities at an early stage of development.

One of the most significant advantages of MRI is visualizing the entire brain, even in late pregnancy. Also, orthogonal sections can be obtained more easily, because the operator can manipulate the direction of spatial encoding gradients at will. With the advancement of rapid MR techniques and MRI software, particularly the half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence, fetal MR could be conducted without sedation, leading to an increase in the use of this imaging tool[1].

LIMITATION OF "FETAL BRAIN MRI"

Three significant problems with fetal MR imaging affect the quality of the images and the accuracy of the anatomical lines. Throughout the second and third trimesters, gyrification and sulcation transform the fetus's previously smooth surface into a highly complicated structure. Second, the changes in water content that come with active myelination cause MR imaging signal intensity and contrast to varying greatly between gestational age (GAs)[2,3]. Third, fetal MRI acquisitions are more susceptible to imaging artifacts. For example, the images often present motion artifacts caused by the mother's breathing and the fetus's jerky movements. Standing wave artifacts can happen when the conductivity of amniotic fluid and tissues differs. Also, the large field of view (FOV) for the mother's abdomen and the short scan time can lead to lower image resolution, and, thus partial volume effects, in which a single image voxel may contain different types of tissues[4]. These MR artifacts are more prevalent in the imaging of fetuses than those of adults. All three of these problems make it difficult to segment the brain of a fetus on MR images[5].

Deep learning for medical imaging

Deep learning (DL) uses simple interconnected units to extract patterns from data and solve complex problems, specifically on image-related tasks. They have matched or surpassed human performance, although the generally accepted performance for detection is that artificial intelligence (AI+) Radiology is better than either alone. Radiology is a natural application area for DL because it relies on extracting useful information from images. Research in this area has grown rapidly in recent years[6].

The incidence of central nervous system abnormalities in fetuses is rather high, ranging from 0.1% to 0.2% in live births and from 3% to 6% in stillbirths[7]. As a result, initial detection and categorization are critical. There is strong potential for machine learning approaches to assist in the early detection of these problems and enhance the diagnosis and follow-up processes.

Inclusion criteria: We examined how machine learning and AI can be applied to fetal brain MRI. The databases for the search were MEDLINE using PubMed, SCOPUS, Web of Science, EMBASE, Cochrane Library, and Google Scholar, up to June 2022. First, we searched keywords including "artificial intelligence", "machine learning", "deep learning", "Fetal brain", "Fetal MRI", as well as "AI + Fetal", "AI + Brain MRI", and "AI or ML + neonates".

Exclusion criteria: Only relevant AI and Machine Learning methods models in fetal brain MRI were included after the second evaluation. Animal and Basic science studies were also excluded.

We divided models into several applications (Table 1).

AI for preprocessing of fetal images

Obtaining high-quality images of a continually moving subject is one of the most challenging tasks in prenatal imaging. Motion correction and preprocessing technologies can help. Usually, qualified technologists must change acquisition planes frequently and re-acquire sequences. The process is time-consuming and subject to operator variation. Pregnant women who are immobile in a claustrophobic MRI scanner for an extended period may find it difficult. Correction for fetal motion during automated and precise initialization could lead to higher-quality images and potentially a shorter scan time[8].

Gagoski *et al*[9] developed a Convolutional Neural Network (CNN) that automatically detects artifacts on T2 HASTE sequences during fetal MRI to improve image quality[9]. The CNN would evaluate each image slice within an acquisition, and only the slices with the lowest image quality ratings would be re-acquired at the end of the study. This could reduce exam time by only re-acquiring motion-degraded images rather than the entire image stack. Ten healthy pregnant women underwent 73 modified HASTE sequence imaging acquisitions throughout the study. Their real-time implementation of the IQA CNN resulted in an accuracy of 85.2% and an area under the curve of 0.899.

Through DL, Xu *et al*[10] developed a system that detects fetal landmarks automatically[10] (with 15 important locations including upper and lower limb joints, eyes, and bladder) to estimate fetal posture, provide movement tracking of the fetus, and maybe automate the readjustment of acquisition parameters. In less than 1 second, their model could predict fetal posture to the nearest 4.5 mm.

Using a preprocessing AI system (SVRnet), Hou *et al*[11] propose a conceptual method of correcting fetal motion by generating 2-dimensional T2-weighted single slices in varying orientations[11]. They achieved a spatial prediction error of 7 mm on simulated data for moving fetuses around 20 wk of gestation and produced qualitatively enhanced reconstructions. The model is able to solve the 2D/3D registration initialization problem in a broad and computationally efficient way, making it appropriate for usage in real-time settings.

Using DL, Singh *et al*[12] have developed a method for predicting fetal motion directly from acquired images in real-time using anatomical information derived from slice sequences. They trained a recurrent neural network made up of spatial and temporal encoder-decoders to infer motion parameters. They proposed a neural network approach that could predict fetal motion within 8 degrees and estimate motion-corrupted slices to schedule subsequent collections[12].

AI for post-processing of fetal images

Post-processing steps associated with image enhancement and correction include noise reduction, image artifact correction, and image resolution enhancement. DL has recently demonstrated promising results in various research fields, including image enhancement for MRI. Recent publications have demonstrated promising results using DL for MR image enhancement[13].

The lack of normative brain templates and the limited possibilities for automated preprocessing make a quantitative analysis of prenatal brain MRI difficult.

Previously, 3D reconstructions of the embryonic brain required manual delineation of 2D pictures. Li *et al*[14] developed a U-net-based brain extraction algorithm to autonomously segment normal fetal brains using a 5-mm slice fetal MRI in three planes[14]. An average Dice coefficient of 0.97 across all three planes was obtained after spending two to three seconds segmenting each fetal brain.

Ebner *et al*[15] used CNN to automate fetal brain reconstruction through localization, segmentation, and super-resolution[15]. Automated segmentation was comparable to manual segmentation performed by technologists and radiologists on healthy and diseased fetal brains.

AI for reconstruction of fetal imaging

Single-Shot Fast Spin Echo is one example of a fast imaging technique used to acquire low-resolution stacks of 2D slices, which can effectively halt fetal movement. Poor 3D image quality and motion artifacts often emerge from stacks of slices acquired at different times due to patient movement between procedures. For assessment and quantification of fetal brain, from multiple low-resolution stacks acquired from different perspectives, it is desirable to reconstruct a single high-resolution, isotropic volume of fetal brain[12]. The brain must currently be located and extracted from many stacks of 2D slices using time-consuming reconstruction techniques that frequently include user participation.

Table 1 Different applications for artificial intelligence for fetal brain magnetic resonance imaging

Classification		Different applications
A	AI for preprocessing of fetal images	(1) Automatic image quality assessment to detect artifacts on T2 HASTE sequences during fetal MRI (Gagoski *et al* [9]); (2) Automatically detects fetal landmarks (using 15 key points–upper limb and lower limb joints, eyes, and bladder) (Xu *et al*[10]); (3) Fetal motion correction (Hou *et al*[11]); and (4) Predicting fetal motion directly from acquired images in real-time (Singh *et al*[12])
B	AI for post-processing of fetal images	(1) U-net-based brain extraction algorithm to autonomously segment normal fetal brains (Li *et al*[14]); and (2) Localize, segment, and perform super-resolution reconstruction for the automated fetal brain (Ebner *et al*[15])
C	AI for reconstruction of fetal imaging	Fully automatic framework for fetal brain reconstruction, consisting of four stages (Ebner *et al*[15])
D	AI for gestational age prediction	(1) Predicting GA from fetal brain MRI acquired after the first trimester, which was compared to a BPD (Kojita *et al* [19]); and (2) An end-to-end, attention-guided deep learning model that predicts GA (Shen *et al*[20])
E	AI for fetal brain extraction	(1) The automatic brain extraction method for fetal MRI employs a multi-stage 2D U-Net with deep supervision (DS U-net) (Lou *et al*[24]); and (2) A brain mask for an MRI stack using a two-phase random forest classifier and one estimated high-order Markov random field solution (Ison *et al*[23])
F	AI for fetal brain segmentation	(1) U-net-like convolutional neural network (Auto-net) (Mohseni Salehi *et al*[29]); CNN using images with synthetically induced intensity inhomogeneity as data augmentation (Mohseni Salehi *et al*[29]); (2) Pipeline for performing ICV localization, ICV segmentation, and super-resolution reconstruction in fetal MR data in a sequential manner (Tourbier *et al*[32]); (3) Automatic method for fetal brain segmentation from MRI data, and a normal volumetric growth chart based on a large cohort (Link *et al*[33]); (4) Fetal Brain magnetic resonance Acquisition Numerical phantom, to simulate various realistic magnetic resonance images of the fetal brain and its class labels (de Dumast *et al*[34]); (5) SIMOU-Net, a hybrid network for fetal brain segmentation. Was inspired by the original U-Net fused with the HED network (Rampun *et al*[36]); and (6) Incorporating spatial and channel dimensions-based multi-scale feature information extractors into its encoding-decoding framework (Long *et al*[35])
G	AI for fetal brain linear measurement	(1) AI for the anteroposterior (A/P) diameter of the pons and the A/P diameter and S/I height of the vermis (Deng *et al*[40]); and (2) A fully automatic method that computes three key fetal brain MRI parameters: 1-CBD, 2-BBD, 3-TCD (Avisdris *et al*[41])
H	AI for automatically localizing fetal anatomy	Automatically localizing fetal anatomy, notably the brain, using extracted superpixels (Alansary *et al*[42])
I	AI for classification of brain pathology	Classification using several machine-learning classifiers, including DQDA, K-NN, random forest, naive Bayes, and RBF neural network classifiers (Attallah *et al*[45])
J	AI for placenta detection	(1) U-net-based CNN to separate the uterus and placenta (Shahedi *et al*[51]); and (2) automatic placenta segmentation by deep learning on different MRI sequences (Specktor-Fadida *et al*[52])
K	AI for functional fetal brain MRI	An auto-masking model with fMRI preprocessing stages from existing software (Rutherford *et al*[53])

AI: Artificial intelligence; MRI: Magnetic resonance imaging; RBF: Radial basis function; K-NN: K-nearest neighbor; DQDA: Diagonal quadratic discriminant analysis; CBD: Cerebral Biparietal Diameter; BBD: Bone Biparietal Diameter; TCD: Trans Cerebellum Diameter; S/I: Superior/inferior; SIMOU-Net: Single-Input Multi-Output U-Net; HED: Holistically nested edge detection; BPD: Biparietal diameter; ICV: Intracranial volume.

A fully automatic framework for embryonic brain reconstruction was proposed by Ebner *et al*[15]. A fully automatic framework for embryonic brain reconstruction was proposed by Ebner *et al*[15]: (1) Fetal brain localization using a CNN and coarse segmentation; (2) Another CNN with a multi-scale loss function was used to fine-tune the segmentation; (3) Super-resolution reconstruction with a single parameter that is resilient to outliers; and (4) High-resolution visualization in conventional anatomical space, ideal for diseased brains, is performed quickly and automatically.

For validation, images of fetuses with normal and ventriculomegaly with open spina bifida were used. Each step of their suggested pipeline outperforms cutting-edge methods in comparisons for segmentation and reconstruction, including quality ratings by experienced readers. The results of this technique's reconstruction were on par with those of labor-intensive, manually segmented brains, suggesting that automatic fetal brain reconstruction studies might be applied in clinical settings.

AI for gestational age prediction

The GA assessment of the first trimester is more accurate than dating in the late stages of pregnancy because, as gestation advances, fetal ultrasound measurements have a greater absolute error[16]. MRI provides unparalleled visibility of the fetal brain, enabling the establishment of age-specific morphologic milestones[17,18]. Determining age-appropriate brain development remains challenging due to the fetal brain's continuous development, image quality variation, and motion artifacts' frequent occurrence. DL algorithms offer a powerful way of estimating fetal age from highly variable imaging

data, with moderate to high prediction accuracy to detect GA.

An AI model was created by Kojita *et al*[19] for predicting GA from fetal brain imaging after the first trimester. T2-weighted images from 126 training and 29 validation exams were used to train the DL model. They compared the model with Biparietal Diameter (BPD) model. Compared to the BPD prediction, the model prediction has a significant Lin's concordance correlation coefficient (value = 0.964). As GA grew, the model's and BPD's predictions diverged more from the reference. According to their model, first-trimester ultrasounds can predict GA with a maximum deviation of 1.66 wk, which falls within the range of sonography-based age predictions in the second trimester (7-14 d). After 28 wk of gestation (over 21 d of gestation), these predictions were superior to those based on ultrasound. From 2nd and 3rd trimester fetal brain MR, their DL accurately predicted GA[19]. DL-based prediction of GA could benefit prenatal treatment in underserved first-trimester pregnancies.

Shen *et al*[20] presented an attention-guided DL model that predicts GA. The CNN was trained using 741 normal fetal brains[20]. The recommended regression technique was a machine-enabled automated tool that could better characterize in-utero neurodevelopment and guide real-time GA estimate beyond the first trimester. (concordance correlation coefficient = 0.970, and mean absolute error = 6.7 d).

AI for fetal brain extraction

Prenatal brain MRI reconstruction begins with fetal brain extraction. It is impossible to employ adult brain extraction techniques for fetuses because maternal tissue is present in the MRI of fetal brain tissue. Brain extraction can be difficult due to changes in the size and shape of the developing brain, motion artifacts from fetal movement within the uterus, and substantial variance in the FOV.

Quantitative brain development analysis requires automatic brain tissue segmentation, generally preceded by intracranial volume segmentation (ICV)[21]. The extraction of fetal brains can, however, be difficult because of sparsely collected imaging stacks. Automated segmentation of brain structures is necessary since semi-automatic segmentation is time-consuming and laborious. A variety of strategies exist for automated segmentation or brain extraction from fetal MRIs[22]. The automated brain extraction and oriented positioning of pediatric exams are not yet as developed as for adult exams. They remain challenging given the wide FOV associated with fetal MRI and the large volume of images from repeated acquisitions that are often necessary. As a result, research has been limited to small-scale studies[23].

Lou *et al*[24] proposed a multistage 2D U-Net with deep supervision technique for automatic brain extraction from fetal MRI (DS U-net)[24]. They started by defining a 3D bounding box for localizing the site of the brain using a crude segmentation generated from DS U-net. The deep supervision loss function trains the DS U-net to improve its discrimination capacity. A second DS U-net was then utilized to focus on the extracted region, resulting in sharper segmentation. Advanced segmentation was used to acquire the final segmentation findings. They used 80 training datasets and 43 testing stacks to validate the suggested approach. With an average Dice coefficient of 91.69%, the experimental results confirmed the precision and robustness of their method, surpassing previously proposed strategies.

As opposed to adult studies, automatic brain extraction and orientation are still a challenge in raw fetal MRI volumes with a wide FOV. Ison *et al*[23] provided a methodology for automatic fetal brain extraction and orientation that overcomes this constraint[23]. A two-phase random forest classifier and a high-order Markov random field solution were used to produce a brain mask for an MRI stack. The extraction that resulted had a detection rate of 98%. Furthermore, when tested on cases ranging in gestational weeks from 18 to 30.2, the mean sensitivity was 88%, indicating a solid pipeline to automated fetal MRI processing procedures.

AI for fetal brain segmentation

Fetal MRI volumetric and morphologic analysis begins with brain segmentation. Because manual segmentation is expensive and time-consuming, automated segmentation could greatly simplify the process. Due to increased intensity inhomogeneity and spontaneous fetal movements, automated brain tissue segmentation in prenatal MRI is difficult.

Different segmentation strategies for automatic delineation of the fetal brain MRI have recently been proposed. Unsupervised, parametric, classification, atlas fusion, and deformable models were used to evaluate the segmentation. In the segmentation procedure, brain atlases are frequently used as training data[25].

However, difficulties with image capture, continuous brain development, and the shortage of imaging data obstruct this segmentation process. Makropoulos *et al*'s paper showed the various segmentation approaches for each category[25]. The use of CNN has gained popularity in recent years for the automatic segmentation of medical images[26]. There have been several studies that investigated different CNN architectures in order to segment brain tissue using adult MRIs[27,28].

Also, Mohseni Salehi *et al*[29] suggested a DL segmentation method that is iterative and employs a U-net-like CNN (Auto-net)[29]. ITK-SNAP software segmented the fetal brain from a manual bounding box[30].

According to Khalili *et al*[31], segmentation can be done with a CNN using images augmented with synthetically induced intensity inhomogeneity rather than with approaches that estimate the bias field prior to segmenting[31]. First, a CNN was used to extract the intracranial volume of the patient. The

collected volume is then segmented into seven brain tissue classes using another CNN with an analogous architecture. A mixture of linear gradients with random offsets and orientations was added to the training data to make a method that worked with slices showing intensity inhomogeneity artifacts. When generated intensity inhomogeneity artifacts enriched the training data, mean squared displacement dropped from 0.78 mm to 0.37 mm and DC overall tissue classifications improved from 0.77 to 0.88. These findings showed that the suggested method might replace or augment preprocessing processes such as bias field adjustments, resulting in better segmentation performance.

Several methods first find the location of the brain in the fetal ICV, which is different from methods that do ICV segmentation without brain localization. Using fetal MR data, Tourbier *et al*[32] propose a pipeline for localizing, segmenting, and reconstructing ICVs sequentially[32]. Using age as prior knowledge, this strategy segmented the ICV in fetal MRI. Template-based approaches have the disadvantage of being computationally more expensive than machine learning algorithms. Significant segmentation errors are likely to occur if representative age-matched templates are unavailable. Furthermore, brain localization approaches require the ICV to be segmented afterward to separate brain tissue classes.

Link *et al*[33] developed a semi-automatic fetal brain segmentation approach utilizing MRI data and a normal volumetric growth chart based on a large cohort to generate an automatic method for clinical use. They used MRI data from 199 usually growing fetuses to construct the Seeded Region Growing algorithm (18-37 wk)[33]. Their model strongly correlates (r^2 = 0.9183, P = 0.001) with manual segmentation. Differences in mean volume and volume overlap were 4.77 and 18.13 percent, respectively. They described their procedure as quick, accurate, repeatable, and user-independent.

Automated multi-tissue fetal brain segmentation algorithms are being developed to assess the human brain's development in utero quantitatively. However, the available annotated fetal brain datasets have limitations in number and heterogeneity, hampering domain adaptation strategies for robust segmentation. FaBiAN, a Fetal Brain Magnetic Resonance Acquisition Numerical Phantom, was utilized by de Dumast *et al*[34] to recreate a variety of accurate magnetic resonance images of the fetal brain and its class labels[34]. They showed that these multiple synthetic annotated data, created for free and then reconstructed using the target super-resolution technique, can be utilized to successfully domain adapt a DL method that segments seven brain tissues. The segmentation accuracy was improved overall, particularly in the cortical gray matter, white matter, cerebellum, deep gray matter, and brain stem.

Example of segmentation: "Expanding the Unet model": U-Net is a popular CNN used for segmenting MR images due to its precision. While U-net often performs well, its performance is often limited by the subtle differences between segments in MRI, as well as the loss of information caused by downsampling and upsampling. One method for solving this problem is to employ a spatial and channel dimension-based framework. The encoding part enhances multi-scale features, while the decoding part recovers the corresponding localization to a higher resolution layer[35]. There have been two proposed methods for extracting multiscale features: Multi-branch pooling and multi-branch dense prediction. A multi-branch output structure is created in the decoding section by combining dense nearby prediction features at various scales.

The hybrid network known as the Single-Input Multi-Output U-Net (SIMOU-Net) was also developed by Rampun *et al*[36] for the purpose of fetal brain segmentation. The original U-Net and the holistically nested edge detection network were the basis for this model[36].

SIMOU-Net has a deeper architecture than U-Net, and takes account of all side outputs. In a similar way, it acts as a neural ensemble. By combining outputs from a single network instead of averaging the results of several independent models, their approach reduced the variance and generalization error of predictions. 200 normal fetal brains with over 11500 2D pictures revealed Dice 94.2 ± 5.9% In 54 abnormal cases , the suggested network achieved Dice of 91.2 ± 6.8%.

A meaningful interpretation of the fetal brain requires brain segmentation. It is essential to accurately segment brain tissue on an MRI for diagnosis, therapy planning, and neurologic state monitoring.

AI for fetal brain linear measurement

Routine clinical assessment of fetal brain development using MRI is mainly subjective, with a few biometric linear measurements. Based on MRI reference growth centiles of normal-developing fetuses, these measurements are compared to those taken in the United States.

Taking manual measurements requires clinician training, takes a lot of time, and is subject to inter-observer and intraobserver variability[37]. In some cases, small measurement errors can pose a risk of misdiagnosis or mismanagement of pregnancy[38]. Several technical challenges involve developing automatic methods for calculating biometric fetal brain measurements. First, the method should follow the guidelines and steps explicitly and implicitly performed by the clinician, including localizing the fetal brain in the MRI volume, selecting the reference slice, and identifying the anatomical landmarks and measurements. MRI scanning planes, resolutions, contrasts, and procedures, fetal brain pathology, and motion artifacts all result in inaccurate observations and observer variability[39].

Deng *et al*[40] at Rush University made a new AI model to find two important fetal biometric parameters from fetal brain MRI: The anteroposterior (A/P) diameter of the pons and the A/P diameter and superior/inferior height of the vermis[40]. There were 55 fetal brains MRI patients and about 100

sets of sagittal T2-weighted HASTE brain images. They made U-net DL model to find six landmarks: Two on the pons and four on the vermis. The steps that were taken were: (1) Image selection and labeling by a neuroradiologist; (2) Dataset augmentation (adding noise, rotating, flipping); (3) Region of interest (ROI) masking and use of the transforming process (Gaussian distribution); and (4) Using the U-net model to find landmarks (Pons-vermis). Both landmarks (2 for pons and 4 for vermis) and four-fold cross-validations were taught to the models simultaneously.

They devised two models of 4-fold cross-validation (by GA weeks or by mixed weeks), and mixed cross-validation was the most accurate (98 and for pons and 88% for vermis). The most accurate measurements were: 100% for the pons; 97.5% for the A/P diameter of the vermis; and 95% for the height of the vermis.

The average accuracy was 98% for Pons1, 99% for Pons2, 98% for Vermis1, 84% for Vermis2, 86% for Hvermis1, and 86% for Hvermis2.

In 2021, Avisdris *et al*[41] studied a new deep-learning method to automatically compute linear measurements in a fetal brain MRI volume based on landmark detection and estimates[41]. This was a fully automatic method that computes three key fetal brain MRI parameters: (1) Cerebral Biparietal Diameter (CBD); (2) Bone Biparietal Diameter (BBD); and (3) Trans Cerebellum Diameter (TCD). Compared to the measurement of an expert (fetal radiologist), their model has yielded a 95% confidence interval agreement of 3.70 mm for CBD, 2.20 mm for BBD, and 2.40 mm for TCD. The authors proposed that their model surpasses previously published results and suggested that this model to be directly applied to other linear measurements.

Their approach consists of four steps: (1) Detection of the ROI with a two-stage anisotropic U-Net; (2) Selection of reference with a CNN; (3) Computation of linear measurement according to landmarks detection with a novel CNN, FMLNet; and (4) Finally, estimation the reliability with a Gaussian Mixture Model. Their model requires fetal brain structure segmentation and is considered robust based on reliability estimation.

Using deep neural networks, Avisdris *et al*[39] proposed an algorithm that performs automatic linear measurements of the fetal brain[39]. The outputs were the measurement values and reference slices in which the measurements were computed. The method, which follows the manual measurements principle, consisted of five stages: (1) Computation of a ROI that includes the fetal brain with an anisotropic 3D U-Net classifier; (2) CNN reference slice selection; (3) Multiclass U-Net classifier slice-wise fetal brain structures segmentation; (4) Fetal brain mid-sagittal line computation; and (5) Measurements. Testing findings on 214 volumes for CBD, BBD, and TCD measures showed a mean L1 difference of 1.55 mm, 1.45 mm, and 1.23 mm, respectively. This automatic method for computing biometric linear measurements of the fetal brain from MR imaging achieved human-level performance, and the authors suggested that it can help assess fetal brain biometry in normal and pathological cases.

AI for automatically localizing fetal anatomy

In MR scans, the location and orientation of the fetus are subject to substantial change. In contrast to standard adult MRI, where the anatomical planes are aligned, these fetal images are difficult to analyze and interpret.

By automatically locating fetal anatomy, including the brain, Alansary *et al*[42] addresed the problem. Using dense scale-invariant feature transform descriptors, they first extracted superpixels, then computed histograms for each superpixel[42]. To discriminate between the brain and non-brain superpixels, they built a superpixel graph and trained a random forest classifier. The framework was tested on 55 MR datasets aged 20 to 38 wk. Using 5-fold cross-validation, the proposed technique was found to have a brain detection accuracy rate of 94.55%

AI for classification of brain pathology

Recently, machine learning techniques have been used to detect fetal brain MRI images and identify and classify these abnormalities[43]. In most early studies of fetal brain images, anomalies were detected by segmenting the images. Only a few studies have examined how machine-learning approaches detect prenatal brain abnormalities[25,44].

A new scheme for organizing fetal brains was proposed by Attallah *et al*[45]. For this purpose, she used several machine-learning classifiers, including K-nearest neighbor (KNN), random forest, and naive Bayes. Bagging and AdaBoosting ensemble models were created using random forest, naive Bayes, and RBF network classifiers. They suggested that this new technique may successfully identify and classify various abnormalities in MRI images of the fetal brain of different GAs. KNN classifiers had the highest classification accuracy (95.6%) and area under receiving operational characteristics (99%). Ensemble classifiers improved model outcomes[45].

Using DL methods, Attallah *et al*[45] suggested a four-step approach for the early diagnosis of Embryonic Neurodevelopmental Disorders (END): Learn-from-previous-experience, deep feature extraction, feature reduction, and classification. The study included three experiments. An end-to-end DL strategy was employed in the first experiment with three CNN structures. As part of experiment II, deep features were extracted from each DCNN's FC layer in order to train support vector machine (SVM) classifiers one by one. These features were reduced using Principal Component Analysis and used to generate various SVM classifiers. Deep features were put together to see how they affected

classification performance, and the best features were selected to improve performance. The proposed framework results showed that it could find ENDs with high accuracy. The authors suggested that their algorithm can assist neuroradiologists in diagnosing fetal brain abnormality, facilitating treatment planning, and follow-up as well as informing the parents of the embryonic conditions. This can reduce the occurrence of NDs among newborns, improving the quality of health management[46].

AI for placenta detection

The placenta plays an important role in maternal-fetal health, but limited non-invasive tools exist to assess placental function in utero[47]. Placental segmentation has been shown to assist in detecting and quantifying pregnancy-related problems such as placenta accreta and growth restriction[48].

MRI is an alternative imaging modality that can be used to quantify placental development in healthy and growth-restricted pregnancies. High-risk pregnancies have shown anomalies in placenta volume, thickness, and intensity on 2-dimensional MRIs[49,50].

Shahedi *et al*[51] differentiate the uterus and placenta in 100 pregnant women using a U-net-based CNN with DICE coefficients of 0.92 and 0.82[51]. Only a few user inputs (reportedly seven 'clicks') are required to obtain the output placental size and placement.

In a recent study, Specktor-Fadida *et al*[52] presented a method for segmenting the placenta using DL on different sequences of MRI[52]. Specktor-Fadida *et al*[52] developed a DL technique for automatically segmenting placentas on various MRI sequences. Placenta ROI detection and segmentation networks use a new loss function based on a contour and a soft Dice. On 21 test cases and only 16 training cases, the experimental Dice score for the FIESTA sequence was 0.847. Switching to the TRUFI sequence improved Dice scores on 15 test cases to 0.78. Sequence transfer bootstrapping and contour Dice loss and self-training led to the best placenta segmentation results ever.

AI for functional fetal brain MRI

Prenatal brain development can now be assessed using resting-state functional MRI (rs-fMRI). Despite this approach's rapid and widespread adoption, we lack neuroimaging processing pipelines to handle this data format's unique issues. The most challenging part of the processing is isolating the fetal brain from the rest of the tissue in hundreds of moving 3D brain volumes. Rutherford *et al*[53] trained a CNN using 1241 manually traced fetal fMRI It performed well on two held-out test sets from different MR scanners and patients. They also added fMRI preprocessing stages from existing software to the auto-masking model[53].

MRI 3T *vs* 1.5 T in fetal MRI: Using 3-T magnets has improved access to advanced imaging sequences and anatomical evaluation in fetal MRI. 3.0-T MRIs have better spatial resolution and signal-to-noise ratios than 1.5-T ones. However, when it comes to fetal MRI, there are concerns about the possibility of the fetus receiving greater radiofrequency energy. Most fetal 1.5- and 3.0-T MRIs had similar energy metrics. Three-dimensional steady-state free precession and two-dimensional T1-weighted spoiled gradient echo may need modifications to reduce patient-delivered energy.

LIMITATIONS OF "AI IN FETAL MRI"

DL-based AI tools require many annotated training datasets to produce acceptably accurate results, which often have limited availability in terms of the dataset. In addition, it is difficult to constantly update models as training data increase and practice patterns change. Among the many DL-based fetal MRI algorithms that have been proposed and are under current development, it remains to be determined which ones possess the potential for widespread adoption. Thus, radiologists should collaborate with AI researchers to understand the latest methods and provide clinical feedback to guide future development. AI tools will likely act as powerful image-processing and decision-support tools to improve radiologists' accuracy and efficiency, not their replacement.

DL methods are anticipated to become more powerful as more large-scale datasets with labels are available. Fetal brain MRI datasets that share data, such as the FeTA Dataset, are crucial due to the scarcity of fetal brain images[54]. Automatic multi-tissue fetal brain segmentation algorithms are needed to facilitate this analysis, requiring open datasets of segmented fetal brains.

CONCLUSION

Several DL-based strategies have been developed to predict specific landmarks and perform automatic segmentation in fetal MRI applications. All gestation age weeks after first trimester[16-37] where various AI models have been suggested (most notably CNN and U-Net). Some models have achieved an accuracy of 95% or higher. AI tools could be deployed in the preprocessing, the post-processing, as well as the reconstruction of fetal MR images. It is also possible to predict GA with an accuracy of one week, extract the fetal brain, segment the fetal brain, and detect the placenta with the help of AI algorithms.

Some linear measurements of the fetal brain have been proposed; these include the cerebellar diameter, the transcerebellar diameter, and the BPD.

As a result of the limited number of publicly available fetal brain MRI data sets, the development of AI algorithms is challenging at this point, but the developments so far have been promising. Research in these fields will continue to rely on the further development of public data sets and the collaborative efforts between physicians (specifically neuroradiologists, general radiologists, and perinatologists) and researchers in this field.

FOOTNOTES

Author contributions: Byrd SE, Vahedifard F, Supanich M, and Kocak M designed the research study; Vahedifard F, Marathu KK, and Adepoju JO performed the literature review; Liu X contributed analytic tools; Vahedifard F, Supanich M, and Ai HA wrote the manuscript; Byrd SE performed the funding support; All authors have read and approve the final manuscript.

Supported by Colonel Robert R McCormick Professorship of Diagnostic Imaging Fund at Rush University Medical Center (The Activity Number is 1233-161-84), No. 8410152-03.

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

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S-Editor: Fan JR
L-Editor: A
P-Editor: Zhao S

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3736-3749

DOI: 10.12998/wjcc.v11.i16.3736

ISSN 2307-8960 (online)

MINIREVIEWS

Diabetes more than retinopathy, it's effect on the anterior segment of eye

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Specialty type: Ophthalmology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Emran TB, Bangladesh; He Z, China

Received: March 23, 2023
Peer-review started: March 23, 2023
First decision: April 11, 2023
Revised: April 25, 2023
Accepted: May 6, 2023
Article in press: May 6, 2023
Published online: June 6, 2023

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Abstract

Diabetes mellitus (DM) is one of the chronic metabolic noncommunicable diseases that has attained worldwide epidemics. It threatens healthy life around the globe, with mild-to-severe secondary complications and leads to significant illness including nephropathy, neuropathy, retinopathy, and macrovascular abnormalities including peripheral vasculopathy, and ischaemic heart disease. Research into diabetic retinopathy (DR), which affects one-third of persons with diabetes, has made considerable strides in recent years. In addition, it can lead to several anterior segment complications such as glaucoma, cataract, cornea, conjunctiva, lacrimal glands and other ocular surface diseases. Uncontrolled DM also caused gradual damage to corneal nerves and epithelial cells, which raises the likelihood of anterior segment diseases including corneal ulcers, dry eye disease, and chronic epithelial abnormalities. Although DR and other associated ocular complications

are well-known, the complexity of its aetiology and diagnosis makes therapeutic intervention challenging. Strict glycaemic control, early detection and regular screening, and meticulous management is the key to halting the progression of the disease. In this review manuscript, we aim to provide an in-depth understanding of the broad spectrum of diabetic complications in the anterior segment of the ocular tissues and illustrate the progression of diabetes and its pathophysiology, epidemiology, and prospective therapeutic targets. This first such review article will highlight the role of diagnosing and treating patients with a plethora of anterior segment diseases associated with diabetes, which are often neglected.

Key Words: Diabetes; Ocular surface; Cataract; Glaucoma; Lens; Uvea

Core Tip: Most of the review articles and meta–analysis on diabetes and ocular science are focused on diabetic retinopathy and posterior segment only. To the best of our knowledge, this is the first such review article on the effect of diabetes on the anterior segment of the eye. It gives a detailed insight into the intricate pathophysiology of the adverse effect of diabetes on the eye-appendages, cornea, lens and uvea of the eye.

Citation: Morya AK, Ramesh PV, Kaur K, Gurnani B, Heda A, Bhatia K, Sinha A. Diabetes more than retinopathy, it's effect on the anterior segment of eye. *World J Clin Cases* 2023; 11(16): 3736-3749
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3736.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3736

INTRODUCTION

Diabetes mellitus (DM) is characterized by chronic hyperglycemia secondary to lack of or diminished efficacy of endogenous insulin and causes significant morbidity and mortality in multiple systems of the body. It is no longer a disease of affluent or industrialized nations. It has the highest prevalence among the populations of developing countries and in migrant and minority communities in industrialized countries. Diabetic eye disease is becoming a problem in developed and developing countries due to longer life expectancy and a sedentary lifestyle. In the eye, manifestations are found in almost every parts including orbit, lids, anterior and posterior segments. Most previous authors have concentrated on diabetic retinopathy (DR), but this disease can affect virtually every part of the eye and sometimes can significantly affect vision. Primary eye care workers and other professionals can easily examine the anterior segment of the eye for features of DM if trained to do so.

Orbital and lid features include boils, chalazia, xanthelasma, cranial nerve palsies (seventh, sixth, third, and fourth), and cellulitis. Conjunctival features include tortuous and dilated vessels commonly found in the inferior bulbar region, pinguecula, and pterygia. Tortuosity and dilatation of veins are part of the microvascular abnormalities found in diabetes. Recent advances in ocular surface imaging techniques have enabled the study of microstructural effects of DM on the ocular surface, which include tear film, cornea and conjunctiva. Identifying the microstructural abnormalities related to DM with routine slit lamp examination is difficult. *In vivo* confocal microscopy (IVCM) has recently become the standard cornea assessment tool. It is being used to detect and monitor the progress of DM and its complications. This instrument has been shown to produce precise and accurate results. The spectrum of abnormalities associated with ocular surface complications includes epithelial fragility, punctate keratopathy, persistent epithelial defects and decreased corneal sensitivity. The corneal endothelium is also shown to be affected in long-standing diabetic patients. Increased corneal endothelial pleomorphism and polymegathism are observed in these patients.

Diabetes also influences lens transparency and pharmacological pupil dilatation. A cataract occurring in diabetic patients can be due to diabetes itself or to accelerated senile cataract, in which case the cataract occurs earlier than normal. As with retinopathy, the duration and control of the diabetes are important factors in cataract development and management. Changes in the eye's refractive state may indicate the onset of diabetes. These may be myopia or hypermetropia. Myopia may be due to an increase in the thickness and curvature of the crystalline lens. Cranial nerve palsies are common in DM, with the facial nerve (seventh) being the most commonly affected, followed by the abducens, oculomotor, and trochlear. The association between DM and glaucoma in the literature is equivocal. Some researchers have not found an association, whereas others in Australia found the prevalence of open-angle glaucoma greater in people with diabetes than in the normal population. Iris atrophy, ectropion uvea, and rubeosis iridis are also seen in diabetic patients. This manuscript will throw light on

understanding the disease process of diabetes affecting the anterior segment of the eye as well as its pathology and treatment options.

METHODOLOGY

We collected highly cited articles in PubMed, Scopus database, Google Scholar, Web of Science, Cochrane Library, and Embase database on Diabetes effect on the anterior segment of the eye published between the year 1984 to 2022. We diligently used *Reference Citation Analysis* (*RCA*) for searching the keywords and articles were ranked based on the "Impact Index Per Article". The latest highlighted articles were selected for review. Only articles published in English were considered and the rest were rejected.

DISCUSSION

Effect of diabetes on eyelid

The eyelid is the anterior most part of both eyes, comprising structures like the upper and lower tarsal conjunctiva, meibomian gland, punctum, and lashes. Eyelid's function involves blinking mechanism, protection of both eyes, maintaining ocular surface health, tear/oxygen supply, *etc.*

DM is a systemic disease that mainly affects microcirculation and can affect the ocular surface integrity through a different mechanism. It is the most complicated disease to manage systematically and from an ophthalmology point of view, as many pathologies are related to it, including regular eyelid inflammatory abnormalities[1,2].

Regarding meibomian gland function in diabetics, there is a significant rise in lipid layer thickness in people with diabetes compared to non-diabetics, and there is also meibomian gland dysfunction present in diabetics, most severely in an asymptomatic diabetic population who needed dry eye treatment[3]. Xanthelasma is a yellowish plaque, benign lesion present on superonasal parts of the upper eyelid, usually bilateral in occurrence can also be triggered by systemic diseases such as diabetes, thyroid, *etc* [4]. Most common eyelid infection with diabetes is warts, poliosis, chalazion and recurrent episodes of styes[1]. There is evidence that the blinking mechanism and rate are significant in diabetic populations having higher blinking rates. Diabetes is one of the well-known causes of excessive blinking (blinking eye syndrome)[5]. However, some studies reported a decrease in the blinking rate in people with diabetes but with an increase in the inter-linking interval[6].

Conjunctiva

Acute bacterial infection is the most common complication of DM. Microvascular abnormalities due to long-standing diabetes will predispose the conjunctiva to infections. Conjunctival angiopathy includes increased microvessel dilation, increased tortuosity and leakage of conjunctival capillaries. These changes mimic vessel changes observed in the retina.

Macro vessel dilation associated with diabetes may result in vessel engorgement and straightening, especially among those with longer disease durations. Increased tortuosity associated with diabetes among conjunctival capillaries mirrors established vessel changes observed in the retina. Conjunctival angiopathy associated with diabetes may contribute to susceptibility to anterior eye disease among patients with diabetes.

Precorneal tear film

Patients with long-standing diabetes typically complain of dry eye symptoms such as burning and foreign body sensations. In more severe cases, diabetic neurotrophic keratopathy occurs. The stability, secretion and lipid layer quality of tear film are reduced in diabetes due to decreased trophic effect of trigeminal sensory nerves on the cornea. The tear fluid in diabetic patients contains higher glucose concentrations due to conjunctival angiopathy and vessel leakage. It decreases the corneal epithelium's wound healing capacity and damages the microvascular supply to lacrimal glands, leading to reduced lacrimation.

Decreased tear film stability is the typical manifestation in people with diabetes. It is found to be due to a reduced number of goblet cell densities, which are the main source of tear film mucins that protect the cornea and maintain a stable preocular tear film. Trigeminal nerve dysfunction also disrupts lacrimal gland function and decreases basal tear production. Schirmer test used to assess the function of the lacrimal gland, shows lower tear production in diabetic patients. The corneal limbus is a narrow band of tissue that encircles the cornea. Under physiological conditions, corneal limbal epithelial stem cells give rise to progeny, differentiating into mature corneal epithelium during their radial migration towards the centre.

The tear film is the primary interface between the ocular surface and the external environment and plays a pivotal role in maintaining the morphological and functional integrity of the cornea. In addition,

the lacrimal glands, lacrimal drainage system, and interconnecting innervation work together as the lacrimal function unit (LFU). DM is also associated with film abnormality and LFU insufficiency, which can deteriorate corneal components. Owing to abnormal tear dynamics, diabetic patients are more prone to suffer from dry eye syndrome (DES). DES is ubiquitous in diabetic patients, especially those with Dr. DES is a potential visual impairment syndrome that can lead to superficial punctuate keratopathy, secondary bacterial infection, and even perforation. The decrease in lacrimal gland secretory function is the cardinal problem in DES.

Many mechanisms, notably chronic inflammation and peripheral neuropathy, contribute to the onset and progression of the tear film abnormality in diabetic patients in DES. Chronic hyperglycemia is the primary causative mechanism underlying the pathogenesis of tear film abnormality. In addition, there was a significant elevation of inflammation or pre-inflammation markers in the tears and conjunctiva of diabetic patients, such as interleukin (IL)-1α, IL-1β, IL-6, and tumor necrosis factor-α. As previously stated, matrix metalloproteinases (MMP) are an essential mediator of inflammation in diabetes and contribute to tissue impairment. It was reported that elevated MMP-9 was significantly correlated with ocular surface inflammation. In addition, the level of substance *P* was considerably lower in the tears of diabetic patients. A recent study showed that increasing metallic elements in patients with DM's tears might indicate ocular damage. In addition, oxidative stress in the diabetic rat model leads to pathological alteration of the lacrimal gland acinar cells. An experimental study demonstrated that overexpression of SIRT1 in the diabetic dry eye model was evident for the DES oxidative stress mechanism.

Furthermore, chronic hyperglycemia may eventually lead to tearing film hyperosmolarity. Exposure of corneal structures, including the corneal epithelium and corneal limbus, to tear film hyperosmolarity leads to a cascade of inflammatory reactions. Additionally, the elevated volume of the tear film of patients with DM may be attributed to tear film instability and rapid evaporation of the tear, which leads to tear secretion in a reflex action. Usually, the secretion of tears in patients with DM is reduced. Furthermore, tear film instability and hyperosmolarity play significant roles in the vicious cycle of diabetic tear film abnormality.

Lacrimal nerve fibres play a pivotal role in the maintenance of tear production and integrity of the LFU. Diabetic neuropathy may compromise the innervation of the LFU. Moreover, impairment of the LFU sensory nerve may also inhibit tear secretion associated with the reduced corneal sensitivity threshold. Interestingly, using IVCM, the number of corneal sub-basal nerves was significantly correlated with Schirmer test values. Such a phenomenon may indirectly reveal alterations in the corneal innervations in DES patients with diabetes. Furthermore, exposure to high glucose levels is deleterious for human meibomian gland epithelial cells and may help explain the importance of hyperglycemia for LFU in patients with DM.

General manifestations of diabetes in the cornea

Uncontrolled diabetes or diabetic alteration can cause clinically significant changes in the cornea[7]. The corneal changes seen are epithelial defect, fragile epithelium, recurrent corneal erosion syndrome, superficial punctate keratitis, increased corneal thickness, corneal infiltrate, oedema, delayed corneal healing, and reduced corneal sensation leading to neuropathy[8]. Another common corneal change seen in people with diabetes is dry eye syndrome. Diabetic corneal neuropathy is characterized by decreased corneal sensitivity, reduced sub-basal nerve fibre and branch density, tortuous and thickened stromal nerves and slow nerve regeneration after any traumatic injury[9].

DIABETIC KERATOPATHY

Epithelial abnormalities

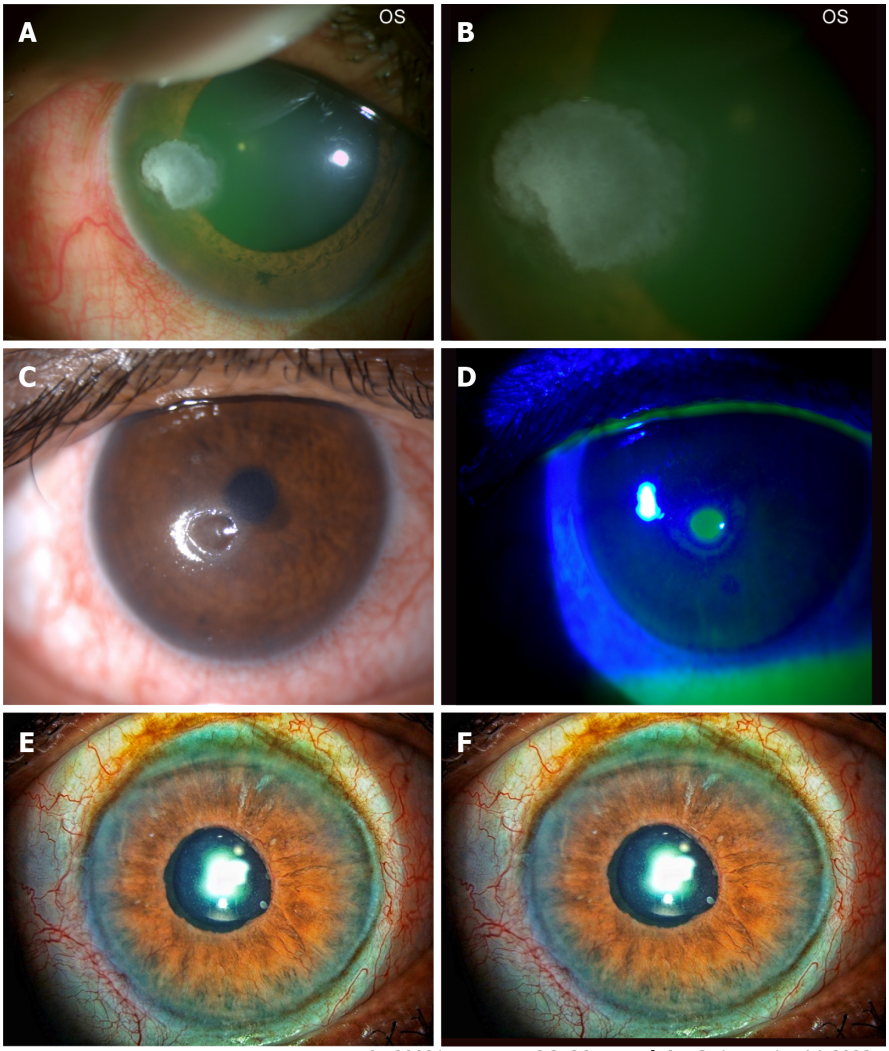
The corneal epithelial changes secondary to diabetes are often labelled as diabetic keratopathy. Common epithelium changes are epithelial defect, fragility, recurrent corneal erosions, superficial punctate keratitis, delayed wound healing, and corneal ulceration[8] (Figure 1A and B).

Uncontrolled diabetes (especially type 2 DM) has been linked to diabetic keratopathy, and the changes are seen more often in females. The presence of diabetic keratopathy is an alarm sign for occult peripheral neuropathy and should alert the physician. Neurotrophic keratopathy has also been reported but is comparatively a rare complication (Figure 1C and D).

Uncontrolled diabetes also causes structural and functional alternation in the epithelium, which may not be directly linked to neuropathy. As per previous studies, hyperglycemia has a direct impact on corneal epithelial cells and also on cultured corneal epithelial cells reducing cell adhesions and slowing down the healing process[10].

Corneal nerve changes

The first findings on decreased corneal sensitivity in diabetics were reported in 1970. Since then, with continued understanding and growing research, it is now well documented that corneal sensations are reduced in diabetic patients, and the severity may increase with age. Reduction in sensations is related



DOI: 10.12998/wjcc.v11.i16.3736

Figure 1 Diabetic keratopathy. A and B: Fungal corneal ulcer in a diabetic patient; C: Slit lamp image of neurotrophic keratopathy in a diabetic patient; D: Stain positive neurotrophic keratitis in a diabetic patient; E and F: Neovascular glaucoma with neovascularization of iris in a diabetic patient.

to abnormalities of corneal nerve structure and function in diabetes[11]. *In vivo* IVCM performed in diabetic cornea reveals structural alterations in nerve fibre density, branch density, length of fibres, tortuosity nerves, and thickened nerves. It has been noted that these changes deteriorate after pan retinal photocoagulation (PRP) in proliferative DR (PDR). In most diabetics, the maximum reduction in nerve fibre density is seen in the sub-basal nerve plexus adjacent to the corneal epithelium indicating a close correlation between diabetic keratopathy and corneal neuropathy. Once the sub-basal nerve plexus is damaged due to injury, regeneration occurs slower in the diabetic cornea than non-diabetic one[12]. In mice models, sub-basal nerve alterations are associated with alteration in dendritic cells that play a crucial role in neurotrophic functions. As per the literature review, corneal neuropathy can manifest early in diabetes, even before the onset of DR. In some rat models, the corneal nerve damage was noted in obese and non-diabetics, indicating the onset of hyperglycemia[13].

Stromal changes

There is only limited literature available on corneal stromal changes in diabetics. In patients with non-insulin-dependent DM, the corneal stroma reveals abnormal bundles of collagen fibrils of varying thickness[14]. It has also been noticed that in diabetic corneas, there is an accumulation of advanced glycation end products (AGES) which may lead to collagen cross-linking and increase central corneal thickness. In mice and rat models, AGES accumulation changes type 4 collagen expression, altered cell adhesion, and increased keratocyte apoptosis. Stromal oedema has also been reported in diabetic corneas. The stromal nerves also appear thickened and tortuous. The levels of MMPs, MMP-3 and MMP-10, were also found to be elevated in corneal stroma of diabetics but not in keratoconus patients [15].

Corneal endothelial abnormalities

Previous studies have intricately studied the endothelial cell count, function, and morphology in diabetic patients. It has been noted that endothelial cell show increased pleomorphism and polymegathism in people with diabetes. Few studies have indicated normal endothelial cell morphology, whereas other recent analyses have quoted reduced endothelial cell count in the cornea of patients with IDDM and NIDDM[16]. Studies on endothelial function also found that oedema was reduced compared to non-diabetic corneas. Compared to other complications of diabetes, corneal endothelial diabetics are a relatively small number. Moreover, there is a high risk of endothelial compromise following corneal surgery[17].

Biomechanical abnormalities

Biomechanical alterations in the cornea result in increased central thickness, altered basement membrane composition, structural changes in the stromal collagen, and accumulation of age-related glycation products that may result in corneal collagen crosslinking[18]. Biomechanical changes have been studied with the help of an ocular response analyzer by measuring corneal resistance factor, which is a measure of corneal elasticity and resistance offered by the cornea (CRF), and corneal hysteresis (CH), which is a measure of viscoelastic property and strength of the cornea. The studies have also reported an increase in corneal thickness with diabetes. The CH and CRF have been reported variably by the studies[19].

Surgical problems

Structural and functional alteration in diabetic cornea predisposes the cornea to an increased risk of surgical complications; even with the best surgical techniques available, the major keratorefractive complications, non-resolving vitreous haemorrhage, and after PRP occur in diabetics. In a few previous reports, diabetic keratopathy has been reported after ocular surgery[20]. In some cases which require epithelial scraping for better intraoperative visualization, in diabetics, the healing is delayed. The sub-basal nerve plexus is damaged and hence grows slower than usual. The damage to epithelial cells and sub-basal nerve plexus cause slow wound healing and reduction in corneal sensations postoperatively. The autologous serum has been tried in diabetic corneas to accelerate wound healing. Cataract surgery causes increased corneal thickness and more loss of endothelial cells in people with diabetes than non-diabetics. It has been seen that the incidence of corneal oedema is higher after phacoemulsification in people with diabetes than non-diabetics, and these patients are also at higher risk for Descemet's membrane keratoplasty[21].

Treatment options

Patients with DR and neuropathy usually remain symptomatic. A large number of drugs have been tried, but they are still in the experimental stage. Some of the experimental drugs in the diabetic cornea are summarized below (Table 1).

DRUGS FOR THE MANAGEMENT OF DIABETIC-CORNEA

Laser in situ keratomileusis

Uncontrolled diabetes is a contraindication for refractive surgery. Phototherapeutic keratectomy, Laser *in situ* keratomileusis (LASIK), and small incision lenticule extraction are riskier and have unfavourable outcomes in diabetics because they can result in recurrent corneal erosions, non-healing epithelial defect, corneal ulcer, epithelial down growth, poor wound healing and increased risk of infections. A previous report quoted an increased risk of DR in LASIK. Hence, it is better to attempt LASIK in non-diabetics having no DR. Few Ophthalmologists prefer non-touching diabetics patients for refractive surgery at all[22].

Contact lens

Diabetic patients using contact lenses are at risk for dry eyes, corneal erosion, neovascularization, and microbial keratitis. Hb1Ac levels are a good indicator of precise diabetic control, and most ophthalmologists take a cut off of 7 for prescribing contact lenses. Daily disposable contact lenses are the best ones for diabetic corneas. Vision can also fluctuate due to changing refractive errors in people with diabetes. Hence, contact lenses should be prescribed only when fasting and postprandial levels are under control [23].

Table 1 Drugs for the management of diabetic-cornea

No.	Drug	Indication
1	Topical thymosin β4	Non-healing epithelial defect
2	Topical autologous serum	Promote corneal wound healing
3	Topical CT-112	Reduction in corneal barrier effect
4	Topical insulin	Quicker reepithelization after epithelial scraping for vitreoretinal surgeries
5	Topical insulin	Prevent sub-basal nerve plexus loss
6	Topical insulin	Promote wound healing
7	Topical ranirestat	Promote wound healing, control the expression of MMP-10 and integrin α3 expression
8	Injection IGF-1	Prevention of stem cell loss and improve sub-basal nerve plexus density
9	Topical naltrexone	Normalize corneal epithelial wound healing, tear film, and corneal sensations
10	Nateglinide and glibenclamide	Inhibit descemet membrane changes
11	Ciliary neurotrophic factor	Improve epithelial stem cells, increase nerve density and promote epithelial healing
12	Topical nerve growth factor	Reduced apoptosis and inflammation
13	IL-1 antagonists	Reduced apoptosis, faster wound healing, sensory stimulation, improved Akt signaling
14	Substance *P*	Improved wound healing, reinnervation, and reactivation of EGFR/Akt signaling

MMP: Matrix metalloproteinases; IGF-1: Insulin-like growth factor-1; EGFR: Epidermal growth factor receptor; IL-1: Interleukin-1.

LENS

Refraction

Chronic hyperglycemia has been linked with myopic refraction, but as sugar levels are under control, the refraction becomes less myopic or more hyperopic. Some researchers have suggested that acute changes in plasma glucose for a month or two will result in hyperopia. In contrast, some have mentioned myopia or hyperopia will occur when plasma glucose increases or decreases. Hence, the exact refractive changes in a diabetic eye have not yet been established, and the mechanism remains to be elucidated[24].

CATARACT

Biochemical mechanism for cataracts in diabetes

Three different mechanisms have been implicated in the pathogenesis of cataracts in diabetics. These include the polyol pathway, osmotic and oxidative stress, and autoimmunity. In the polyol pathway, the enzyme aldol reductase catalyzes the reduction of glucose into sorbitol which is the primary mechanism in cataract development[25]. The extra sorbitol accumulation causes the hyperosmotic effect, resulting in the degeneration of hydropic lens fibres and cataract formation. Osmotic stress causes rapid swelling of the cortical lens fibres, which is a significant factor in the rapid development of cataracts, especially in type 1 DM patients. Osmotic stress accumulates sorbitol in the endoplasmic reticulum (ER), the leading site of protein synthesis and forms free radicals. Fluctuating glucose levels also initiate ER stress, producing reactive oxygen species and causing oxidative damage to lens fibres. Elevated glucose in aqueous, AGEs, elevated hydrogen peroxide, free radicals from nitrogen peroxide, and superoxide radicals are other mechanisms that cause damage to the lens fibres and lead to cataract formation. Another mechanism linked with bilateral type 1 cataract development is the autoimmune mechanism [26]. Autoantibodies are present in the blood within three months of treatment, which correlates with cataract development. Senile and snowflake cataracts are common forms linked with DM, especially type 1 cataracts. Posterior Subcapsular Cortical Cataract has also been linked to diabetes. Elevated Hb1Ac has been linked with cortical and nuclear cataracts. As per previous studies, the duration of diabetes has been associated with cortical cataracts[27].

Cataract incidence in diabetics

It has been well proven that cataract incidence is higher and occurs at an earlier age in diabetics compared to non-diabetics. The reported incidence is four times higher in diabetics before age 65. In patients above 65, the incidence is twice that of non-diabetics. The major risk factors for cataract

development are more prolonged duration of diabetes and poor metabolic control. Strict metabolic control can reverse snowflake cataracts in young diabetics. The Beaver Dam Study showed the increased incidence and progression of cortical and posterior subcapsular cataracts in DM patients. Increased nuclear and cortical cataract incidence was reported with elevated glycated haemoglobin levels[28]. The incidence of cataract surgery is also higher in diabetics. The Wisconsin Epidemiologic Study of DR reported that 8.3% of type 1 diabetics and 24.9% of type 2 diabetics had an incidence of diabetes. The other risk factors related to diabetes are age, DR severity, proteinuria, type 2 DM, and the use of insulin. The Blue Mountain Study assessed the relationship between nuclear, cortical, and posterior subcapsular cataracts and DM. The Barbados Eye Study evaluated the association between DM and lens changes and found that a history of DM was related to all the changes, especially at a young age[29].

Pre-operative consideration and timing of surgery

Counselling is crucial in cataract surgery in diabetic patients. Excellent glycaemic control is mandatory, and no evidence of any infection. If the refractive error is changing, it should be documented. Changes in topography during uncontrolled DM can lead to errors in intraocular lens (IOL) power calculation. Complete anterior and posterior segment examination, best corrected visual acuity, relative afferent pupillary defect, neovascularization of iris (NVI), tonometry, dilated fundus, and gonioscopy is mandatory. In selected cases, fundus fluorescein angiography, ocular coherence tomography, and a B scan will be needed. An experienced surgeon should attempt surgery. A thorough evaluation by a retina surgeon is a must. PRP[30] is required in patients with PDR because of rapid progression after cataract surgery, and in cases with dense cataracts can be performed after cataract surgery. Some cases require combined surgery in the form of cataract, vitrectomy, and endolaser for tractional retinal detachment.

Moreover, maculopathy should be controlled pre-operatively to prevent deterioration of macular oedema (ME). The cataract surgery approach in diabetic patients is changing worldwide. The majority of surgeons now prefer early surgery in diabetic patients. As per previous studies, ME is the leading cause of poor visual outcomes in these patients. Hence, cataract surgery was preferred at a visual acuity of 6/30 to 6/36. The cataract patient may wish to postpone surgery if there is severe DR or PDR. Early surgery offers a good chance for PRP and treatment for Diabetic ME[31].

Cataract surgery and intraocular lens

Phacoemulsification has good outcomes in diabetic patients as it yields better results compared to manual small incision cataract surgery and extracapsular cataract extraction (ECCE). A common sequela in diabetic patients is anterior capsular phimosis. The capsulorhexis size is should be larger but smaller than the optic to prevent anterior capsular phimosis, posterior capsular opacification, and movement of the lens in the sulcus. A larger diameter IOL is also important as it helps diagnose and treat peripheral retinal pathologies. Retinopathy can progress in patients with DR. The duration of diabetes and cataract complexity are primary reasons for retinopathy progression. Pupillary dilatation will be poor due to reduced parasympathetic supply and elevated prostaglandin levels. Pupil dilatation is poor. Hence, pupillary expansion devices, such as iris hooks, B-HEX pupil dilators, *etc.*, are required. Amsler's sign with bleeding in the anterior chamber can be seen during the surgery in patients having NVI. DM causes changes in corneal stem cells, epithelial cells, and endothelial cells. This results in epithelial defects post-surgery, which heal slowly. Endothelial cell loss is higher in diabetic corneas as compared to non-diabetics; hence routine specular microscopy is recommended[31].

Choice of IOL

IOL implantation is imperative in patients with DR as it helps visualise and treat patients with Non-PDR and PDR. Posterior capsular opacification (PCO) is another challenge after cataract extraction. The onset and severity of PCO are accelerated in DM patients compared to non-diabetics. Square edge IOL inhibits lens epithelial cell proliferation and therefore prevents PCO formation. The biocompatibility of three different types of IOL has been studied to assess the rate of PCO formation. Hydrophilic IOL has good capsular biocompatibility but causes more anterior chamber flare. They have a low tendency for silicon oil adhesion, meaning they are the IOL of choice for diabetic patients. Silicon IOL is contraindicated in patients who have undergone vitreoretinal surgery[32]. Hydrophilic IOLs can experience opacification in patients with PDR, as elevated serum phosphorus levels combined with aqueous humor of diabetics result in opacification. Progressive IOL calcification has been reported for hydrophilic IOLs in diabetic patients. Multifocal and accommodative IOLs should be avoided in people with diabetes as they pose difficulty because of the optics of these lenses. Moreover, ME may cause visual dissatisfaction for these patients with pre-existing maculopathy. The IOL should be implanted in the capsular bag as sulcus fixated, iris claw and angle fixated ones cause iritis, NVI, and increased risk of Cystoid ME.

Postoperative complications in retinopathy patients

Diabetics are at increased risk for PCO, diabetic ME or cystoid ME, and progression of retinopathy. Few of the previous studies have quoted a high incidence of PCO in diabetics; others have shown fewer cases of PCO in diabetics, irrespective of retinopathy, over two years[33]. Hayashi *et al*[34] reported that

PCO rates were more in diabetics after 18 mo post cataract surgery, although the rates were comparable after the first 12 mo of the surgery. The severity of retinopathy didn't reveal any impact on the development of PCO. Diabetic ME, cystoid ME or Irvin Gas syndrome, and pseudophakic ME cause reduced vision in diabetics. Various angiogenic factors have been implicated, which aggravate maculopathy. Increased macular thickness has been documented on OCT in eyes without retinopathy as compared to non-diabetics. The risk factor for DR progression is male sex, disease duration, and poor DM control. Progression of retinopathy is more with ECCE and intra capsular cataract extraction as compared to phacoemulsification.

Endophthalmitis

Endophthalmitis is a grave complication post cataract surgery in diabetics. It progresses faster in diabetics, and diabetics are more prone to irreversible visual sequelae. This has been linked to changes in immune and inflammatory factors that intervene with wound healing and local adnexal ocular bacterial flora[35].

Diabetes, glaucoma and uvea

Glaucoma is the leading cause of worldwide irreversible blindness, as defined by best-corrected central visual acuity of less than 3/60 or a visual field of less than 10° in the better-seeing eye, characterized by pathognomonic optic nerve changes which result in progressive visual field loss over the period of time [36]. Association between diabetes and glaucoma has always been in debate, and there is an increase in the evidence to suggest that diabetic patients have a greater risk for glaucoma as well.

Epidemiology

A meta-analysis by Zhao *et al*[37] which included 47 studies, reported a pooled relative risk of glaucoma of 1.48 in patients with diabetes compared to those without diabetes. Duration of diabetes has a direct impact on the risk for glaucoma. Diabetic patients had a pooled average increase in intra ocular pressure (IOP) of 0.09 mmHg for every 10 mg/dL increase in fasting glucose. Goldacre and colleagues found that the rate ratio for glaucoma among patients admitted for diabetes was substantially increased at 2.47 compared to the reference cohort[38].

Pathophysiology

Though the pathophysiology of glaucoma is not entirely understood, diabetes and glaucoma appear to share some common risk factors. The pathophysiologic similarities with studies also report that diabetes and elevated fasting glucose levels are associated with elevated IOP. Diabetes and hyperglycaemia are related to the glycation of lipids and abnormalities in lipid metabolism. This, in turn, increases oxidative stress and promotes cellular apoptosisthe same mechanism by which retinal ganglion cell loss occurs in glaucoma. Vascular dysregulation has been described in both diabetic eye disease and glaucoma. Upregulation of nitric oxide, a potent vasodilator, has been reported in both conditions[39-42]. Protein kinase-C (PKC) plays a role in the pathophysiology of DR. At the same time, there is evidence to suggest that elevated PKC may be associated with abnormalities of matrix metalloprotease in the trabecular meshwork that causes impaired aqueous outflow and ultimately elevated IOP[43,44]. Dysfunction of the glial cells is also evidenced to contribute to neuroinflammatory pathways of apoptosis in both diabetes and glaucoma. It has also been proven that alterations in connective tissue remodeling due to diabetes may affect both the lamina cribrosa and the trabecular meshwork, thereby potentially increasing susceptibility to glaucoma through biomechanical changes at the optic nerve and impairment of aqueous humour outflow affecting IOP homeostasis[45].

Alterations in neurotrophic factor expression, such as insulin-like growth factor and neurotrophin-3, are also seen in the presence of elevated IOP, the primary risk factor for glaucomatous optic neuropathy [46]. Retrospective cohort of diabetic patients with open-angle glaucoma reported that metformin, a first-line agent used to treat insulin resistance in type 2 diabetes, is associated with a decreased risk of developing open-angle glaucoma even after accounting for variations in glycaemic control[47].

Risk factors

Risk factors common for diabetes and glaucoma can be listed as follows: Dyslipidaemia; hypertension; vascular dysregulation; and hypoxia. Other risk factors for glaucoma: Age over 40; family history of glaucoma; race-African, hispanic, or Asian heritage; high IOP; and thin cornea.

Clinical implications and treatment strategies

Glaucoma is called the silent killer of the eye as the affected individuals are not symptomatic, especially in the early stage of the disease. So, an opportunistic, case-finding approach to glaucoma screening may be of value in a high-risk population. This highlights the implications of the purported significant glaucoma risk associated with diabetes. Glaucoma that can be diagnosed commonly can be primary or secondary. Primary glaucoma can be primary open-angle or closed-angle glaucoma. Secondary glaucoma, especially neovascular glaucoma (NVG), is common in advanced diabetic eye disease (Figure 1E and F).

Ischaemia leads to neovascularization of the iris and neovascularization of the angle or both, ultimately leading to a rise in IOP due to various mechanisms leading to optic nerve damage. The formation of a fibrovascular membrane can be seen histologically in these eyes. This membrane initially obstructs the aqueous outflow through the trabecular meshwork, resulting in open-angle glaucoma. At this stage, pharmacological management of the elevated IOP is possible. PRP of the underlying DR is essential. As the disease progresses, the proliferating myofibroblasts of the fibrovascular membrane contract, leading to ectropion uveae, peripheral anterior synechiae and, ultimately, total synechial angle-closure. The resultant secondary glaucoma is often refractory to pharmacological management and requires surgical intervention.

Medical management

Aqueous suppressants can be of great help in reducing raised IOP. Anticholinergics should be avoided as they can increase inflammation and worsen synechial closure. Prostaglandins are relatively contraindicated in these eyes since they can increase inflammation, and the presence of synechiae limits the flow of aqueous *via* the uveoscleral pathway. Topical corticosteroids can be used for inflammation in a controlled manner. Cycloplegic agents can be used to relieve the ciliary spasm and to control the pain. Topical glycerine may help to clear corneal edema, facilitating accurate diagnosis and delivery of PRP when required. Osmotic agents may provide acute but transient lowering of IOP by reducing vitreous volume. Anti-vascular endothelial growth factor (VEGF) agents can be used as an additional measure.

SURGICAL MANAGEMENT

Trabeculectomy

Trabeculectomy has limited success in the setting of NVG. It is usually complicated by intraoperative bleeding and the progression of the fibrovascular membrane postoperatively. By reducing active NVI and neovascularization of the angle, PRP treatment may decrease intra- and post-operative complications. The use of antimetabolites may improve the outcome. Tsai and colleagues reported a success rate of approximately 30 percent at five years with the help of 5-fluorouracil during trabeculectomy in cases with NVG[48].

Glaucoma drainage device

Aqueous drainage implants have been experimented with in NVG since last many decades with variable success. Success rate with glaucoma drainage device (GDD) also decreases, as with glaucoma filtration surgery, over time. No significant differences have been noted among the various types of implants. Mermoud and co-workers used Molteno implants in 60 eyes with NVG. They reported a success rate of 62 percent at one year but only 10 percent at five years[49]. Sidoti and colleagues reported a success rate of nearly 80 percent at one year but only 56 percent at 18 mo using Baerveldt implants in 36 eyes[50].

Cyclodestruction

Cyclodestructive procedures using either Nd: YAG or diode lasers have been used to destroy the ciliary body to reduce aqueous humor production. This method can reduce IOP with fewer complications, but the long-term success rate and treatment protocol are not well established.

Alcohol Injection/enucleation

These treatment options are reserved for the eyes that are not responding to the conventional treatment options. Despite exhaustive measures to lower IOP, most eyes have a poor visual outcome.

Diabetes and mucormycosis

Mucormycosis, previously known as Zygomycosis, is a severe but rare fungal pathology caused by a group of moulds known as Mucormycetes. Commonly found in our environment, the common route of infection is inhalation, ingestion and traumatic inoculation. The disease is rare among the healthy population. Predisposing factors are immunocompromised conditions such as HIV/AIDS patients, organ transplant patients, cancer patients, stem cell transplant patients, also uncontrolled diabetes.

DM creates an ideal environment for Mucorales as they often exhibit impaired innate and adaptive immunity increasing the susceptibility to any infection, particularly mucormycosis. In a study by Corzo-León *et al*[51], which was a retrospective study corresponding to the clinical presentation of 181 patients of diabetes with mucormycosis, 159 (88%) cases had a sinus infection, 5% had a skin infection, 4% with pulmonary presentation and 2% had disseminated with the intra-abdominal presentation[51]. In a study by Bhansali *et al*[52], which was a retrospective, non-comparative, interventional analysis of a cohort of 23 men and 12 with a mean (SD) age of 47.3 years were studied, five patients had type 1 diabetes, and 29 had type 2 diabetes. Nine patients had Rhino-orbital-cerebral mucormycosis as the first clinical manifestation of diabetes. This study reported the ophthalmic symptoms and signs as follows: External

ophthalmoplegia (89%), proptosis (83%), visual loss (80%), chemosis (74%), and eyelid gangrene (14%). The study concluded that in patients with diabetes and rhino-orbito-cerebral mucormycosis was the presenting feature in one-fourth of patients[52].

A case reported by Bavikar *et al*[53], a 38-year-old female, presented with complaints of headache, fever, inability to open right eyelid and seizures. The microbiologist confirmed the growth of the micromycetes from the nasal swabs[53]. In the case of a patient diagnosed with diabetes and contracting mucormycosis, a rapidly corrected underlying metabolic derangement is the most important criterion for considering the conservation of the orbit, even in the presence of total ophthalmoplegia and central retinal artery obstruction.

Snaith *et al*[54] documented the first hematogenous cerebral spread in rhino-orbital-mucormycosis in a patient presenting with diabetic ketoacidosis (DKA) and sinusitis. The patient had a history of recurrent DKA, Foot ulcers with osteomyelitis, retinopathy and albuminuria. A right orbital exenteration and maxillary sinus debridement were performed.

Innovations in screening and treatment protocols

Despite the recommendation for an annual eye exam in DM patients as an innovative, inexpensive way to avoid blindness, screening is ineffectively carried out and unable to meet the rising demand from the expanding population of newly diagnosed DM patients[55]. The introduction of advanced digital technologies, including artificial intelligence (AI), and telehealth technology has created new opportunities in screening, diagnosis, and management of DM-related ocular complications. Novel hybrid telemedicine systems have been well introduced to allow a wider range of DM-related eye screening. It carries diagnostic sets including a combination of mobile ultra-field mounted cameras on vehicles in vans[56-58]. Recently, two technologies for community-based teleophthalmology DR screening were successfully deployed in India: The MII RetCam and the Remidio Fundus on Phone[59,60].

The use of deep learning techniques in AI, in particular, has increased in large data management and automated image-recognition tasks, which is beneficial for the early diagnosis of DR and other ocular problems associated with DM[61-63].

The use of remote monitoring technology has increased throughout the COVID-19 pandemic and has been recognized as an efficient way to provide timely pathology identification and appropriate management for patients with DM-related ocular disorders outside of hospitals and clinics[64,65].

Recently, a brand-new anti-VEGF therapy was introduced to treat diabetic ME. Conbercept (Chengdu Kanghong Biotech, Sichuan Province, China) is a recombinant human VEGF receptor-Fc fusion protein that efficiently treats ME. It has a considerably stronger affinity to VEGF than bevacizumab and ranibizumab and inhibits VEGF-A/B/C isoforms and PGF[66].

Though there is more controversy in treating DM-related ocular complications effectively, new technologies and treatment strategies have been evolving to enhance the treatment protocol and screening concept.

CONCLUSION

DM not only led to major posterior segment abnormalities but also lead to various anterior segment abnormalities involving conjunctiva, cornea, lens and iris. Anterior segment abnormalities associated with systemic uncontrolled DM abnormalities like reduced tear secretion and unstable tear film, decreased sub-basal nerve plexus density and corneal sensitivity, lens abnormalities, and other problems can occur before the clinical evidence of any major ocular diseases such as DR, NVG, *etc.*, with DM. To predict DM problems earlier, these characteristics have the potential to be employed as non-invasive biomarkers for starting the treatment of DM[67].

Although many treatment modalities for treating and preventing anterior segment disorders linked to DM have been developed, more research is still required to create more effective treatment plans. A proper guideline for screening ocular surface pathologies resulting from uncontrolled DM should also be developed and established. For the best management of DM, it is crucial that patients and healthcare professionals, particularly diabetologists, ophthalmologists, and paramedical personnel, have a better awareness of the effects of DM on the anterior portion of the eye.

FOOTNOTES

Author contributions: Morya AK and Venktash P contributed equally to writing and editing the manuscript; Kaur K and Gurnani B downloaded the relevant articles from the RCA system and other Pubmed and Embase databases; Heda A, Sinha A, and Bhatia K contributed to writing a few sub-speciality sections and provided original images and tables.

Conflict-of-interest statement: There are no conflicts of interest to report.

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S-Editor: Chen YL
L-Editor: A
P-Editor: Zhao S

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3750-3755

DOI: 10.12998/wjcc.v11.i16.3750

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Long term outcomes of Cohen's cross trigonal reimplantation for primary vesicoureteral reflux in poorly functioning kidney

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Specialty type: Urology and nephrology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: He G, China; Sarier M, Turkey

Received: February 15, 2023
Peer-review started: February 15, 2023
First decision: April 11, 2023
Revised: April 19, 2023
Accepted: May 6, 2023
Article in press: May 6, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Open ureteric reimplantation by cross trigonal technique described by Cohen is considered a common surgical option for correction of vesicoureteral reflux (VUR). There is a lack of evidence in literature though for what happens to such kidneys, in the long run, particularly those which are poorly functioning.

AIM

To assess the long-term outcomes of ureteric reimplantation in poorly functioning kidneys in children with unilateral primary VUR.

METHODS

Children with unilateral primary VUR and a relative renal function of less than 35% who underwent open or laparoscopic ureteric reimplantation between January 2005 and January 2017 were included in the study. Patients who had a follow up of less than five years were excluded. Preoperative evaluation consisted of a voiding cystourethrogram and Dimercaptosuccinic acid (DMSA) scan. In the follow-up period, patients underwent a diuretic scan at 6 weeks and 6 months. Follow up ultrasound was done for change in grade of hydronephrosis and retrovesical ureteric diameter. Subsequent follow up was done at 6 monthly intervals with evaluation for proteinuria and hypertension and any recurrent urinary tract infection (UTI). For assessment of cortical function, DMSA was repeated annually for 5 years after surgery. A paired-samples *t*-test was used to test the mean difference of DMSA between pre-post observations.

RESULTS

During this period, 36 children underwent ureteric reimplantation for unilateral primary VUR. After excluding those with insufficient follow-up, 31 were included in the analysis. Most of the patients were males (n = 26/31, 83.8%). Patient's age (mean ± SD, range) was 5.21 ± 3.71, 1-18 years. The grades of VUR were grade II (1

patient), grade III (8 patients), grade IV (10 patients), and grade V (12 patients). The pre and postoperative DMSA was 24.064 ± 12.02 and 24.06 ± 10.93, which was almost the same (statistically equal, paired-samples *t*-test: $P = 0.873$). The median (range) follow-up duration was 82 (60-120) mo. One patient had persistent reflux after surgery (preoperative: grade IV, postoperative: grade III), and the very same patient developed recurrent UTI. The difference in the preoperative and postoperative DRF was less than 10% in 29 patients. In one patient, the DRF decreased by 17% (22% to 05%) while in another patient, the DRF increased by 12% (25% to 37%) after surgery. None of the patients had an increase in scarring after surgery. 15% of patients were hypertensive before surgery and all of them continued to be hypertensive after surgery while none developed hypertension after surgery. None of the patients had significant proteinuria (> 150 mg/d) during the follow-up period.

CONCLUSION

Children with unilateral primary VUR and poorly functioning kidney maintain the renal function over the long term in most cases. Hypertension and proteinuria do not progress over time in these patients.

Key Words: Vesicoureteral reflux; Ureteric reimplantation; Relative renal function; Poorly functioning kidney; Unilateral; Long term

Core Tip: This article presents the outcomes of reimplantation of ureters in patients with vesicoureteral reflux in patients without any secondary causes of reflux. In this study, we found that children with unilateral primary vesicoureteral reflux and poorly functioning kidney maintain the renal function over the long term in most cases. All the patients who were hypertensive before surgery continued to be hypertensive after surgery while no patient developed new hypertension after surgery.

Citation: Ansari MS, Banthia R, Jain S, Kaushik VN, Danish N, Yadav P. Long term outcomes of Cohen's cross trigonal reimplantation for primary vesicoureteral reflux in poorly functioning kidney. *World J Clin Cases* 2023; 11(16): 3750-3755

URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3750.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3750

INTRODUCTION

Vesicoureteral reflux (VUR) is defined as the retrograde flow of urine from the bladder to the upper urinary tracts[1]. Its clinical challenges arise from the fact that it is usually asymptomatic and even in asymptomatic cases it is responsible for pyelonephritic scarring and can be associated with congenital renal dysmorphism. In most cases, VUR resolve spontaneously; 20% to 30% will have further infections, and few of them will experience long-term sequelae like renal scarring[2]. Extensive renal scarring decreases renal function and can result in renal insufficiency, hypertension, or end-stage renal disease [3]. A dilemma exists whether to opt for nephrectomy or ureteric reimplantation for the poorly functional kidney. Open ureteric reimplantation by cross trigonal technique described by Cohen is amongst the most common options for surgical correction of VUR, but there is a dearth of evidence in the literature for what happens to such kidneys, in the long run, particularly those which are poorly functioning. We at our institute conducted a retrospective study to assess the long-term outcomes of unilateral ureteric reimplantation in poorly functioning kidneys in children with unilateral primary VUR. The primary objective of our study was to determine if a kidney with significant unilateral reflux nephropathy maintains relative renal function after ureteric reimplantation on long term follow up (5 years or more).

MATERIALS AND METHODS

We retrospectively reviewed data of 168 patients who underwent ureteric reimplantation from 2003-2019. Children with unilateral primary VUR and a relative renal function of less than 35% who underwent open or laparoscopic ureteric reimplantation between January 2005 and December 2017 were included in the study. Patients who had a follow up of less than five years, patients older than 18

years, having a neurogenic bladder, posterior urethral valves, bladder exstrophy and bilateral VUR were excluded. Data was collected by two independent researchers to minimize bias. Preoperative evaluation consisted of a voiding cystourethrogram and Dimercaptosuccinic acid (DMSA) scan, EC scan, and S. Creatinine. In the follow-up period, patients underwent an EC scan at 6 wk and 6 mo. Ultrasounds for hydronephrosis and retrovesical ureteral diameter were done at 6 mo interval. Subsequent follow up was done at 6-monthly intervals with evaluation for proteinuria and hypertension. For assessment of cortical function, DMSA was repeated 1 year after surgery and annually thereafter. A paired-samples *t*-test was used to test the mean difference between pre-post observations. Only the patients with complete data records and regular follow up were included in the study.

RESULTS

During this period, 36 children underwent ureteric reimplantation for unilateral primary VUR. After excluding those with insufficient follow-up (*i.e.* follow up less than 5 years), 31 were included in the analysis. Most of the patients were males (n = 26/31, 83.8%). Patient's age (mean ± SD, range) was 5.21 ± 3.71, 1-18 years. The grades of VUR were grade- II (1 patient), grade- III (8 patients), grade- IV (10 patients), and grade- V (12 patients)[4]. The renal function estimated by pre and postoperative DMSA scan was 24.06 ± 12.02 and 24.06 ± 10.93, which was almost the same (statistically equal, paired-samples *t*-test: P = 0.873). The median (range) follow-up duration was 82 (60-120) months. One patient had persistent reflux after surgery (preoperative: Grade IV, postoperative: grade III). One patient had recurrent UTI. The difference in the preoperative and postoperative DRF was less than 10% in 26 patients. In one patient, the DRF decreased by 17% (22% to 05%) while in another patient, the DRF increased by 12% (25% to 37%) after surgery. There was no significant change in Serum creatinine in almost all patients, as mean serum creatinine preoperatively and postoperatively was 0.866 ± 0.68 and 0.811 ± 0.54 respectively (statistically equal, paired – sample *t*-test: P = 0.583). None of the patients had any increase in scarring after surgery or any development of new scars. A total of 15% of patients were hypertensive before surgery and all of them continued to be hypertensive after surgery, while no new patients developed hypertension. None of the patients showed significant proteinuria (> 150 mg/d) during the follow-up period. No patients presented an increase in hydronephrosis or retrovesical ureteric diameter after surgery.

DISCUSSION

Primary VUR is still a significant health problem for many children and young adolescents, as these patients are at high risk of developing reflux nephropathy[5]. The association of nephropathy with UTI and VUR is well established[6]. Reflux nephropathy is irreversible and may lead to renal insufficiency, renin-mediated hypertension, chronic renal failure, decreased somatic growth and morbidity during pregnancy. To avoid renal scarring these patients must be tested appropriately and promptly treated with antibiotics. In the present study, we found that the majority of children who have primary VUR and a poorly functioning kidney, maintain their renal function for a long time. In addition, hypertension and proteinuria in these patients usually do not progress with time.

Earlier studies used IVP for follow up after ureteric reimplantation to look for new scar formation and most of them reported a substantial rate of new scar formation (5% to 31%) and scar progression (12%to 20%)[7-10]. But soon the accuracy of IVP to assess reflux related renal scars was questioned and renal scintigraphy became a well-established method to quantitatively measure renal damage in kidneys with reflux and accuracy of this modality is well established now. A study performed by Choi *et al*[11] was the first of its kind which used dimercaptosuccinic acid renal scintigraphy instead of IVP. This study reported 0% new scar formation and 2.6% progression of renal scarring. Our study results are similar to study by Choi *et al*[11] and we also report 0% new scar formation and 0% progression of renal scarring.

The observation of our study is not in accordance with studies conducted by Atwell *et al*[12], Scott *et al*[13], and Carson *et al*[14] who reported accelerated renal growth after surgical correction of VUR. Conversely, large series reported by Rushton *et al*[15] and Olbing *et al*[16] concluded that there was no significant difference in renal size after surgical correction in children with primary VUR which is like the observations of our study.

Renal functional impairment is one of the most devastating complications associated with VUR and is rare fortunately. The outcome of relative and overall renal function after ureteric reimplantation in children with unilateral primary VUR with significantly diminished relative renal function was assessed. A study by Schiepers *et al*[17]. Found that DMSA uptake did not change significantly during the 5 years interval in 89% of children after surgical correction of VUR, although this study had only 13 children with diminished RRF. A previous study by Nepple *et al*[18] in 2005, which included 32 children showed that relative renal function is maintained in such patients, although the mean follow-up period in their study was 3.7 years (0.3 to 12.9 years). In our series we observed 31 children who had strictly

minimum 5 year follow up with mean follow up of 82 mo (60-120 mo) and most of our patients maintained their RRF in the long term. In this study we identified only one patient who had significantly decreased renal function and one patient also had significantly improved renal function.

Serum creatinine was measured preoperatively and was measured on follow up along with DMSA scan. Preoperative and post-operative serum creatinine show insignificant difference.

Ureteral reflux resolution rate was 96.4% which is similar to the success rate of 92%-99% reported by others. In a study by Nepple *et al*[18] reflux persisted in 4 of 32 children, which was treated with the Glenn-Anderson ureteral advancement procedure. Reflux persisted in 2 of 51 in the study by Grossklaus *et al*[19]. In the present study reflux persisted in 1of 31 children (preoperative: grade IV, postoperative: grade III) which was treated by endoscopic method, and we continue to use this modality in patients with recurrence with a lower grade of reflux and surgical treatment is reserved for those with a higher or similar grade of reflux with UTI.

Hypertension is a known complication of reflux for many years and was present in 15% of the patients, while no patient developed newly detected hypertension after surgery. Wallace *et al*[20] conducted a study 12 years after correcting reflux, found hypertension in 12.8% of the patients (18.5% among children with bilateral scarring and 11.3% among those with unilateral scars). On the contrary, Belloli *et al*[21] detected hypertension in only 4.4% of patients who had corrective surgery. In our study we followed up patients with a mean period of 82 mo (60-120 mo) and none of the patients developed new-onset hypertension or proteinuria.

A similar study was conducted by Mor *et al*[22] showed that even patients who were treated successfully by ureteric reimplantation during childhood are prone to recurrent UTI, progressive renal scarring, hypertension, and complications during pregnancy. In that study only 31% (100) of the potential original study group of 322 patients could be fully evaluated. It was assumed that patients who had an uneventful did not enrolled themselves for the study and therefore showed the above results. This was the drawback of the study which reflected negatively biased results.

There are limitations to this retrospective study. The finding of no change in relative renal function may be the result of low statistical power from a small sample size. Although the follow-up period was good enough to determine that these patients maintain overall relative renal function. Since most of the patients in our study were males, we did not compare the outcomes between males and females. Future studies can take this limitation into account. Further, we did not explore the effect of bilateral VUR on renal function and thus, similar renal dynamics may not be observed with bilateral reflux nephropathy.

CONCLUSION

Even poorly functional kidneys maintain their function in the long term and there is need to establish a protocol for the long-term follow-up of patients who have had ureteric reimplantation during childhood. Management with ureteric reimplantation rather than nephrectomy may be warranted even in children with significantly reduced RRF based on the continued stability of relative renal function of the affected kidney. Hypertension and proteinuria do not progress over time in these patients.

ARTICLE HIGHLIGHTS

Research background

Vesicoureteral reflux (VUR) is when urine flows backwards from the bladder to the upper urinary tracts. It often has no symptoms but can cause kidney damage and scarring, leading to renal insufficiency, hypertension, or end-stage renal disease. Surgical options like ureteric reimplantation may be considered for poorly functioning kidneys, but there is limited evidence on long-term outcomes.

Research motivation

The motivation behind the research was to address the lack of evidence in the literature regarding the long-term outcomes of open ureteric reimplantation for poorly functioning kidneys with VUR. This research was conducted to provide better insights and guidance on the optimal management of VUR with poorly functioning kidneys.

Research objectives

The aim of the study was to determine if poorly functioning kidneys with VUR maintain relative renal function after the surgery on long-term follow-up of 5 years or more.

Research methods

The study involved a retrospective review of medical data for 168 patients who underwent ureteric reimplantation between 2003-2019. The research focused on children with unilateral primary VUR and a

relative renal function of less than 35% who underwent open or laparoscopic ureteric reimplantation between January 2005 and December 2017. Data was collected by two independent researchers, and patients were excluded based on specific criteria. Preoperative evaluation included a voiding cystourethrogram and Dimercaptosuccinic acid (DMSA) scan, EC scan, and S. Creatinine. Follow-up was done at 6-month intervals, and data was collected through various tests to assess the patient's cortical function. A paired-samples t-test was used to compare pre- and post-surgery observations. Only patients with complete data records and regular follow-up were included in the study.

Research results

The study included 31 children who underwent ureteric reimplantation for unilateral primary VUR. The patients were predominantly male, and their mean age was 5.21 ± 3.71 years. The pre- and postoperative renal function, as measured by DMSA scan, remained statistically equal in most patients, and there was no significant change in serum creatinine. Only one patient had persistent reflux after surgery, and one had a recurrent UTI. None of the patients showed an increase in scarring, proteinuria, or hydronephrosis after surgery, and there were no new cases of hypertension.

Research conclusions

The study found that even poorly functioning kidneys maintain their function in the long term after undergoing ureteric reimplantation, suggesting that this procedure may be a better option than nephrectomy. The results also indicate the need to establish a protocol for long-term follow-up of patients who have undergone this procedure, as hypertension and proteinuria do not progress over time in these patients.

Research perspectives

The study findings suggest the need for further research on the long-term outcomes of ureteric reimplantation in poorly functioning kidneys in children with VUR. Future studies could investigate the factors that influence the success of ureteric reimplantation, such as age of the patient, severity of VUR, and degree of renal scarring. Additionally, studies could explore alternative treatments for VUR and their long-term outcomes, such as endoscopic injection of bulking agents or laparoscopic ureteric reimplantation.

FOOTNOTES

Author contributions: Ansari MS and Yadav P designed the research study; Banthia R, Jain S, and Kaushik VN performed the research; Danish N and Banthia R analyzed the data and wrote the manuscript; Ansari MS and Yadav P edited the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences (Approval No. 2020-185-IP-EXP-24).

Informed consent statement: This is to inform that consent waiver has been obtained from the Institutional Ethics Committee for the research article.

Conflict-of-interest statement: All the authors declare that there are no conflicts of interest regarding the publication of this study.

Data sharing statement: No additional data are available.

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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S-Editor: Liu JH
L-Editor: A

P-Editor: Liu JH

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3756-3764

DOI: 10.12998/wjcc.v11.i16.3756

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Dexmedetomidine-induced anesthesia in elderly patients undergoing hip replacement surgery

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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 scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Roh DJ, United States; Shefelbine SJ, United States

Received: March 13, 2023
Peer-review started: March 13, 2023
First decision: March 28, 2023
Revised: April 13, 2023
Accepted: April 24, 2023
Article in press: April 24, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

A femoral neck fracture is a common and frequently reported issue in orthopedics, with a greater rate of incidence among the elderly. Due to their advanced age and the presence of some primary diseases, both anesthesia and surgery are increasingly difficult in elderly patients with a femoral neck fractures. In fact, general anesthesia can easily induce complications such as cognitive dysfunction, which is not conducive to postoperative recovery.

AIM

To analyze the efficacy of dexmedetomidine in inducing anesthesia for elderly patients undergoing hip replacement surgery.

METHODS

A total of 98 elderly patients undergoing hip replacement in our hospital from June 2020 to June 2021 were randomly divided into control group (49 cases) and observation group (49 cases). The control group was given general anesthesia, and the observation group was combined with dexmedetomidine for anesthesia on the basis of the control group. Both groups were observed until the patients were discharged. The vital signs, serum inflammatory factors and renal function indexes of the two groups were compared before, during and 6 h after operation. The postoperative recovery and adverse events of the two groups were statistically analyzed.

RESULTS

Compared with the mean arterial pressure of the two groups, the intraoperative and postoperative 6 h was higher than that before the operation, the intraoperative was lower than the postoperative 6 h ($P < 0.05$); the blood oxygen saturation of the two groups was higher than that before operation and 6 h after operation, and the observation group was higher than the control group 6 h after

operation ($P < 0.05$). The heart rate of the two groups was lower during and 6 h after operation than that before operation, and higher at 6 h after operation than that during operation ($P < 0.05$). The levels of serum C-reactive protein, tumor necrosis factor-α, interleukin-1β and kidney injury molecule-1 in the two groups were higher during operation and 6 h after operation than those before operation ($P < 0.05$). The level of serum urea nitrogen in the two groups was higher than that before operation, and that in the observation group was lower than that in the control group ($P < 0.05$). During hospitalization, the first time of getting out of bed, recovery time of grade II muscle strength, recovery time of grade III muscle strength and hospitalization time in the observation group were shorter than those in the control group ($P < 0.05$).

CONCLUSION

Dexmedetomidine can effectively improve the vital signs of elderly patients undergoing hip replacement surgery, reduce the body's inflammatory response and renal function damage, and promote postoperative recovery. Meanwhile, dexmedetomidine showcased a good safety profile and a good anesthetic outcome.

Key Words: Hip replacement; Old age; Dexmedetomidine; Anesthetic effect; Vital signs

Core Tip: Dexmedetomidine is a type of drug that selectively activates the α2-adrenergic receptors. It stimulates the postsynaptic membrane receptors, inhibits sympathetic nerves, and effectively maintains the hemodynamic fluctuations in the body to achieve the desired sedative effects.

Citation: Li JQ, Yuan H, Wang XQ, Yang M. Dexmedetomidine-induced anesthesia in elderly patients undergoing hip replacement surgery. *World J Clin Cases* 2023; 11(16): 3756-3764
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3756.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3756

INTRODUCTION

Recent years have witnessed an increase in the aging population of China and hence in its population structure. Because the hip bone of the elderly bears a huge load and is subjected to a relatively greater extent of activity, it is more prone to fracture. Hip replacement is the main approach for the treatment of the hip fracture. Due to the decline in the dopaminergic, cholinergic, and other neuroregulatory system functions in elderly patients, the extent of postoperative inflammatory response is significantly increased, which can easily cause multiple organ dysfunction. This factor is detrimental to the postoperative healing of elderly patients. Recent studies have revealed that maintaining the function of important organs in elderly patients undergoing hip replacement surgery during anesthesia and reducing any potential bodily damage is conducive to postoperative recovery[1-4]. Midazolam and propofol are commonly applied anesthetics in elderly patients during surgery. The combination of these two agents has a good anesthetic outcome, but it cannot effectively protect organ functions[4,5]. Dexmedetomidine is a highly selective α2 receptor agonist, which has a good effect in reducing the body's stress response and in stabilizing the patient's intraoperative hemodynamics. Hence, it has a good application prospect in perioperative organ protection[6,7]. However, the applicability of dexmedetomidine as anesthesia in elderly patients with hip replacement surgery is not established yet. This study intended to analyze the anesthetic outcome of dexmedetomidine in elderly patients with hip replacement.

MATERIALS AND METHODS

General information

A total of 98 elderly patients scheduled for hip replacement surgery who were admitted to our hospital during June 2020–2021, were randomly assigned to two groups: Control (n = 49) and observation (n = 49). In the observation group: There were 23 women and 26 men with body mass index (BMI) of 20–26 kg/m^2 (average: 24.02 ± 0.41 kg/m^2) and average age 67.69 ± 2.79 years (age range: 62–74 years). The study included patients with injuries ranging from 18 to 65 years old, with 10 cases of injury resulting from crush injuries, 24 from traffic accidents, and 15 from falls. In the control group, there were 22

women and 27 men of BMI 20–27 kg/m^2 (average: 23.67 ± 0.37 kg/m^2). The average age of the control subjects is 68.55 ± 2.25 years (age range: 63–73 years). In these subjects, 25 cases of injury were caused by traffic accidents, 9 by squeezing, and 15 by falling. The general data of the two groups were comparable ($P > 0.05$).

Inclusion and exclusion criteria

Inclusion criteria: The diagnostic criteria of hip fracture met the "Expert consensus on the diagnosis and treatment of hip fracture in the elderly (2017)"[8], which was confirmed by preoperative X-ray examination: Age ≥ 60 years; those who met the surgical indications of hip replacement; traumatic fracture admission; complete clinical data; informed consent of this study. Exclusion criteria: Preoperative severe malnutrition; patients with severe infectious diseases; patients with severe organ dysfunction and malignant tumors.

Anesthesia method

The control group was administered the general anesthesia, as follows: Anesthesia induction: Midazolam (Jiangsu Enhua Pharmaceutical Co., Ltd., Sinopharm H19990027, 1 mL: 5 mg) 0.03–0.05 mg/kg, sufentanil (Yichang Renfu Pharmaceutical Co., Ltd., Sinopharm H20054171, 1 mL: 50 μg) 0.3–0.5 μg/kg, etomidate (Jiangsu Enhua Pharmaceutical Co., Ltd., Sinopharm H20020511, 10 mL: 20 mg) 0.2–0.3 mg/kg. Rocuronium bromide (N. V. Organon, import drug registration number H20140847, 5 mL: 50 mg) 0.6–1.0 mg/kg. A tracheal catheter or I-GEL laryngeal mask was inserted after 2–5 min of muscle relaxation. Anesthesia maintenance was performed as follows: Sevoflurane (Albert Pharmaceutical Trading Co., Ltd., import drug registration number H20150020, 250 mL) inhalation concentration 1%–2%, propofol (Xi'an Libang Pharmaceutical Co., Ltd., Sinopharm approval number: H19990282, 20 mL: 0.2 g) 2–5 mg/(kg·h), remifentanil (Yichang Renfu Pharmaceutical Co., Ltd., Sinopharm approval number H20030197, 1 mg) 0.05–0.2 μg/(kg·min). Intermittent intravenous injection of cisatracurium (Zhejiang Xianju Pharmaceutical Co., Ltd., Sinopharm H20090202, 5 mg) 3–4 mg to maintain muscle relaxation. Sufentanil was added, with the total amount not exceeding 1 μg/kg, depending on the patient's response to anesthesia. The parameters of mechanical ventilation were set as follows: The recommended respiratory parameters were a tidal volume of 6–10 mL/kg, a respiratory rate of 8–12 breaths/min, and an inspiratory-to-expiratory ratio of 1:2. The mean arterial pressure (MAP) and heart rate (HR) were maintained within the basic value of ± 20%, and vasoactive drugs were administered based on the blood pressure of the patient during the surgery. Postoperative patient-controlled intravenous analgesia included sufentanil 200 μg, dezocine (Yangzijiang Pharmaceutical Group Co., Ltd., Sinopharm H20184150, 1 mL: 5 mg) 10 mg, tropisetron (Hainan Lingkang Pharmaceutical Co., Ltd., Sinopharm H20060287, 5 mg) 10 mg, normal saline 144 mL, total 150 mL; duration of 75 h, intravenous self-control 2 mL/h, load 0–2 mL, continuous volume 1.5–2 mL/h, and a lock time of 30 min.

Based on the anesthesia scheme of the control group, the observation group was treated with dexmedetomidine (Yangzijiang Pharmaceutical Group Co., Ltd., Chinese Pharmacopoeia: H20183219, 2 mL: 0.2 mg). Anesthesia induction and maintenance were performed consistently between the two groups. Before anesthesia induction, the patients were intravenously administered 4 μg/mL dexmedetomidine for 10 min, which was then changed to 0.2 μg/(kg·h). Both groups were observed until the patient was discharged from the hospital.

Observation indicators

Vital signs Multifunctional ECG monitor [MX550, Philips (China) Investment Co., Ltd.] was used to measure the MAP, HR, and blood oxygen saturation (SpO_2) of the two groups before, during, and 6 h after the surgery.

The levels of serum inflammatory factors C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) were determined by enzyme-linked immunosorbent assay (ELISA) before, during, and 6 h after the surgery for the two study groups (Shanghai Enzyme-linked Biotechnology Co., Ltd.).

To examine the renal functions, the levels of serum kidney injury molecule-1 (KIM-1), urea nitrogen (BUN), and creatinine (Cr) were detected by ELISA before, during, and 6 h after the surgery.

The following postoperative recovery factors were assessed and recorded: The first time getting out of bed, the recovery time of grade II muscle strength, the recovery time of grade III muscle strength, and the time of hospitalization.

The incidence of the following adverse events was recorded for the two groups of elderly patients, intraoperative hypotension, bradycardia, hypoxemia, and general body movement-related adverse events.

Statistical analysis

SPSS 21.0 statistical software was used for data analysis, with $P < 0.05$ considered to indicate a statistically significant difference. The measurement data included vital signs, serum inflammatory factor levels, renal function, and postoperative recovery. The mean ± SD represented the use of repeated measures analysis of variance for comparison. If the football symmetry test failed, the G–G correction

Table 1 Comparison of vital signs between the two groups (mean ± SD)

Group	*n*	MAP (mmHg)	SpO_2 (%)	HR (beat/min)
Preoperative				
Control group	49	90.02 ± 3.39	96.24 ± 3.07	88.12 ± 4.16
Observation group	49	91.12 ± 3.37	97.29 ± 2.45	87.14 ± 4.11
F value	-	2.136	1.871	1.389
P value	-	0.147	0.064	0.242
Intraoperative				
Control group	49	75.61 ± 4.49[a]	99.63 ± 0.49[a]	81.59 ± 3.21[a]
Observation group	49	79.61 ± 3.41[a]	99.80 ± 0.41[a]	79.12 ± 3.26[a]
F value	-	23.995	1.863	3.779
P value	-	< 0.001	0.066	< 0.001
6 h after operation				
Control group	49	82.78 ± 3.74[a,d]	98.49 ± 0.68[a,d]	86.73 ± 4.28[a,d]
Observation group	49	88.49 ± 4.67[a,d]	98.92 ± 0.28[a,d]	83.43 ± 3.45[a,d]
F value	-	46.040	10.001	4.202
P value	-	< 0.001	0.056	< 0.001

[a]$P < 0.05$ *vs* preoperative.
[d]$P < 0.05$ *vs* intraoperative.
MAP: Mean arterial pressure; HR: Heart rate; SpO_2: Blood oxygen saturation.

method was applied. Under the interaction, the separation effect between the population and time was analyzed further. The adverse events were counted as data, expressed as cases (percent) [*n* (%)], and passed through χ^2 tests for comparison.

RESULTS

Comparison of the vital signs between the two groups of patients

The vital signs of MAP, SpO_2, and HR data of the patients in the control and observation groups met the spherical symmetry test. The MAP, SpO_2 between the groups, time, and the interaction between the groups and time should be subjected to detailed analysis to understand the individual effect. The MAP of the two groups was lower than that before and after 6 h of the surgery; the MAP value was higher in the observation group than in the control group ($P < 0.05$). The SpO_2 standards in both groups were greater than that before and 6 h after the surgery. The HR in the observation group was higher than that in the control group ($P < 0.05$). In contrast with the HR of the two groups, the HR during and 6 h after the surgery was below that recorded before surgery, while the HR at 6 h after surgery was greater than that during surgery ($P < 0.05$). During and 6 h after surgery, the HR in the observation group was lower than that in the control group ($P < 0.01$) (Table 1).

Comparison of serum inflammatory factor levels between the two groups

The levels of serum CRP, TNF-α, and IL-1β between the two groups were not satisfied with the results of the football symmetry test and the G–G correction method. The interaction among the groups, time, and between the groups and time was found to be significant, after which the individual effects were analyzed. The serum levels of CRP and TNF-α were recorded at 6 h after surgery in both two groups. The levels of TNF-α and IL-1β were higher than those before and during surgery, but lower than those of the control group ($P < 0.05$) (Table 2).

Comparison of renal function indexes between the two groups

The renal function satisfied the spherical symmetry test. The group, time, and interaction between the group and time of KIM-1 and BUN have significant further analysis of the individual effect. As shown in Table 3, there was no interaction between the Cr index time and group ($P > 0.05$). Comparison of the serum KIM-1 Levels between the two groups showed that the levels during and 6 h after the surgery were higher than that before the surgery, those at 6 h after the surgery were higher than those during

Table 2 Comparison of serum inflammatory factor levels between the two groups (mean ± SD, ng/L)

Group	*n*	CRP	TNF-α	IL-1β
Preoperative				
Control group	49	3.33 ± 1.21	15.11 ± 4.20	173.55 ± 23.52
Observation group	49	3.15 ± 1.20	15.50 ± 4.03	173.15 ± 22.50
F value	-	0.562	0.220	0.086
P value	-	0.455	0.640	0.932
Intraoperative				
Control group	49	15.53 ± 4.22[a]	53.23 ± 8.12[a]	199.25 ± 22.10[a]
Observation group	49	7.25 ± 3.20[a]	31.20 ± 5.21[a]	190.23 ± 21.33[a]
F value	-	119.785	255.597	4.222
P value	-	< 0.001	< 0.001	0.043
6 h after operation				
Control group	49	18.25 ± 4.13[a,d]	60.27 ± 9.23[a,d]	293.25 ± 11.50[a,d]
Observation group	49	11.73 ± 2.50[a,d]	38.25 ± 8.20[a,d]	203.19 ± 12.37[a,d]
F value	-	89.449	156.076	1393.312
P value	-	< 0.001	< 0.001	< 0.001

[a]*P* < 0.05 *vs* preoperative.
[d]*P* < 0.05 *vs* intraoperative.
CRP: C-reactive protein; TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin-1β.

Table 3 Comparison of renal function between two groups (mean ± SD)

Group	*n*	KIM-1 (ng/L)	BUN (ng/L)	Cr (μmol/L)
Preoperative				
Control group	49	16.27 ± 5.11	5.20 ± 1.29	76.15 ± 11.09
Observation group	49	16.83 ± 4.07	5.29 ± 1.26	75.56 ± 12.59
t value	-	0.361	0.130	0.062
P value	-	0.549	0.720	0.804
Intraoperative				
Control group	49	28.22 ± 6.55[a]	6.98 ± 1.22[a]	95.52 ± 11.51[a]
Observation group	49	21.09 ± 5.55[a]	6.07 ± 1.13[a]	91.12 ± 13.30[a]
t value	-	33.745	14.779	3.976
P value	-	< 0.001	< 0.001	0.049
6 h after operation				
Control group	49	89.55 ± 8.55[a,d]	6.08 ± 1.23	86.05 ± 10.34[a,d]
Observation group	49	52.50 ± 6.76[a,d]	5.98 ± 1.13	81.25 ± 11.36[a,d]
F value	-	566.402	0.197	4.787
P value	-	< 0.001	0.658	0.031

[a]*P* < 0.05 *vs* preoperative.
[d]*P* < 0.05 *vs* intraoperative.
KIM-1: Serum kidney injury molecule-1; BUN: Urea nitrogen; Cr: Creatinine.

the surgery, during and 6 h after surgery, the observation group was lower than the control group ($P < 0.05$). The serum BUN levels after the surgery were elevated in both groups when compared to that before surgery. The observation group showed significantly lower levels than the control group ($P < 0.05$) for the measured parameter. The comparison of serum Cr levels between the two groups revealed that the levels during and 6 h after surgery were higher than those before surgery. It is lower during and 6 h after surgery. Table 3 depicts that the levels of the measured parameter in the observation group during and 6 h after surgery were significantly lower compared to those in the control group ($P < 0.05$).

Comparison of postoperative recovery between the two groups

The factors of the first time of getting out of bed, the recovery time of grade II muscle strength, grade III muscle strength, and hospitalization time were shorter in the observation group than in the control group ($P < 0.05$; Table 4).

Comparison of adverse events between the two groups of patients

During hospitalization, the rate of incidence of adverse events in the control group was higher than that in the observation group ($P < 0.05$; Table 5).

DISCUSSION

Hip fracture is the most common type of fracture occurring in the elderly. Hip fractures are commonly treated in clinics through total hip arthroplasty as one of the main preferred methods for the elderly. Due to the reduction of all aspects of the body in elderly patients undergoing hip arthroplasty, the stress response and inflammatory response induced by surgery can aggravate the damage to important organs of the patients, which is not conducive to the recovery of the patients[9-11]. During the surgery, the use of certain anesthetic drugs can maintain the hemodynamic stability of the patient and reduce the damage to the patient's organs. Midazolam and propofol are common anesthetics applied in clinical practice, which have proven good sedative and analgesic effects, but they are not effective in protecting the functions of important organs of patients and need to be combined with other anesthetics for anesthesia[12,13]. In elderly patients undergoing hip replacement surgery, changes in hemodynamics, respiratory functions, and elevated levels of the inflammatory response can lead to short-term postoperative cognitive impairment[14-16]. Based on the current findings, the MAP of the observation group was higher than that of the control group during surgery. In addition, the HR of the observation group was lower than that of the control group during and after surgery. At 6 h after surgery, the MAP and SpO_2 levels as well as the serum CRP and TNF-α levels were higher for the patients in the observation group than for those in the control group. The levels of IL-1β and dexmedetomidine were significantly lower in the observation group than in the control group. This finding suggests that dexmedetomidine administration may be an effective intervention for improving vital signs and reducing inflammation in elderly patients with hip joint disorders. Dexmedetomidine can facilitate reaching the depth of anesthesia as soon as possible and thereby speed up the surgery process. Meanwhile, it can stabilize the hemodynamics of patients by inhibiting the secretion of norepinephrine and the activity of sympathetic nerves. In addition, it can maintain the patient's respiratory drive and improve the levels of MAP, HR, and SpO_2[17]. Dexmedetomidine can alleviate the synthesis of corticosteroids and glucocorticoids by enhancing parasympathetic activity and inhibiting sympathetic activity, which can effectively reduce the body's stress response and inflammatory response in elderly hip-replacement patients[18]. In elderly patients undergoing hip replacement surgery, increased levels of inflammatory response and hemodynamic changes may cause kidney damage. KIM-1 is a transmembrane protein that is not expressed during normal renal functions, but appears after renal injury, thereby serving as a marker of early renal injury. BUN and Cr are the traditional indicators of renal functions, with elevated levels of renal functions. The present results revealed that the average serum levels of KIM-1, BUN, and Cr in the observation group were lower than those in the control group during and 6 h after the surgery, thereby indicating that dexmedetomidine can effectively alleviate renal injury in elderly hip-replacement patients and protect renal functions. Dexmetomidine can effectively reduce the inflammatory response and damage caused by them to the renal cells in elderly patients undergoing hip-replacement surgery. On the other hand, dexmedetomidine can effectively inhibit the release of norepinephrine, reduce sympathetic nerve excitability, and increase renal blood flow, which cumulatively protects renal functions. The present results also suggest that the postoperative recovery of the observation group was better than that of the control group. Moreover, the total frequency of adverse events was lesser than that of the control group, which signifies that dexmedetomidine can effectively enhance the recovery of articulatio coxae in the elderly. We thus found that dexmetomidine could reduce the body's inflammatory response and kidney damage and stabilize the patient's vital signs, thereby indicating a good safety profile. Meanwhile, its sedative effect is non-anesthetic, rapidly metabolized in the body, and shows a strong dose dependency. The low-dose dexmedetomidine infusion used in this study led to quick awakening and restoration of consciousness in elderly patients after anesthesia, implying its safety and efficacy.

Table 4 Comparison of postoperative recovery between the two groups (mean ± SD)

Group	*n*	The first time to get out of bed (h)	II grade muscle strength recovery time (h)	III grade muscle strength recovery time (h)	Hospitalization time (d)
Control group	49	26.84 ± 8.73	20.41 ± 7.72	36.41 ± 8.71	7.94 ± 3.72
Observation group	49	20.67 ± 8.78	12.82 ± 6.48	27.61 ± 7.85	5.92 ± 3.62
t value	-	3.485	5.274	5.253	2.725
P value	-	< 0.001	< 0.001	< 0.001	< 0.001

Table 5 Comparison of adverse reactions between the two groups, *n* (%)

Group	*n*	Hypotension	Bradycardia	Hypoxemia	General body movement	Total incidence of adverse reactions
Control group	49	3 (6.12)	1 (2.04)	2 (4.08)	2 (4.08)	8 (16.33)
Observation group	49	1 (2.04)	1 (2.04)	0 (0.00)	0 (0.00)	2 (4.08)
χ^2 value	-	-	-	-	-	4.009
P value	-	-	-	-	-	0.045

CONCLUSION

In summary, dexmedetomidine could effectively improve the vital signs of elderly patients undergoing hip replacement surgery, reduce the body's inflammatory response and renal function damage, and promote postoperative recovery. Meanwhile, it demonstrated good safety and anesthetic outcomes. This finding has significant clinical implications and merits further investigations for optimized application. The relevant indicators included in this study only compared the data of three different time points, before, during, and 6 h after the surgery, because of which the conclusion may be biased. In addition, as this study was conducted on a small sample size from a single center, the results may not apply to different populations. Subsequent research should include large sample size, a diverse subject population, and different age-group patients. We believe that a follow-up study on the changes of indicators at multiple time points and further analyses of the effect of dexmedetomidine in anesthesia during hip replacement surgery in the elderly are warranted to supplement the present findings.

ARTICLE HIGHLIGHTS

Research background

A femoral neck fracture is a common and frequently-occurring disease in orthopedics, with a high incidence in the elderly population. For elderly patients with a femoral neck fracture, due to their older age and more basic diseases, the difficulty of anesthesia and surgery is increased. General anesthesia can easily induce complications such as cognitive dysfunction, which is not conducive to postoperative recovery.

Research motivation

This study analyzed the anesthetic effect of dexmedetomidine in elderly patients undergoing hip replacement.

Research objectives

This study aimed to provide a reference for the prognosis and anesthesia of clinical-related surgeries.

Research methods

A total of 98 elderly patients undergoing hip replacement were randomly divided into control group and observation group. Both groups were observed until the patients were discharged. The vital signs, serum inflammatory factors and renal function indexes of the two groups were compared before, during and 6 h after operation.

Research results

Dexmedetomidine has good safety and good anesthetic effect.

Research conclusions

Dexmedetomidine can effectively improve the vital signs of elderly patients undergoing hip replacement, reduce the body's inflammatory response, reduce renal function damage, and promote postoperative recovery. At the same time, it has good safety and good anesthetic effect.

Research perspectives

This study indicates that diazepam has good application prospects in elderly patients undergoing hip replacement surgery. Future research can further explore the anesthesia effect and safety of diazepam, search for more optimized anesthesia plans, and improve the success rate of hip replacement surgery in elderly patients.

FOOTNOTES

Author contributions: Li JQ and Yuan H proposed concepts for this study; Wang XQ and Yang M collected data; Li JQ, Yuan H, and Wang XQ contributed to formal analysis; Li JQ and Yang M contributed to the survey; Li JQ, Yuan H, and Yang M contributed to this method; Li JQ, Yuan H, Wang XQ, and Yang M supervised the study; Li JQ validated this study; Yuan H and Wang XQ contributed to the visualization of research; Li JQ and Yuan H initially drafted this manuscript; Li JQ, Yuan H, Wang XQ, and Yang M reviewed and edited the manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Committee of the First Hospital Affiliated to Anhui Medical University.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: We declare that there are no conflicts of interest.

Data sharing statement: No additional data are available.

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S-Editor: Wang JL
L-Editor: A
P-Editor: Fan JR

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3765-3779

DOI: 10.12998/wjcc.v11.i16.3765

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Hypoperfusion context as a predictor of 28-d all-cause mortality in septic shock patients: A comparative observational study

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Specialty type: Critical care medicine

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cai J, China; Cure E, Turkey; Hakimi T, Afghanistan

Received: November 30, 2022
Peer-review started: November 30, 2022
First decision: January 17, 2023
Revised: January 17, 2023
Accepted: April 18, 2023
Article in press: April 18, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

As per the latest Surviving Sepsis Campaign guidelines, fluid resuscitation should be guided by repeated measurements of blood lactate levels until normalization. Nevertheless, raised lactate levels should be interpreted in the clinical context, as there may be other causes of elevated lactate levels. Thus, it may not be the best tool for real-time assessment of the effect of hemodynamic resuscitation, and exploring alternative resuscitation targets should be an essential research priority in sepsis.

AIM

To compare the 28-d mortality in two clinical patterns of septic shock: hyperlactatemic patients with hypoperfusion context and hyperlactatemic patients without hypoperfusion context.

METHODS

This prospective comparative observational study carried out on 135 adult patients with septic shock that met Sepsis-3 definitions compared patients with hyperlactatemia in a hypoperfusion context (Group 1, n = 95) and patients with hyperlactatemia in a non-hypoperfusion context (Group 2, n = 40). Hypoperfusion context was defined by a central venous saturation less than 70%, central venous-arterial PCO_2 gradient [P(cv-a)CO_2] ≥ 6 mmHg, and capillary refilling time (CRT) ≥ 4 s. The patients were observed for various macro and micro hemodynamic parameters at regular intervals of 0 h, 3 h, and 6 h. All-cause 28-d mortality and all other secondary objective parameters were observed at specified intervals. Nominal categorical data were compared using the χ^2 or Fisher's exact test. Non-normally distributed continuous variables were compared using the Mann-Whitney U test. Receiver operating characteristic curve analysis with the Youden index determined the cutoff values of lactate, CRT, and metabolic perfusion parameters to predict the 28-d all-cause mortality. A P value of < 0.05 was

considered significant.

RESULTS

Patient demographics, comorbidities, baseline laboratory, vital parameters, source of infection, baseline lactate levels, and lactate clearance at 3 h and 6 h, Sequential Organ Failure scores, need for invasive mechanical ventilation, days on mechanical ventilation, and renal replacement therapy-free days within 28 d, duration of intensive care unit stay, and hospital stay were comparable between the two groups. The stratification of patients into hypoperfusion and non-hypoperfusion context did not result in a significantly different 28-d mortality (24% *vs* 15%, respectively; $P = 0.234$). However, the patients within the hypoperfusion context with high P(cv-a)CO_2 and CRT ($P = 0.022$) at baseline had significantly higher mortality than Group 2. The norepinephrine dose was higher in Group 1 but did not achieve statistical significance with a $P > 0.05$ at all measured intervals. Group 1 had a higher proportion of patients requiring vasopressin and the mean vasopressor-free days out of the total 28 d were lower in patients with hypoperfusion (18.88 ± 9.04 *vs* 21.08 ± 8.76; $P = 0.011$). The mean lactate levels and lactate clearance at 3 h and 6 h, CRT, P(cv-a)CO_2 at 0 h, 3 h, and 6 h were found to be associated with 28-d mortality in patients with septic shock, with lactate levels at 6 h having the best predictive value (area under the curve lactate at 6 h: 0.845).

CONCLUSION

Septic shock patients fulfilling the hypoperfusion and non-hypoperfusion context exhibited similar 28-d all-cause hospital mortality, although patients with hypoperfusion displayed a more severe circulatory dysfunction. Lactate levels at 6 h had a better predictive value in predicting 28-d mortality than other parameters. Persistently high P(cv-a)CO_2 (> 6 mmHg) or increased CRT (> 4 s) at 3 h and 6 h during early resuscitation can be a valuable additional aid for prognostication of septic shock patients.

Key Words: Capillary refill time; Central venous saturation; Hypoperfusion; Lactate; Mortality; PCO_2 gap; Septic shock

Core Tip: Two different clinical patterns among hyperlactatemic septic shock patients can be effectively differentiated when utilizing three easily employable perfusion parameters. Lactate levels are still the best available tool, but persistence of high central venous-arterial PCO_2 gradient (> 6 mmHg) or raised capillary refill time (> 4 s) at 3 h and 6 h along with lactate metrics during early resuscitation can be valuable for guiding resuscitation of septic shock patients.

Citation: Kataria S, Singh O, Juneja D, Goel A, Bhide M, Yadav D. Hypoperfusion context as a predictor of 28-d all-cause mortality in septic shock patients: A comparative observational study. *World J Clin Cases* 2023; 11(16): 3765-3779

URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3765.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3765

INTRODUCTION

Septic shock remains the most frequent cause of mortality in patients admitted to the intensive care unit (ICU), contributing to 33%-50% to the total inpatient hospital deaths[1-3]. Early recognition and adequate resuscitation of patients with sepsis-associated circulatory dysfunction is a fundamental challenge for an intensivist. Undertreatment may lead to persistently impaired tissue oxygenation, whereas overtreatment may lead to a positive fluid balance that can result in pulmonary edema, prolonged mechanical ventilation (MV), and death[4-8].

Viewing the strong relationship between hyperlactatemia, lactate kinetics, and mortality[9] and following the study results by Jansen *et al*[10], Surviving Sepsis Campaign (SSC) guidelines 2012 suggested fluid resuscitation guided by repeated measurement of blood lactate levels until normalization[11]. However, as per SSC guidelines 2021, lactate level interpretation should be based on the clinical context, and other causes of elevated lactate levels, such as adrenergic-driven aerobic lactate production and impaired hepatic lactate clearance, should be considered[12]. Thus, lactate levels might not be the best tool for real-time assessment of the effect of hemodynamic resuscitation[13,14].

Therefore, exploring alternative resuscitation targets is an important research priority in sepsis.

Variables such as central venous saturation ($ScvO_2$), central venous-arterial PCO_2 gradient [$P(cv-a)CO_2$], and peripheral (skin) perfusion markers exhibit a very fast normalization rate concerning systemic flow optimization[14]. A concomitant low $ScvO_2$, high $P(cv-a)CO_2$, or abnormal peripheral perfusion define a "hypoperfusion context" in which increasing systemic blood flow may reduce blood lactate levels. Thus, multimodal perfusion monitoring could aid in identifying a hypoperfusion context.

This study aimed to analyze septic shock patients and compare the outcome in two clinical patterns: Hyperlactatemic patients with hypoperfusion and hyperlactatemic patients without hypoperfusion. The hypoperfusion context in the present study was defined similarly to the study by Alegría *et al*[15]: $ScvO_2$ less than 70%; $P(cv-a)CO_2$ greater than or equal to 6 mmHg; capillary refilling time (CRT) greater than or equal to 4 s; and hyperlactatemia after initial fluid resuscitation in septic shock patients admitted in the ICU.

MATERIALS AND METHODS

The present study was a prospective comparative observational study conducted in the medical ICU, Institute of Critical Care Medicine, Max Super Specialty Hospital, Saket, New Delhi from March 2021 to November 2021. Institutional Human Ethics Committee approval was obtained before the commencement of the study (Reference number: TS/MSSH/MHIL/SKT-1/MHEC/CC/20-14). All consecutive adult non-pregnant patients aged 18 years and above who were admitted to the medical ICU with septic shock (according to Sepsis-3 definition[1]), for whom concomitant values for $ScvO_2$, $P(cv-a)CO_2$, and CRT could be obtained were considered eligible for this study. Patients with severe cardiorespiratory disease and active bleeding were excluded. Written informed consent was obtained from all the patients. Our estimated sample size was based on a previous study[15], which analyzed the mortality in septic shock patients with hypoperfusion *vs* those without hypoperfusion. With reference to this previous study, we defined a relevant clinical difference of 11% (5% in non-hypoperfusion *vs* 16% in hypoperfusion) in mortality between the two groups. Thus, a sample size of 95 patients per group provided an 80% power for detecting a significant difference between the two groups at an alpha level of 0.05. As observed from the previous study[15], the number of patients with and without hypoperfusion was in a ratio of 3:7. Thus, 135 patients in total were taken during the study period: 95 patients with hypoperfusion and 40 patients without hypoperfusion. Patients were enrolled and categorized as follows: Group 1. Patients with hypoperfusion; and Group 2. Patients without hypoperfusion.

Preload optimization was guided by an algorithm (Figures 1 and 2) that included early fluid loading, followed by vasopressor infusion as needed to maintain a mean arterial pressure > 65 mmHg. SSC guidelines 2016 were followed to guide the treatment of septic shock[1]. All patients were followed for 28 d. The following primary and secondary outcomes were measured as part of the multimodal perfusion assessment.

Primary outcome: all-cause mortality at the 28th d (asked by telephone if patient discharged earlier).

Secondary outcomes: (1) Macro hemodynamic variables measured at baseline including systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, norepinephrine (NE), or vasoactive drug doses; (2) Metabolic-related perfusion variables measured at 0 h (baseline), 3 h, and 6 h including $ScvO_2$ and $P(cv-a)CO_2$; (3) Lactate measurement and percentage of lactate clearance at 0 h (baseline), 3 h, and 6 h. The normal level was defined as less than 2 mmol/L. Lactate was assessed using an arterial sample and processed by a point of care common gas analyzer. The percentage of lactate clearance was defined as: Lactate clearance = (Lactate initial-Lactate time) × 100/Lactate initial; (4) CRT measured at 0 h (baseline), 3 h, and 6 h: Normal values were considered to be ≤ 4.0 s. It was measured by applying firm pressure to the ventral surface of the distal phalanx of the right index finger with a glass microscope slide. The pressure was increased until the skin blanched, was maintained for 10 s, and then released. The time for the return of the normal skin color was recorded using a chronometer, and a refill time greater than 3 s was defined as abnormal; (5) Amount of fluid administered measured at 0 h, 6 h, and 24 h; (6) Vasopressor dose measured at 0 h, 3 h, 6 h, 12 h, and 24 h; (7) Duration of vasopressor use in days; (8) Need of invasive MV, duration on invasive MV in days, and MV-free days within 28 d; (9) Need for renal replacement therapy and renal replacement therapy-free days within 28 d; and (10) ICU and hospital length of stay.

Statistical analysis

Continuous variables were presented as mean ± standard deviation for normally distributed data and median ± interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The comparison of normally distributed continuous variables between the groups was performed using Student's *t*-test. Nominal categorical data between the groups were compared using the χ^2 test or Fisher's exact test. Mann Whitney *U* test was performed to compare two group means. Receiver operating characteristic curve (ROC) analysis with the Youden index was performed to determine each the cutoff value of each parameter to predict the outcome. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were

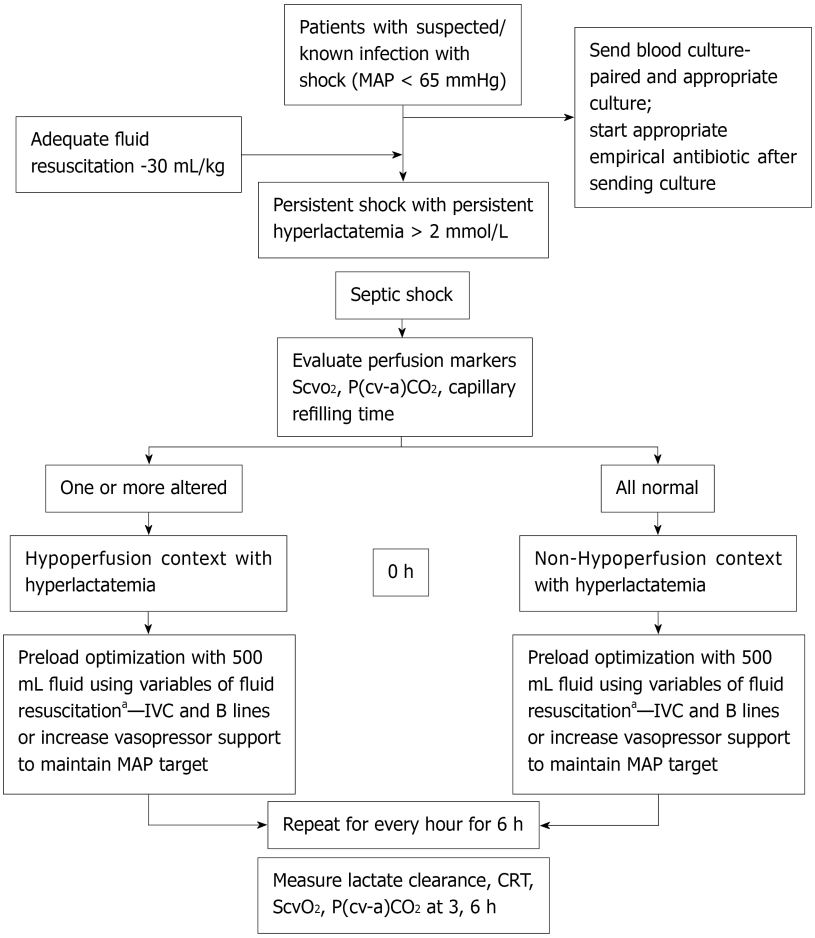

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Figure 1 Resuscitation algorithm. [a]Fluid resuscitation using inferior vena cava and lung ultrasound. CRT: Capillary refill time; IVC: Inferior vena cava; MAP: Mean arterial pressure; P(cv-a)CO_2: Central venous-arterial pCO_2 gradient; ScvO_2: Central venous oxygen saturation.

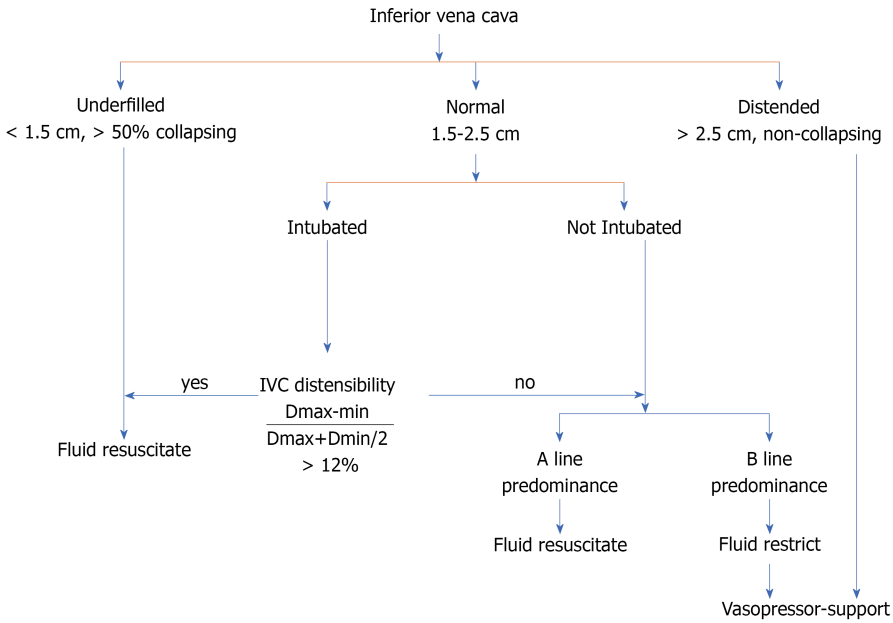

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Figure 2 Fluid resuscitation guide using inferior vena cava and lung ultrasound. IVC: Inferior vena cava.

calculated based on those cutoff values. For all statistical tests, a $P < 0.05$ indicated a significant difference.

RESULTS

A total of 148 patients met the inclusion criteria in the present study, out of which 7 patients had severe left ventricular systolic dysfunction, 1 patient was pregnant, and 5 patients refused to consent to participate. Therefore, 135 patients were included in the study; 95 patients were in the hypoperfusion context (Group 1), and 40 patients were in the non-hypoperfusion context (Group 2). Patient demographics, comorbidities, baseline laboratory and vital parameters, source of infection, and Sequential Organ Failure scores were comparable between the two groups (Tables 1 and 2). The Acute Physiology and Chronic Health Evaluation (APACHE) II score was higher in Group 2 (23.78 ± 5.414 *vs* 23.78 ± 5.414; $P < 0.002$). The baseline lactate levels were 4.84 ± 1.7 mmol/L and were comparable in both the groups at baseline (4.87 ± 1.69 *vs* 4.76 ± 1.75 mmol/L; $P = 0.594$) and all measured intervals. The primary and secondary outcomes of Group 2 were compared with Group 1 and with the subgroups of Group 1 (Supplementary Tables 1 and 2).

The overall 28-d mortality was 21% in 135 patients, 24% in the hypoperfusion context group *vs* 15% in the non-hypoperfusion context ($P = 0.234$). However, the patients within the hypoperfusion context with high P(cv-a)CO_2 and CRT (P-value 0.022) at baseline had significantly higher mortality as compared to Group 2 (Supplementary Tables 1 and 2). The mean dose of noradrenaline at baseline in all the study patients was 0.19 ± 0.14 μg/kg/min. Although the NE requirement was higher in Group 1, it did not attain statistical significance at any specified interval ($P > 0.05$). Group 1 had a higher proportion of patients requiring vasopressin, with lower mean vasopressor-free days out of the total 28 d (18.88 ± 9.04 *vs* 21.08 ± 8.76; $P = 0.011$). Similarly, Group 1 had a higher fluid requirement than Group 2 at 0 h and 6 h ($P = 0.045$ and 0.008, respectively). The need for invasive MV, days on MV, renal replacement therapy-free days within 28 d, and ICU and hospital stay duration were comparable between the groups (Supplementary Table 2).

Univariate analysis of baseline variables and primary and secondary outcomes was also performed between the survivors and non-survivors (Table 3). We also analyzed the prognostic value of mean lactate levels, lactate clearance, $ScvO_2$, CRT, and P(cv-a)CO_2 at 0 h, 3 h, and 6 h for 28-d all-cause mortality. In the current study, although the lactate levels at baseline were higher in non-survivors than the survivors, they were statistically insignificant (5.2 ± 1.72 *vs* 4.74 ± 1.69; $P = 0.151$). Nevertheless, a significant association between lactate levels at 3 h and 6 h and lactate clearance at 3 h and 6 h was observed with the 28-d mortality, with lactate levels at 6 h having a better predictive value than lactate clearance at 6 h [area under the ROC (AUROC) for lactate at 3 h and 6 h: 0.776 and 0.845, respectively; AUROC for lactate clearance at 3 h and 6 h 0.754 and 0.834, respectively] (Figure 3). The optimal cutoff value for lactate values at 3 h in predicting 28-d mortality was ≥ 4.2 mmol/L, with a sensitivity of 55.2%, a specificity of 63.2%, a PPV of 29.1%, and an NPV of 83.8%. Similarly, the cutoff for the 6 h lactate levels was ≥ 4.1 mmol/L with a sensitivity of 74.2%, a specificity of 84.9%, a PPV of 55.6%, and an NPV of 92.8% (Tables 4 and 5).

A statistical significant ($P = 0.033$) difference in $ScvO_2$ at baseline between non-survivors and survivors was observed in the present study. However, mean $ScvO_2$ at 3 h and 6 h was comparable between non-survivors and survivors ($P = 0.304$ and 0.299, respectively) (Table 5).

In the current study, P(cv-a)CO_2 ≥ 6 mmHg at baseline was used as one of the criteria of hypoperfusion and was measured at baseline, 3 h, and 6 h. At baseline, the mean P(cv-a)CO_2 was 5.92 ± 1.91 mmHg. P(cv-a)CO_2 was higher in survivors than non-survivors at baseline, 3 h, and 6 h, which achieved statistical significance with a P value of 0.036, < 0.001, and < 0.001, respectively. In the current study, the cutoff value of P(cv-a)CO_2 in predicting 28-d mortality at baseline was ≥ 7.6 mmHg (AUROC: 0.627; sensitivity: 44.8%; specificity: 81.1%; PPV: 39.4%; NPV: 84.3%; accuracy: 73.3%; $P = 0.004$). Similarly, cutoff values for P(cv-a)CO_2 at 3 h and 6 h were ≥ 5.9 and 6.45 mmHg, respectively (Tables 4 and 5).

Similarly, a statistically significant association was found between the 28-d mortality and CRT levels at baseline, 3 h, and 6 h. ($P = 0.004$, < 0.001, and < 0.001, respectively). The AUROC to estimate mortality for CRT at baseline was 0.623 [95% confidence interval (CI): 0.536-0.705) and at 3 h and 6 h was 0.768 (95%CI: 0.688-0.837) and 0.705 (95%CI: 0.675-0.827), respectively, with the asymptotic significance of < 0.001 and < 0.001, respectively. In the present study, the cutoff point to predict 28-d mortality for CRT at baseline was 4 s, with a sensitivity of 55.2% and specificity of 67.9%, while the cutoff point for CRT at 6 h was 7 s, with a sensitivity of 51.9% and a specificity of 94.3% ($P < 0.001$) (Tables 4 and 5).

We also performed a multivariate logistic regression analysis to predict variables associated with 28-d mortality. Only lactate levels at 6 h (odds ratio = 1.344; 95%CI: 1.168-1.546; $P < 0.001$) and baseline serum creatinine (odds ratio = 1.515; 95%CI: 1.036-2.216; $P < 0.001$) were identified as independent risk factors of 28-d mortality (Table 6).

Table 1 Comparison of Group 1 and Group 2

Variable	Group 1			Group 2			*P* value
	mean ± SD	Min-Max	Median (Q1-Q3)	mean ± SD	Min-Max	Median (Q1-Q3)	
Age	62.34 ± 14.32	20-92	64 (56-73)	61.03 ± 15.10	25-82	66.5 (52-72)	0.843
APACHE II	20.82 ± 5.47	9-32	20 (17-25)	23.78 ± 5.41	8-33	24 (21-28)	0.002[a]
SOFA score	9.26 ± 4.22	2-18	8 (6-13)	8.88 ± 3.44	4-16	8 (6-11.75)	0.751
Hemoglobin	11.24 ± 6.30	7.1-16.70	10.2 (9.10-12.20)	10.26 ± 1.93	7.1-16	10.25 (8.75-11.7)	0.299
TLC	12.37 ± 7.92	0.1-46.50	11.9 (6.70-16.70)	12.56 ± 9.34	1.4-42.80	9.65 (6.5-16.65)	0.668
Platelet count	2.17 ± 1.01	0.1-5.26	1.98 (1.63-2.78)	2.08 ± 0.72	0.25-3.18	2.02 (1.61-2.75)	0.904
Serum bilirubin	1.84 ± 2.78	0.16-18.57	0.8 (0.55-1.6)	1.68 ± 2.24	0.28-10.93	0.81 (0.41-1.84)	0.507
Serum albumin	3.0 ± 0.60	1.5-4.4	2.9 (2.60-3.50)	2.9 ± 0.60	1.7-4	2.9 (2.30.-3.40)	0.584
INR	1.35 ± 0.36	0.95-3.83	1.28 (1.12-1.49)	1.31 ± 0.30	1.01-2.52	1.26 (1.08-1.44)	0.323
Creatinine	1.59 ± 1.31	0.2-10.50	1.3 (0.70-1.90)	1.34 ± 0.91	0.20-4.20	1.15 (0.6-1.85)	0.265
Urea	51.68 ± 34.75	7.8-229	41.7 (29.70-64.60)	54.12 ± 35.30	3.3-157	44 (33.1-69.88)	0.565
Heart rate	104.15 ± 15.44	64-156	107 (94-114)	106.73 ± 15.65	70-137	112 (98-118.75)	0.216
SBP	101.6 ± 22.16	50-166	102 (90-117)	99.5 ± 21.53	60-133	102 (81-117.75)	0.629
DBP	56.92 ± 15.26	24-97	58 (45-66)	58.58 ± 15.65	36-90	59 (44-68.75)	0.685
MAP	71.62 ± 16.08	31-106	70 (64-82)	72.5 ± 16.47	44-103	70.5 (61.75-87)	0.808
Lactate at 0 h	4.87 ± 1.69	2.1-9.70	4.6 (3.50-5.90)	4.76 ± 1.75	2.3-9.8	4.15 (3.5-5.65)	0.594
Lactate at 3 h	4.22 ± 2.0	1.3-12.00	3.6 (2.80-5.20)	3.82 ± 2.06	1.9-12.40	3.4 (2.45-4.10)	0.16
Lactate at 6 h	3.91 ± 3.01	0.6-14.10	2.8 (2.0-4.60)	3.88 ± 3.48	0.9-16.70	2.7 (2.0-4.20)	0.7
CRT at 0 h	5.14 ± 2.16	2-12	5 (3-7)	2.25 ± 0.67	1-3	2 (2-3)	< 0.001[a]
CRT at 3 h	4.72 ± 2.68	1.0-13.00	4 (3-7)	3.55 ± 2	2-9	3 (2-4)	0.011[a]
CRT at 6 h	4.50 ± 3.30	1.0-13.00	3 (2-7)	3.88 ± 3.22	1-13	3 (2-4)	0.255
$ScvO_2$ at 0 h	64.5 ± 9.10	42.8-74.20	70.4 (56.40-71.80)	71.8 ± 1.30	68.1-74.0	71.8 (70.9-72.70)	< 0.001[a]
$ScvO_2$ at 3 h	60.1 ± 7.0	36.8-73.70	60.8 (56.70-64.70)	63.8 ± 4.70	52.8-73.50	63.6 (61.7-67.3)	0.002[a]
$ScvO_2$ at 6 h	58.6 ± 9.0	36.7-89.20	60.2 (52.30-64.90)	62.4 ± 6.80	42.3-71.0	63.7 (58.7-68.3)	0.010[a]
P(cv-a)CO_2 at 0 h	6.63 ± 1.78	2.9-9.80	7.2 (5-7.9)	4.24 ± 0.84	2.8-5.80	4.2 (3.6-4.86)	< 0.001[a]
P(cv-a)CO_2 at 3 h	5.81 ± 2.03	2.6-12.30	5.5 (4.10-7)	5.05 ± 1.51	2.7-10	4.4 (4-5.98)	0.035[a]
P(cv-a)CO_2 at 6 h	5.70 ± 2.30	2.6-12.40	5.1 (4-60.5)	5.88 ± 6.88	2.6-47	4.3 (3.6-6.375)	0.059
Lactate clearance at 3 h	10.2 ± 38.5	(-183.3-57.7)	22.7 (-7.30-36.0)	18.3 ± 29.8	(-103.3-58.2)	26.7 (5.4-36.4)	0.332
Lactate clearance at 6 h	15.3 ± 76.0	(-433.3-100.0)	39.6 (5.1-57.1)	20.3 ± 54.8	(-173.8-76.9)	39.1 (2.4-57.9)	0.973

[a]Denotes statistical significance.

Group 1 referred to patients with hyperlactatemia in a hypoperfusion context. Group 2 referred to patients with hyperlactatemia in a non-hypoperfusion context. APACHE: Acute Physiology and Chronic Health Evaluation; CRT: Capillary refill time; DBP: Diastolic blood pressure; INR: International normalized ratio; MAP: Mean arterial pressure; P(cv-a)CO_2: Central venous-arterial pCO_2 gradient; Q1: First quartile; Q3: Third quartile; SBP: Systolic blood pressure; $ScvO_2$: Central venous oxygen saturation; SOFA: Sequential Organ Failure Assessment; TLC: Total leukocyte count; SD: Standard deviation.

DISCUSSION

Although serum lactate has been established as an objective surrogate marker for tissue hypoxia and disease severity in septic shock, an absolute dependence on serial lactate levels to guide fluid resuscitation may lead to over-resuscitation in some cases. Hence, alternative measures for assessing perfusion, such as CRT, $ScvO_2$, and P(cv-a)CO_2, might be more pragmatic. A recent study by Algeria *et al*[15] used CRT, P(cv-a)CO_2, and $ScvO_2$ to define hypoperfusion context and demonstrated that patients with hyperlactatemia plus hypoperfusion context exhibited a severe circulatory dysfunction with increased morbidity. However, this study was retrospective and did not examine the superiority of

Table 2 Comparison of baseline patient characteristics between Group 1 and Group 2

Characteristics	Group 1		Group 2		Total		*P* value
	Frequency	%	Frequency	%	Frequency	%	
Sex							
Female	43	45%	20	50%	63	95%	0.614
Male	52	55%	20	50%	72	105%	
Comorbidities							
DM	30	32%	12	30%	42	31%	0.856
HTN	39	41%	15	38%	54	40%	0.700
COPD	6	6%	5	13%	11	8%	0.393
CLD	7	7%	4	10%	11	8%	0.868
CKD	12	13%	8	20%	20	15%	0.271
Malignancy	7	7%	4	10%	11	8%	0.868
CAD	8	8%	6	15%	14	10%	0.403
Others IMM	5	5%	2	5%	7	5%	1.000
Source of infection							
Intra-abdominal infection	27	28%	12	30%	39	29%	0.853
Bacteremia	11	12%	3	8%	14	10%	0.689
Pneumonia	30	32%	11	28%	41	30%	0.638
UTI	12	13%	8	20%	20	15%	0.271
Others	10	11%	2	5%	12	9%	0.484
Unknown	5	5%	4	10%	9	7%	0.529

Group 1 referred to patients with hyperlactatemia in a hypoperfusion context. Group 2 referred to patients with hyperlactatemia in a non-hypoperfusion context. CAD: Coronary artery disease; CKD: Chronic kidney disease; CLD: Chronic liver disease; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; HTN: Hypertension; IMM: Immunocompromised diseases; UTI: Urinary tract infection.

serial measurements of CRT, P(cv-a)CO_2, and $ScvO_2$ over serial lactate measurements in predicting poor outcome in patients with septic shock.

In the present prospective observational study involving 135 patients with septic shock, the outcome in two different clinical patterns of septic shock was analyzed: hypoperfusion context *vs* non-hypoperfusion context. Similar to the results by Algeria *et al*[15], the stratification of patients in the present study into hypoperfusion and non-hypoperfusion contexts did not result in a significant difference in 28-d mortality. However, in the present study, the subgroup of patients within the hypoperfusion context with a high P(cv-a)CO_2 and CRT exhibited significantly higher mortality than those in the non-hypoperfusion context.

Baseline characteristics were comparable between the groups, apart from the APACHE II score, which was higher in Group 2. As the APACHE II score calculation involves chronic comorbidities, a higher APACHE II score in the non-hypoperfusion context could be attributed to more patients with cirrhosis and dialysis dependence.

Although the dose requirement of NE was higher in patients with hypoperfusion at all intervals compared to Group 2, it did not achieve statistical significance. These results differ from Algeria *et al* [15], who reported significantly higher NE requirements ($P < 0.005$) in the hypoperfusion context group. This difference could be due to a higher proportion of patients requiring vasopressin in the hypoperfusion context group in the present study. The present study also observed a higher fluid requirement in Group 1 at 0 h and 6 h. Consequently, this signifies the presence of more severe circulatory dysfunction in Group 1 than in Group 2. The rest of the secondary outcomes were comparable between Group 1 and Group 2.

Serum lactate has been established to be of prognostic value in patients with septic shock. Marty *et al* [16] showed a significant difference between the lactate values at baseline, 6 h, 12 h, or 24 h between the survivors and non-survivors group ($P < 0.05$ for each time interval). Analysis of the AUROC for lactate levels at baseline, 3 h, and 6 h to predict the 28-d mortality revealed that initial lactate levels had a poor predictive value compared to those at 3 h and 6 h. These results were similar to the study by Lee *et al*

Table 3 Comparison of survivors and non-survivors

Variable	Non-Survivors			Survivors			*P* value
	mean ± SD	Min-Max	Median (Q1-Q3)	mean ± SD	Min-max	Median (Q1-Q3)	
Age	62.41 ± 14.61	28-82	66 (55.5-74.0)	61.82 ± 14.55	20-92	64 (53.75-71.25)	0.653
APACHE II	23.93 ± 4.91	14-32	24 (20.5-28.0)	21.08 ± 5.64	8-33	21 (17.00-25.25)	0.012[a]
SOFA score	10.38 ± 4.71	2-17	11 (6-15)	8.81 ± 3.73	2-18	8 (6-11)	0.094
HB	12.2 ± 11.0	7.2-16.7	10 (8.8-12.0)	10.6 ± 2.0	7.1-16.9	10.3 (9.1-12.0)	0.493
TLC	10.0 ± 6.9	0.2-24.3	8.5 (5.4-13.8)	13.1 ± 8.6	0.1-46.5	11.9 (6.8-16.7)	0.101
PLT	1.99 ± 0.89	0.25-4.08	1.83 (1.58-2.01)	2.18 ± 0.95	0.10-5.26	2.10 (1.65-2.78)	0.188
SBIL	1.02 ± 0.84	0.28-4.70	0.78 (0.57-1.27)	2.00 ± 2.90	0.16-18.57	0.8 (0.5-2.0)	0.489
SALB	2.4 ± 0.4	1.6-3.1	2.3 (2.1-2.7)	3.1 ± 0.6	1.5-4.4	3.1 (2.7-3.5)	< 0.001[a]
INR	1.28 ± 0.29	0.97-2.14	1.18 (1.09-1.31)	1.36 ± 0.36	0.95-3.83	1.30 (1.12-1.48)	0.099
CREAT	2.08 ± 0.95	0.50-4.90	1.80 (1.50-2.40)	1.36 ± 1.23	0.20-10.50	1.10 (0.60-1.80)	< 0.001[a]
Urea	61.24 ± 44.91	9.90-229.00	45.60 (30.50-86.70)	49.99 ± 31.30	3.30-168.90	41.83 (30.10-61.60)	0.280
HR	107.00 ± 15.22	70-128	112 (98-118)	104.34 ± 15.58	64-156	106.50 (94.00-116.00)	0.228
SBP	94.66 ± 22.81	60-138	90 (74-116)	102.71 ± 21.45	50-166	102 (90-118)	0.065
DBP	52.41 ± 14.21	26-87	50 (41-60)	58.77 ± 15.41	24-97	60.00 (46.00-69.25)	0.060
MAP	66.24 ± 16.61	31-101	67.0 (53.0-76.5)	73.42 ± 15.74	33-106	71 (64-85)	0.057
Lactate at 0 h	5.20 ± 1.72	2.10-9.40	5.20 (4.0-5.70)	4.74 ± 1.69	2.30-9.80	4.40 (3.40-5.90)	0.151
Lactate at 3 h	5.54 ± 2.14	2.40-10.70	5.20 (3.80-6.70)	3.71 ± 1.80	1.30-12.40	3.40 (2.50-4.20)	< 0.001[a]
Lactate at 6 h	6.61 ± 3.35	2.10-14.60	6.30 (3.90-8.60)	3.21 ± 2.70	0.60-16.70	2.45 (1.90-3.30)	< 0.001[a]
CRT at 0 h	5.07 ± 2.46	2-12	5 (3-7)	4.07 ± 2.18	1-9	3 (2-6)	0.040[a]
CRT at 3 h	6.38 ± 2.95	2-13	6 (4-8)	3.82 ± 2.14	1-10	3 (2-5)	< 0.001[a]
CRT at 6 h	7.10 ± 4.10	2-13	9 (3-11)	3.63 ± 2.64	1-13	2.5 (2.0-5.0)	< 0.001[a]
$ScvO_2$ at 0 h	68.30 ± 7.80	43.20-73.90	71.9 (70.2-72.8)	66.20 ± 8.50	42.80-74.20	70.80 (58.90-71.90)	0.033[a]
$ScvO_2$ at 3 h	61.90 ± 7.10	45.80-73.50	62.8 (58.9-66.2)	61.00 ± 6.50	36.80-73.70	61.70 (57.80-64.90)	0.304
$ScvO_2$ at 6 h	58.10 ± 11.80	36.70-89.20	58.9 (49.7-66.2)	60.2 ± 7.60	37.90-71.0	61.90 (56.10-65.90)	0.299
$P(cv\text{-}a)CO_2$ at 0 h	6.50 ± 1.90	2.80-9.40	7.3 (4.9-7.9)	5.70 ± 1.90	2.80-9.80	5.50 (4.20-7.40)	0.036[a]
$P(cv\text{-}a)CO_2$ at 3 h	7.00 ± 2.10	3.40-12.30	6.5 (5.6-8.6)	5.20 ± 1.60	2.7-11.0	4.8 (4.0-6.2)	< 0.001[a]
$P(cv\text{-}a)CO_2$ at 6 h	7.10 ± 2.50	2.60-10.80	7.4 (4.9-9.2)	5.40 ± 4.50	2.60-8.70	4.70 (3.60-5.80)	< 0.001[a]
Lactate clearance at 3 h	(-10.20 ± 35.10)	(-88.10-40.40)	(-8.6) (-37.1-24.7)	18.80 ± 34.20	(-183.30-58.20)	26.80 (7.30-37.20)	< 0.001[a]
Lactate clearance at 6 h	(-28.70 ± 72.80)	(-187.0-100.0)	(-46.4) (-61.5-29.9)	29.20 ± 64.40	(-433.80-81.30)	44.90 (23.40-58.70)	< 0.001[a]

[a]Denotes statistical significance.

APACHE: Acute Physiology and Chronic Health Evaluation; CREAT: Creatinine; CRT: Capillary refill time; DBP: Diastolic blood pressure; HB: Hemoglobin; HR: Heart rate; INR: International normalized ratio; MAP: Mean arterial pressure; $P(cv\text{-}a)CO_2$: Central venous-arterial pCO_2 gradient; PLT: Platelet; Q1: First quartile; Q3: Third quartile; SALB: Serum albumin; SBIL: Serum bilirubin; SBP: Systolic blood pressure; $ScvO_2$: Central venous oxygen saturation; SD: Standard deviation; SOFA: Sequential Organ Failure Assessment; TLC: Total leukocyte count.

[17], conducted in 2021, in which the lactate levels at 6 h had a better prognostic performance. In the present study, the optimal cutoff value for lactate values in predicting 28-d mortality was ≥ 4.2 mmol/L, with a sensitivity of 55.2%, specificity of 63.2%, PPV of 29.1%, and NPV of 83.8%. Similarly, the cutoff value for the lactate levels at 6 h was ≥ 4.1 mmol/L with a sensitivity of 74.2%, specificity of 84.9%, PPV of 55.6%, and NPV of 92.8%. These findings differ from the study mentioned above by Lee *et al*[17], where the optimal cutoff of 6 h lactate levels was ≥ 2 mmol/L, with the highest sensitivity [89.2% (95%CI: 83.0%-93.7%)], but the specificity was relatively lower [35.3% (95%CI: 29.0%-42.1%)].

Table 4 Area under the curve to predict 28-d mortality for various perfusion markers at specified intervals

Test result variable	Area	Std. Error	*P* value	Asymptomatic 95%CI	
				Lower bound	Upper bound
Lactate at 0 h	0.587	0.058	0.133	0.499	0.671
Lactate at 3 h	0.776	0.048	< 0.001[a]	0.696	0.843
Lactate at 6 h	0.845	0.04	< 0.001[a]	0.772	0.902
Lactate clearance at 3 h	0.754	0.053	< 0.001[a]	0.672	0.824
Lactate clearance at 6 h	0.834	0.041	< 0.001[a]	0.76	0.893
CRT at 0 h	0.623	0.056	0.028[a]	0.536	0.705
CRT at 3 h	0.768	0.047	< 0.001[a]	0.688	0.837
CRT at 6 h	0.757	0.054	< 0.001[a]	0.675	0.827
$ScvO_2$ at 0 h	0.630	0.062	0.035[a]	0.542	0.711
$ScvO_2$ at 3 h	0.562	0.064	0.325	0.474	0.648
$ScvO_2$ at 6 h	0.565	0.072	0.367	0.476	0.651
P(cv-a)CO_2 at 0 h	0.627	0.060	0.033[a]	0.540	0.709
P(cv-a)CO_2 at 3 h	0.754	0.052	< 0.001[a]	0.673	0.824
P(cv-a)CO_2 at 6 h	0.736	0.060	< 0.001[a]	0.652	0.808

[a]Denotes statistical significance.

CI: Confidence interval; CRT: Capillary refill time; P(cv-a)CO_2: Central venous-arterial pCO_2 gradient; $ScvO_2$: Central venous oxygen saturation.

Table 5 Cutoff values of perfusion markers at specified intervals

Marker	Cutoff value	Sensitivity	Specificity	PPV	NPV	Accuracy	*P* value
Lactate at 0 h	> 4.9	55.2%	63.2%	29.1%	83.8%	61.5%	0.074
Lactate at 3 h	> 4.2	65.5%	77.4%	44.2%	89.1%	74.8%	< 0.001[a]
Lactate at 6 h	> 4.1	74.1%	84.9%	55.6%	92.8%	82.7%	< 0.001[a]
Lactate clearance at 3 h	≤ -20.6 (≥ 20.6% from baseline)	44.8%	93.4%	65.0%	86.1%	83.0%	< 0.001[a]
Lactate clearance at 6 h	≤ -46.4 (≥ 46.4% from baseline)	55.6%	94.3%	71.4%	89.3%	86.5%	< 0.001[a]
CRT at 0 h	> 4	55.2%	67.9%	32.0%	84.7%	65.2%	0.022[a]
CRT at 3 h	> 4	69.0%	70.8%	39.2%	89.3%	70.4%	< 0.001[a]
CRT at 6 h	> 8	51.9%	94.3%	70.0%	88.5%	85.7%	< 0.001[a]
$ScvO_2$ at 0 h	> 71.7	55.2%	71.7%	34.8%	85.4%	68.2%	0.007[a]
$ScvO_2$ at 3 h	> 61.7	69.0%	53.8%	29.0%	86.4%	57.0%	0.03[a]
$ScvO_2$ at 6 h	≤ 58.9	55.6%	65.1%	28.9%	85.2%	63.2%	0.05
P(cv-a)CO_2 at 0 h	> 7.6	44.8%	81.1%	39.4%	84.3%	73.3%	0.004[a]
P(cv-a)CO_2 at 3 h	> 5.9	72.4%	73.6%	42.9%	90.7%	73.3%	< 0.001[a]
P(cv-a)CO_2 at 6 h	> 6.4	63.0%	83.0%	48.6%	89.8%	79.0%	< 0.001[a]

[a]Denotes statistical significance.

CRT: Capillary refill time; NPV: Negative predictive value; P(cv-a)CO_2: Central venous-arterial pCO_2 gradient; PPV: Positive predictive value; $ScvO_2$: Central venous oxygen saturation.

Table 6 Stepwise logistic regression to predict 28-d all-cause mortality

Step		*B*	S.E.	Wald test	df	Significance	Exp(B)	95%CI for Exp(B)	
								Lower	Upper
1[a]	Lactate at 6 hours	0.302	0.073	17.230	1	0.000	1.353	1.173	1.561
	Constant	-2.731	0.421	42.115	1	0.000	0.065		
2[b]	Creatinine	0.416	0.194	4.595	1	0.032	1.515	1.036	2.216
	Lactate at 6 hours	0.295	0.071	17.091	1	0.000	1.344	1.168	1.546
	Constant	-3.416	0.552	38.348	1	0.000	0.033		

[a]Variable(s) entered on step 1: lactate at 6 h.
[b]Variable(s) entered on step 2: baseline creatinine. CI: Confidence interval; df: Degree of freedom; S.E.: Standard error.

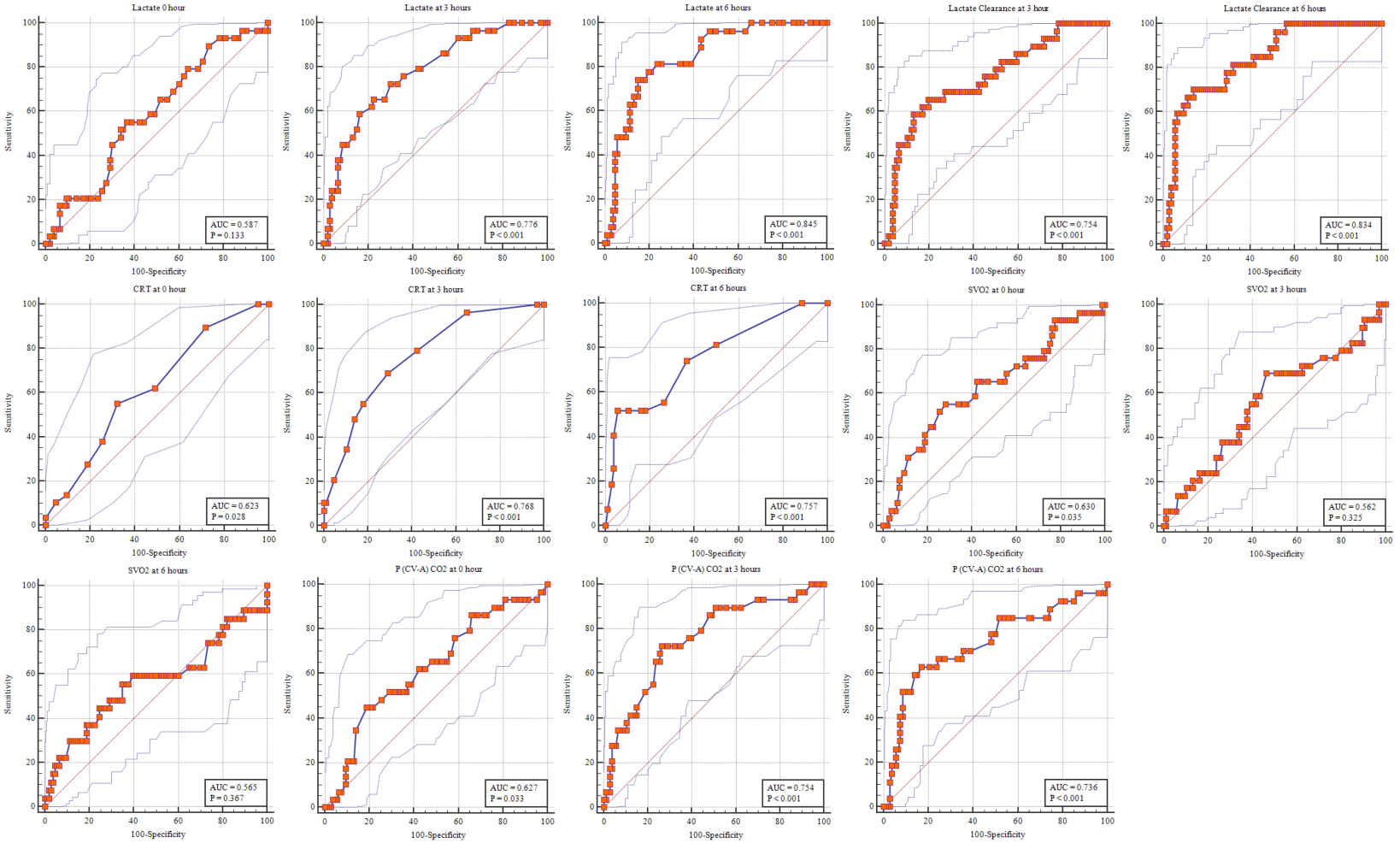
Lactate clearance is defined as the rate of decline in lactate concentration. It has been extensively studied and is a strong independent predictor of survival in patients with septic shock, with lactate non-clearance consistently linked to increased mortality[16]. In our study, lactate clearance remained higher in survivors than non-survivors at all time intervals in the study period. Although the prognostic value of lactate clearance at 6 h was better than at 3 h, the metrics were inferior to the static lactate levels at the corresponding time intervals. Similar results were observed in a study by Ryoo *et al*[18] in which lactate and lactate clearance at 6 h was associated with higher mortality; lactate levels had significantly higher prognostic value than lactate clearance. On multivariate analysis to evaluate mortality, among all variables assessed, only lactate at 6 h and baseline serum creatinine were independently associated with 28-d mortality (Table 6).

$ScvO_2$ trends correlate well with mixed central venous oxygen saturation and have been independently associated with mortality in septic shock[19,20], with threshold values supporting those published in the SSC guidelines 2012[11]. Normalization of $ScvO_2$ does not rule out persistent tissue hypoperfusion, and the latter can still occur due to severe microcirculatory disorders and mitochondrial dysfunction[21,22]. Moreover, if $ScvO_2$ < 70% is associated with mortality[23], it does not mean that $SvcO_2$ ≥ 70% is associated with survival[24]. Thus, in some circumstances, the use of $ScvO_2$ might mistakenly drive an intensivist to conclude that the patient's physiologic state has improved when, in fact it has not. According to the results of the current study, $ScvO_2$ appeared to be a valuable tool for initial resuscitation but cannot distinguish between survivors and non-survivors after initial resuscitation.

The P(cv-a)CO_2 gap represents an excellent surrogate indicator of the adequacy of cardiac output and tissue perfusion under a given condition of CO_2 production. Recently, Ospina-Tascón *et al*[25] showed that the persistence of high P(v-a)CO_2 (≥ 6 mmHg) during the first 6 h of resuscitation of septic shock patients is associated with severe multiple organ dysfunction and increased mortality rate (relative risk = 2.23; P = 0.01). There is a strong agreement between P(v-a)CO_2 and P(cv-a)CO_2, though it should not be interchanged. In the present study, it was observed that P(cv-a)CO_2 was higher in survivors than non-survivors at all time intervals, and persistence of the PCO_2 gap > 6.5 mmHg at 3 h and 6 h during early resuscitation of septic shock patients was associated with higher mortality rates. The cutoff values of P(cv-a)CO_2 in predicting 28-d mortality at baseline was ≥ 7.6 mmHg (AUROC: 0.627; sensitivity: 44.8%; specificity: 81.1%; PPV: 39.4%; NPV: 84.3%; accuracy: 73.3%; P = 0.004). Similarly, the cutoff value at 6 h was ≥ 6.45 mmHg (AUROC: 0.685; sensitivity: 58.6%; specificity: 83.0%; PPV: 48.6%; NPV: 88.0%; accuracy: 77.8%; P < 0.001). A study by Helmy *et al*[26] observed a P(cv-a)CO_2 cutoff of ≥ 8.4 mmHg at 0 h and ≥ 7.8 mmHg at 6 h as a predictor of all-cause hospital mortality. The difference in cutoff values may be because of the increased specificity. Consequently, high P(cv-a)CO_2 > 6 mmHg at 6 h could identify patients with septic shock at high mortality risk in apparently resuscitated patients.

CRT has emerged as a reasonable alternative to guide septic shock resuscitation. The skin territory lacks autoregulatory flow control; therefore, sympathetic activation can impair skin perfusion during circulatory dysfunction, a phenomenon that can be assessed by measuring CRT[27]. CRT can be easily measured at the bedside with no additional equipment required beyond a chronometer (*i.e.* a clock or the stopwatch on your phone). Measurement of CRT upon admission assesses the alteration in microcirculation at 3 h and 6 h; it also evaluates the response to resuscitation. The present study found a statistically significant association between the 28-d mortality and CRT at baseline, 3 h, and 6 h. Similar results were described by Morocho *et al*[28], who concluded that the measurement of CRT at baseline, 3 h, and 6 h was a strong predictor of mortality in septic shock, even above the widely studied markers such as lactate.

Castro *et al*[29] demonstrated that CRT-targeted fluid resuscitation was associated with higher and faster achievement of resuscitation targets and exhibited similar improvement in hypoxia surrogates and regional blood flow to those observed with lactate-targeted fluid resuscitation. These results were in



DOI: 10.12998/wjcc.v11.i16.3765

Figure 3 Graphs of area under the receiver operating characteristic curve for capillary refill time, central venous oxygen saturation, and central venous-arterial pCO_2 gradient. AUC: Area under the curve; CRT: Capillary refill time; $P(cv\text{-}a)CO_2$: Central venous-arterial pCO_2 gradient; $ScvO_2$: Central venous oxygen saturation.

contradiction with that of the ANDROMEDA-SHOCK trial[30]. It may be due to the difference in the duration of intervention periods of both studies and the different kinetics of CRT and lactate. In accordance with the current literature and the results of the present study, CRT is a reliable marker for assessing the severity of clinical perfusion. Its frequent bedside assessment alone can improve

resuscitation in septic shock, especially in low-resource settings.

In the present study, it was observed that the cutoff point to predict 28-d mortality for CRT at baseline was 4 s, with a sensitivity of 55.2% and specificity of 67.9%, while the cutoff point for CRT at 6 h was 7 s, with a sensitivity of 51.9%, and a specificity of 94.3%. The corresponding CRT cutoffs by Morocho *et al*[28] at admission and 6 h were 4.5 s at admission and 3.5 s at 6 h post-resuscitation. This cutoff at 6 h was different from the present study, which may be because of temperature-associated variation, inter-rater variability, and high melanin concentration in our population[31,32]. In dark-skinned people (phototypes V and VI), the high concentration of melanin in the epidermis absorbs much of the light, so the reflected light contribution comes mainly from the melanin contribution and not from the perfusion change caused in the dermis during compression, causing an error in the CRT measurement[33]. This can be overcome by newly developed optical devices to objectively assess CRT. Recently the role of melanin pigment in controlling the immune response has been increasingly recognized. Melanocytes containing little melanin produce more cytokines, such as TNF, IL-1β, IL-6, and IL-10, and can cause fluctuation in the immune response levels[34].

The current study had a few limitations. This non-experimental observational study could only demonstrate an association between hypoperfusion context and 28-d mortality but could not establish the cause-and-effect relationship. We used all-cause in-hospital mortality as our primary outcome; patients might have died from non-sepsis-related causes. Given the various etiologies of hyperlactatemia, drugs or comorbidities causing hyperlactatemia of any clinical significance could not be accounted for, making interpretation of hyperlactatemia challenging. Although the personnel were thoroughly trained to assess CRT using a standardized technique, we did not consider the inter-rater variability and skin temperature, which could alter CRT values. Lastly, this was a single-center study with a small sample size. Future multicenter prospective studies with larger sample sizes must conclusively establish the endpoints of early resuscitation in septic shock to reduce patient mortality.

CONCLUSION

Septic shock patients fulfilling the hypoperfusion and non-hypoperfusion context exhibit similar 28-d all-cause hospital mortality, although patients with hypoperfusion displayed a more severe circulatory dysfunction. Targeting $ScvO_2$ may not be desirable as normalization of $ScvO_2$ does not rule out persistent tissue hypoperfusion. Lactate levels at 6 h had a better prognostic value in predicting 28-d mortality than other parameters. Persistently high P(cv-a)CO_2 (> 6 mmHg) or increased CRT (> 4 s) at 3 h and 6 h during early resuscitation can be a valuable additional tool for prognostication of septic shock patients.

ARTICLE HIGHLIGHTS

Research background

As per the latest Surviving Sepsis Campaign guidelines, fluid resuscitation should be guided by repeated measurements of blood lactate levels until normalization.

Research motivation

Serum lactate is a non-specific biomarker that may be increased by a myriad of clinical conditions. Thus, it may not be the best tool for real-time assessment of the effect of hemodynamic resuscitation, and exploring alternative resuscitation targets should be an essential research priority in sepsis.

Research objectives

To compare the 28-d mortality in two clinical patterns of septic shock: hyperlactatemic patients in the hypoperfusion context and hyperlactatemic patients in the non-hypoperfusion context.

Research methods

This prospective comparative observational study carried out on 135 adult patients with septic shock that met Sepsis-3 definitions compared patients of hyperlactatemia with hypoperfusion (Group 1, n = 95) and hyperlactatemia without hypoperfusion (Group 2, n = 40). The patients were observed for various macro and micro hemodynamic parameters at regular intervals of 0 h, 3 h, and 6 h. All-cause 28-d mortality and all other secondary objective parameters were observed at specified intervals.

Research results

The stratification of patients into hypoperfusion and non-hypoperfusion did not result in a significantly different 28-d mortality (24% *vs* 15%, respectively; P = 0.234). However, the patients within the hypoperfusion context with high P(cv-a)CO_2 and CRT (P = 0.022) at baseline had significantly higher mortality

than Group 2. Group 1 had a higher proportion of patients requiring vasopressin and the mean vasopressor-free days out of the total 28 d were lower in patients with hypoperfusion (18.88 ± 9.04 *vs* 21.08 ± 8.76; $P = 0.011$). The mean lactate levels and lactate clearance at 3 h and 6 h, CRT, and P(cv-a)CO_2 at 0 h, 3 h, and 6 h were found to be associated with 28-d mortality in patients with septic shock, with lactate levels at 6 h having the best predictive value (area under the receiver operating characteristic: 0.845).

Research conclusions

Septic shock patients fulfilling the hypoperfusion and non-hypoperfusion context exhibit similar 28-d all-cause hospital mortality, although patients with hypoperfusion displayed a more severe circulatory dysfunction. Lactate levels at 6 h had a better predictive value in predicting 28-d mortality. Persistently high P(cv-a)CO_2 (> 6 mmHg) or increased CRT (> 4 s) at 3 h and 6 h during the early resuscitation can be a valuable additional aid for prognostication of septic shock patients.

Research perspectives

Multicenter large scale trials should be conducted to further evaluate the role of CRT and PCO_2 gap as markers for resuscitation in patients with septic shock.

FOOTNOTES

Author contributions: Kataria S, Singh O, and Juneja D designed the study; Kataria S, Bhide M, and Yadav D collected the data and analyzed the results; Kataria S and Juneja D performed the majority of the writing and prepared the tables; Singh O, Goel A, Devraj Y, and Bhide M provided input in writing the paper and reviewed the manuscript; All authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Max Super Specialty Hospital, Saket, Institutional Review Board (Approval No. TS/MSSH/MHIL/SKT-1/MHEC/CC/20-14).

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

Data sharing statement: No additional data are available.

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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S-Editor: Chang KL
L-Editor: Filipodia
P-Editor: Chang KL

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3780-3790

DOI: 10.12998/wjcc.v11.i16.3780

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Psychological review of hemodialysis patients and kidney transplant recipients during the COVID-19 pandemic

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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 scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Tang W, China; Wijaya JH, Indonesia

Received: December 17, 2022
Peer-review started: December 17, 2022
First decision: January 12, 2023
Revised: February 11, 2023
Accepted: May 6, 2023
Article in press: May 6, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Kidney transplantation (KT) and end-stage renal disease (ESRD) requiring hemodialysis (HD) increase the incidence of morbidity and mortality associated with coronavirus disease 2019 (COVID-19) infection. The COVID-19 pandemic has had a negative effect on the psychological well-being of COVID-19 patients, especially those with a high-risk of infectious complications. The prevalence of anxiety and depression is known to be higher in ESRD patients undergoing HD than in the general population. On the other hand, KT recipients have different treatment requirements compared to HD patients, including adherence to complex immunosuppressive regimens and compliance with follow-up appointments. We hypothesized that psychosocial difficulties and stressors would differ between ESRD patients undergoing HD and KT recipients during the COVID-19 pandemic. If so, each group may require different interventions to maintain their psychosocial well-being.

AIM

To measure and compare the levels of stress, anxiety, depression, concerns related to the pandemic, and coping skills in ESRD patients undergoing HD and KT recipients during the COVID-19 pandemic.

METHODS

This cross-sectional study was performed at a training and research hospital. The study included ESRD patients undergoing HD (HD group) and KT recipients (with stable graft function for ≥ 6 mo prior to the study) (KT group). Patients completed a demographics form, the impact of events scale, the hospital anxiety and depression scale, and the Connor-Davidson resilience scale. Laboratory findings at the last clinical follow-up were recorded. The χ^2 test was used to assess the relationship between the HD and KT groups and the categorical variables. The relationships between the scale scores were analyzed using Pearson's correlation test, and differences between the groups were analyzed using the independent groups *t*-test.

RESULTS

The study included 125 patients, of which 89 (71.2%) were in the HD group and 36 (28.8%) were in the KT group. The levels of anxiety and depression were higher in the HD group than in the KT group [9.36 ± 4.38 *vs* 6.89 ± 4.06 (P = 0.004) and 8.78 ± 4.05 *vs* 6.42 ± 4.26 (P = 0.004), respectively], whereas the post-traumatic stress score was higher in the KT group [46.75 ± 13.98 *vs* 37.66 ± 18.50 (P = 0.009)]. The concern with the highest intensity in the HD group was transmission of COVID-19 to family and friends (93.3%) and in the KT group was loss of caregiver and social support (77.8%). Concerns regarding financial hardship, stigmatization, loneliness, limited access to health care services, failure to find medical supplies, and transmission of COVID-19 to family and friends were more prevalent in the HD group. Connor-Davidson resilience scale tenacity and personal competence, tolerance, and negative affect scores were higher in the KT group than in the HD group [43.47 ± 11.39 *vs* 33.72 ± 12.58, 15.58 ± 4.95 *vs* 11.45 ± 5.05, and 68.75 ± 17.39 *vs* 55.39 ± 18.65 (P < 0.001), respectively]. Biochemical parameters, such as creatine, urea, phosphorus, parathyroid hormone, and calcium, were lower, and the albumin and hemoglobin values were higher in the KT group than in the HD group (P < 0.001).

CONCLUSION

Psychosocial difficulties and the level of stress differ in ESRD patients undergoing HD and KT recipients; therefore, psychosocial interventions should be tailored for each patient group.

Key Words: Kidney transplantation; Dialysis; Anxiety; Depression; Psychological resilience

Core Tip: Hemodialysis patients and kidney transplantation recipients with viral infections have higher mortality and morbidity rates compared to the general population. These patients are at a high risk of infectious complications due to immunosuppression, and this risk triggers psychosocial stress. Considering the possible negative effects of this psychosocial stress, an in-depth psychological analysis was performed using validated scales. Specific concerns and stressors related to coronavirus disease 2019 (COVID-19) were identified in both patient groups. Overall, the main concern was transmitting COVID-19 to family and friends, followed by financial hardship, loneliness, and stigmatization. The present findings showed that it is crucial to tailor supportive psychological interventions to these vulnerable patient groups.

Citation: Gundogmus AG, Oguz EG, Guler-Cimen S, Kocyigit Y, Dogan AE, Ayli MD. Psychological review of hemodialysis patients and kidney transplant recipients during the COVID-19 pandemic. *World J Clin Cases* 2023; 11(16): 3780-3790

URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3780.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3780

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has a higher mortality rate in end-stage renal disease (ESRD) patients compared to the general population as these patients have comorbid immunosuppression[1]. Patients with ESRD and immunocompromised transplant recipients constitute one of the highest risk groups for COVID-19 infection[2]. In 2019 there were 61341 ESRD patients on hemodialysis (HD) in Turkey, and the number has increased by 10000 patients each year since[3]. Worldwide approximately 2 million people annually undergo HD or receive a kidney transplant to stay alive. The best treatment for ESRD is kidney transplantation (KT). The COVID-19-related mortality rate in KT recipients is reported to be 22%-50%[4]. This mortality rate can be higher in developing countries, such as Turkey. Turkey has

an insufficient budget for health care services[5]. Moreover, ESRD patients undergoing HD three times a week are at risk of contracting COVID-19 at HD centers[6,7], as they have a weakened immune system and receive dialysis in crowded conditions. The literature on COVID-19 is primarily focused on treatment and complication management. Clinical studies on the effect of the COVID-19 pandemic, including stressors and psychological trauma, in specific patient populations are lacking[8-17]. Nevertheless, it is predicted that the COVID-19 pandemic negatively affects the psychological well-being of patients, especially those at high-risk for contracting COVID-19[9].

Given the need for a better understanding of affect disorders in ESRD patients undergoing HD and KT recipients during the COVID-19 pandemic, the present study aimed to determine the prevalence and degree of anxiety and depression in KT recipients and HD patients and to compare them in terms of psychological resilience, traumatic stress, and the severity of depression and anxiety. It was hypothesized that psychosocial difficulties and areas of concern would differ between the ESRD patients undergoing HD and the KT recipients during the COVID-19 pandemic.

MATERIALS AND METHODS

Study population and data collection

This cross-sectional study was conducted at Saglik Bilimleri University, Ankara Diskapi Research and Training Hospital, Transplantation and Nephrology Clinic, Ankara, Turkey. The study included ESRD patients undergoing HD and KT recipients with stable graft function for ≥ 6 mo prior to the study. Data were collected between September 2020 and January 2021. Patients aged < 18 years and > 65 years, patients with documented organic mental disorders, epilepsy, dementia, delirium, and intellectual disability, patients that could not complete the study scales due to hearing-vision problems or a medical illness with significant cognitive sequelae, and those with a history of alcohol or substance abuse were excluded. Additionally, illiterate patients were excluded, as they could not complete the study scales. The Saglik Bilimleri University, Ankara Diskapi Research and Training Hospital Ethics Committee approved the study protocol, No. 10.08.2020-93/01, which was carried out in accordance with the declaration of Helsinki and the declaration of Istanbul. All study participants provided written informed consent.

Data for ESRD patients were collected during HD sessions between the first and last hours. KT recipients' data were collected during KT outpatient follow-up visits. All participants completed a sociodemographic data form, the impact of events scale-revised (IES-R), the Connor-Davidson resilience scale (CD-RISC), and the hospital anxiety and depression scale (HADS). HD initiation and KT dates were recorded. Additionally, routine laboratory parameters, including blood urea, creatinine, albumin, phosphorus, parathyroid hormone, calcium, hemoglobin, and C-reactive protein levels, were collected. Participants were also administered a visual analog scale to evaluate the level of perceived stress related to COVID-19 infection (1: None; 2: A little bit; 3: Moderate; 4: A lot; 5: Extreme). Non-compliance with medication and follow-up care was determined based on a yes/no question. Patients were divided into two groups: the HD group and the KT group.

Sociodemographic data form

This form was used to record patient age, sex, level of education, marital status, occupational status, and tobacco and alcohol use. Additional questionnaire items queried concerns related to the COVID-19 pandemic such as personal health, the health of loved ones, loneliness, isolation, and financial hardship to discern the causes of distress.

HADS

HADS is a self-report scale used to screen for anxiety and depression. The depression subscale considers anhedonia as the primary symptom. The cutoff points for the Turkish version are 10 for the anxiety subscale and 7 for the depression subscale. The scale was developed by Zigmond and Snaith[18] (1983) and was subsequently validated for use in the Turkish population by Aydemir *et al*[19] (1997).

IES-R

IES-R is used to assess post-traumatic stress disorder (PTSD) using a 5-point Likert-type scale. The scale evaluates the severity of symptoms and has three sub-dimensions: re-experiencing; avoidance; and hyper-arousal. It was developed by Weiss and Marmar[20] (1997) and was validated for use in the Turkish population by Çorapçıoğlu *et al*[21] (2006). The original cutoff value is 33[20]. The Turkish version of the scale is shown to have good diagnostical performance for cutoff points between 24 and 33 [21].

CD-RISC

CD-RISC is used to assess psychological resilience using a 5-point Likert-type scale. The scale was developed by Connor and Davidson[22] and has five sub-dimensions; (1) Personal competence, high

standards, and tenacity; (2) Trust in one's instincts, tolerance of negative affect, and the strengthening effects of stress; (3) Positive acceptance of change and secure relationships; (4) Control; and (5) Spiritual influences. The Turkish reliability and validity study performed by Karairmak *et al*[23] (2010) determined that the Turkish version has three sub-dimensions: tenacity and personal competence; tolerance of negative affect; and tendency towards spirituality. Higher scores indicate higher levels of psychological resilience.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows v.21.0 (IBM Corp., Armonk, NY, United States) and a 95% confidence interval was used. Categorical (qualitative) variables were shown as frequency and percentage, whereas quantitative variables were shown as mean ± SD. Data were considered to have normal distribution if the kurtosis and skewness values were between −3 to +3. Accordingly, the skewness and kurtosis statistics of the measurements showed they were normally distributed. Therefore, parametric methods were used for analysis.

The χ^2 test was used to assess the relationships between the two groups and the categorical variables. The relationships between the measurements/scores were analyzed using Pearson's correlation test, and differences between the groups were analyzed using the independent groups *t*-test. The level of statistical significance was set at $P < 0.05$.

RESULTS

Descriptive statistics and group comparisons

The study included 125 patients: 89 (71.2%) in the HD group and 36 (28.8%) in the KT group (Table 1). Among the KT recipients, 26 received live-related KT and 10 were transplanted from a deceased donor allocated through the Turkish Ministry of Health matching system. Live-related donors included 16 first-degree relatives and 10 second-degree relatives. Sex, occupational status, marital status, social support, cigarette smoking, and alcohol consumption did not differ between the HD and KT groups. The mean age in the HD group was 54.75 ± 15.43 years *vs* 44.54 ± 9.93 years in the KT group; the difference was significant ($P < 0.001$). Additionally, the level of education was higher in the KT group ($P < 0.001$).

More of the patients in the HD group had comorbidities than those in the KT group ($P = 0.028$). Mean duration of ESRD was 8.9 ± 7.2 years in the HD group *vs* 15.2 ± 6.4 years in the KT group ($P < 0.001$). The mean duration of follow-up was 8.23 ± 5.15 years in the KT group. Biochemical parameters were significantly better in the KT group ($P < 0.001$). Psychological variables, such as a history of psychiatric admission, and active psychiatric treatment did not differ significantly between the two groups (Table 1). Treatment non-compliance was reported by 20 (55.6%) of the patients in the KT group *vs* 5 (5.6%) in the HD group ($P < 0.001$) (Table 1).

Concerns regarding the COVID-19 pandemic

Patients in the two study groups had different concerns regarding the COVID-19 pandemic. The intensity of concerns is presented in Table 2. The main concern with the highest intensity was the transmission of COVID-19 to family and friends. This concern had moderate to severe intensity in 83 (93.3%) of the HD patients and 25 (69.4%) of the KT recipients. Significantly more of the patients in the HD group had this concern than those in the KT group. Similarly, concerns regarding financial hardship, loneliness, stigmatization, and failure to find medical supplies were more intense in the HD group. The intensity of concerns regarding contracting COVID-19, inability to access medical treatment, loss of caregiver and social support, limited access to health care services, and contracting COVID-19 from family and friends did not differ significantly between the two groups. The overall perceived stress score was significantly higher in the HD group than in the KT group ($P < 0.001$) (Table 2).

Assessment of depression, anxiety, and PTSD according to scale scores

The HADS anxiety subscale score was significantly lower in the KT group than in the HD group [9.36 ± 4.38 *vs* 6.89 ± 4.06 ($P = 0.004$)] (Table 3), and the HADS depression subscale score was significantly lower in the KT group than in the HD group [8.78 ± 4.05 *vs* 6.42 ± 4.26 ($P = 0.004$)]. The IES-R re-experiencing score did not differ significantly between the groups; however, the hyper-arousal, avoidance, and total scores were significantly higher in the KT group than in the HD group ($P = 0.031$, $P < 0.001$, and $P = 0.009$, respectively). CD-RISC tenacity and personal competence and tolerance and negative affect scores were higher in the KT group ($P < 0.001$ and $P < 0.001$, respectively). There was not a significant difference between the groups in the tendency towards spirituality. The CD-RISC total score was higher in the KT group (68.75 ± 17.39) than in the HD group (55.39 ± 18.65) ($P < 0.001$) (Table 3).

Based on the cutoff score for the HADS anxiety sub-scale, 55.1% ($n = 49$) of the HD patients and 25.0% ($n = 9$) of the KT recipients had anxiety ($P = 0.004$). According to the cutoff score for the HADS depression sub-scale, 73.0% ($n = 65$) of the HD patients and 47.2% ($n = 17$) of the KT recipients had

Table 1 Sociodemographic and clinical data

Characteristic	HD group, *n* = 89	KT group, *n* = 36	*P* value
Age in yr	54.75 ± 15.43	44.54 ± 9.93	< 0.001
Sex			
Male	42	22	0.225
Female	47	14	
Occupational status			
Permanent job	7	8	0.101
Temporary job	5	2	
Unemployed	77	26	
Marital status			
Single	40	12	0.321
Married	49	24	
Level of educational			
Low	36	2	< 0.001
Middle	42	14	
High	11	20	
Social network			
Support available	69	22	0.1
Not available	20	14	
Smoking	14	5	0.999
Alcohol consumption	2	1	0.999
Comorbidities	68	20	0.028
ESRD duration in yr	8.9 ± 7.23	15.2 ± 6.4	< 0.001
Transplant follow-up in yr	-	8.23 ± 5.15	-
Creatinine in mg/dL	8.64 ± 1.36	1.37 ± 0.52	< 0.001
Urea in mg/dL	212.72 ± 71.13	45.1 ± 18.83	< 0.001
Albumin in g/L	4.17 ± 0.36	4.43 ± 0.31	< 0.001
Phosphorus in mg/dL	5.29 ± 1.38	3.38 ± 0.8	< 0.001
Parathyroid hormone in ng/L	690.63 ± 580.97	84.22 ± 58.65	< 0.001
Calcium in mg/dL	7.78 ± 0.83	9.38 ± 0.58	< 0.001
Hemoglobin in g/dL	10.43 ± 1.61	13.01 ± 2.02	< 0.001
Previous psychiatric diagnosis	21	10	0.794
Active psychiatric treatment	9	4	0.999
Non-compliance with treatment	5	20	< 0.001

ESRD: End-stage renal disease; HD: Hemodialysis; KT: Kidney transplantation.

depression (P = 0.011). The IES-R cutoff score showed that significantly more patients in the KT group (n = 32) were experiencing post-traumatic stress as compared to those in the HD group (n = 57) (P = 0.010).

DISCUSSION

ESRD is a global health problem, and the best treatment option is KT; however, both ESRD and KT render patients susceptible to infectious diseases, including COVID-19[6,7,24]. ESRD patients cannot

Table 2 Patient concerns regarding the coronavirus disease 2019 pandemic

Concerns	Intensity	HD group, *n*	%	KT group, *n*	%	*P* value
Contracting COVID-19	None/very mild	9	10.1	7	19.4	
	Mild	8	9.0	6	16.7	0.118
	Moderate/severe	72	80.9	23	63.9	
Inability to access medical treatment	None/very mild	9	10.1	5	13.9	
	Mild	9	10.1	8	22.2	0.125
	Moderate/severe	71	79.8	23	63.9	
Loss of caregiver and social support	None/very mild	7	7.9	6	16.7	
	Mild	7	7.9	2	5.6	0.337
	Moderate/severe	75	84.3	28	77.8	
Financial hardship	None/very mild	3	3.4	6	16.7	
	Mild	8	9.0	11	30.6	< 0.001
	Moderate/severe	78	87.6	19	52.8	
Loneliness	None/very mild	9	10.1	14	38.9	
	Mild	11	12.4	10	27.8	< 0.001
	Moderate/severe	69	77.5	12	33.3	
Stigmatization	None/very mild	10	11.2	20	55.6	
	Mild	7	7.9	3	8.3	< 0.001
	Moderate/severe	72	80.9	13	36.1	
Limited access to health care services	None/very mild	8	9.0	8	22.2	
	Mild	13	14.6	8	22.2	0.05
	Moderate/severe	68	76.4	20	55.6	
Failure to find medical supplies	None/very mild	9	10.1	7	19.4	
	Mild	11	12.4	14	38.9	< 0.001
	Moderate/severe	69	77.5	15	41.7	
Transmission of COVID-19 to family and friends	None/very mild	2	2.2	7	19.4	
	Mild	4	4.5	4	11.1	0.001
	Moderate/severe	83	93.3	25	69.4	
Contracting COVID-19 from family and friends	None/very mild	2	2.2	3	8.3	
	Mild	8	9.0	7	19.4	0.064
	Moderate/severe	79	88.8	26	72.2	
Overall perceived stress score	None/very mild	3	3.4	6	16.7	
	Mild	6	6.7	11	30.6	< 0.001
	Moderate/severe	80	89.9	19	52.8	

COVID-19: Coronavirus disease 2019; HD: Hemodialysis; KT: Kidney transplantation.

survive without dialysis, and HD requires patients to travel to a dialysis center ≥ three times per week. This increases the risk of exposure to patients with COVID-19 infection[6]. Moreover, ESRD patients and KT recipients need to adhere to strict treatment protocols, including dietary/fluid restriction, physical activity, poly-medication use, and follow-up visits.

In the present study COVID-19-related concerns in the HD and KT groups were analyzed. Additionally, depression, anxiety, post-traumatic stress, and psychological resilience scores were measured using HADS, IES-R, and CD-RISC, respectively, and compared between the HD and KT groups. Sociodemographic data in both groups were consistent with Turkish national data showing that KT recipients are younger and have a higher level of education than HD patients. A high level of

Table 3 Scale scores

Scores	HD group, mean ± SD	KT group, mean ± SD	*P* value
HADS			
Anxiety score	9.36 ± 4.38	6.89 ± 4.06	0.004
Depression score	8.78 ± 4.05	6.42 ± 4.26	0.004
IES-R			
Re-experiencing score	13.70 ± 7.31	16.25 ± 6.07	0.066
Hyper-arousal score	9.44 ± 5.91	11.56 ± 4.41	0.031
Avoidance score	14.53 ± 6.38	18.94 ± 4.85	< 0.001
Total score	37.66 ± 18.50	46.75 ± 13.98	0.009
CD-RISC			
Tenacity and personal competence score	33.72 ± 12.58	43.47 ± 11.39	< 0.001
Tolerance and negative affect score	11.45 ± 5.05	15.58 ± 4.95	< 0.001
Tendency towards spirituality score	10.28 ± 2.83	9.75 ± 2.90	0.347
Total score	55.39 ± 18.65	68.75 ± 17.39	< 0.001

CD-RISC: Connor-Davidson resilience scale; HADS: Hospital anxiety and depression scale; HD: Hemodialysis; IES-R: The impact of events scale-revised; KT: Kidney transplantation.

education (high school or university) may make it easier to navigate the healthcare system and consequently obtain better healthcare services. Additionally, individuals with a high level of education might have higher levels of self-efficacy and internal control, which may lead to improved treatment compliance. Individuals with a high level of education may have better health literacy, which might also result in better treatment compliance. The relationship between the level of education and psychosocial stress, coping skills, and treatment compliance are likely multifactorial and complex. As such, the difference in the level of education between the present study's HD and KT groups might contribute to the differences in depression/anxiety and psychological resilience levels that were observed. Until the mechanisms underlying these observed differences are elucidated, medical professionals should be cognizant of the detrimental effects of a low level of education (less than high school) on stress, anxiety, and coping skills.

Sex distribution in the present study's groups did not differ significantly and was consistent with Turkish national data[3]. In addition, a history of psychiatric diagnosis and active psychiatric treatment did not differ significantly between the HD and KT groups. The self-reported treatment non-compliance rate was higher in the KT group than in the HD group, which might have been related to the ongoing nature of HD treatment.

There were several concerning issues for patients receiving HD and KT patients during the COVID-19 pandemic[25]. In the present study the KT recipients reported having less concern than HD patients for financial hardship. Concerns about loneliness and stigmatization were more intense in the HD group. Similarly, concerns about the failure to find medical supplies and transmitting COVID-19 to family and friends were more common in the HD group, which might have been due to their dependence on HD treatment. In contrast, the KT recipients might have had a false sense of security, as they do not require routine HD post-transplantation and therefore have a high rate of non-compliance with medications and follow-up visits. Considering all these factors, the overall perceived stress score was significantly higher in the HD group.

The present study's HD group had significantly higher HADS anxiety and depression scores than the KT group, which agrees with the higher perceived stress levels in the HD group. Cimen *et al*[26] studied HD patients who were waitlisted for KT and reported that the diagnosis of ESRD and undergoing HD and arteriovenous fistula surgery had an anxiety-inducing effect. A study on solid organ transplant recipients showed that wait-listed patients reported higher levels of anxiety related to the COVID-19 pandemic than patients that had already undergone transplantation, which agrees with the present findings[11]. Moreover, it was previously reported that depression and anxiety levels in HD patients are higher than in KT recipients, as in the present study[27]. The mean age in the present study's HD group was higher than in the KT group and the fact that the risks associated with COVID-19 infection increase with age might have played a role in the observed higher level of anxiety in the HD group[2]. The necessity of regular treatment at a dialysis center and the inability to comply with recommended quarantine/social distancing rules may play a role in the high level of anxiety among HD patients[15].

IES-R avoidance, hyper-arousal, and total scores in the present study were higher in the KT group than in the HD group. When the scores were evaluated for their cutoff values the significance of the IES-R scale persisted. This highlighted the fact that the KT recipients had a higher level of post-traumatic stress than the HD patients. Starting from the immediate post-transplant surgery phase transplant recipients must live in isolation for 1 year, must pay particular attention to the home environment, and must limit social interaction due to the high risk of infection associated with immunosuppressive multidrug treatment, including prophylactic anti-viral, anti-bacterial, and immunosuppressive medications[28]. The COVID-19 pandemic required social isolation policies that mimicked those required by transplant recipients post-surgery. This similarity might have led the present study's KT recipients to experience post-traumatic stress more intensely than HD patients, who lacked any prior experience of social isolation. The KT recipients that had already experienced an existential discontinuity (*i.e.* a sudden interruption of self and everyday life) also experienced isolation and potential trauma related to post-transplantation isolation; these experiences might have led them to develop PTSD during the COVID-19 pandemic[4].

Psychological resilience and positive coping strategies can prevent PTSD[29]. It was reported that psychological resilience can also positively affect treatment compliance in HD patients. There is an inverse relationship between psychological resilience and psychological stress in KT recipients[30,31]. It has been shown that interventions that increase psychological resilience have positive effects on depression, anxiety, and perceived stress in transplant recipients[32]. CD-RISC tenacity and personal competence, tolerance and negative affect, and total scores were higher in the present study's KT group. This shows that the KT group had higher psychological resilience and lower levels of depression and anxiety. A low level of psychological resilience is among the risk factors for psychopathology. Research emphasizes the importance of strengthening the psychological resilience of individuals and societies [31].

Although the present study used a single-center design, it provides important insights into the psychosocial status of HD patients and KT recipients during the COVID-19 pandemic. The use of self-report scales can be considered a limitation of the present study. Additionally, due to the present study's cross-sectional design causality could not be determined. Another limitation of the study is the absence of a healthy control group, as COVID-related distress can also afflict healthy persons. The present findings might have been more valuable if the psychosocial status of the KT and HD patients during COVID-19 pandemic had been compared to that prior to the pandemic.

CONCLUSION

In conclusion, the present findings show that HD patients had higher levels of stress and anxiety than KT recipients during the COVID-19 pandemic. The HD patients also had a higher degree of concern regarding financial hardship, loneliness, stigmatization, and failure to find medical supplies and treatment than KT recipients. In contrast, KT recipients had higher IES-R scores, indicating a greater degree of post-traumatic stress. The KT recipients also reported a higher rate of non-compliance with treatment than HD patients. Furthermore, the HD patients and KT recipients experienced different psychosocial difficulties during the COVID-19 pandemic.

ARTICLE HIGHLIGHTS

Research background

The recent coronavirus disease 2019 (COVID-19) pandemic has had significant psychological and social effects on the world's population. Research has highlighted the effect on the psychological well-being of the most at risk groups, including hemodialysis (HD) patients and kidney transplantation (KT) recipients, who are highly likely to develop post-traumatic stress disorder (PTSD), anxiety, depression, and other symptoms of distress. COVID-19-related social distancing negatively affected interpersonal relationships and empathy toward others. The aim of the present clinical study was to identify the effect of the COVID-19 pandemic on these two patient groups and consider possible interventions based on the findings.

Research motivation

The psychological construct of coping, anxiety, depression, and psychological resilience has been studied in various patient populations and has more recently been applied in the field of transplant and end-stage renal disease (ESRD) psychology. The COVID-19 pandemic provided a good opportunity to study and explore the nature of stressors and their origins in KT recipients and ESRD patients undergoing HD.

Research objectives

Prolonged stress during the COVID-19 pandemic can trigger anxiety, depression, and the inability to manage traumatic and negative emotions. Furthermore, the constant fear of contracting the disease negatively affects daily life and leads to social isolation, modifying human relations. These features can be more profoundly observed in patients with chronic illnesses, such as ESRD. The present study aimed to analyze the levels of anxiety and depression in ESRD patients undergoing HD and KT recipients. Additionally, the primary stressors and psychological resilience were surveyed and compared between the KT recipients and HD patients, which is crucial in order to tailor specific treatment for each group.

Research methods

The participants of this cross-sectional study completed a sociodemographic data form, the impact of events scale-revised, Connor-Davidson resilience scale, and hospital anxiety and depression scale. HD initiation and KT surgery dates were recorded. Additionally, routine laboratory parameters, including blood urea, creatinine, albumin, phosphorus, parathyroid hormone, calcium, hemoglobin, and C-reactive protein, were measured. Participants were administered a visual analog scale to evaluate the level of perceived COVID-19-related stress. Non-compliance with medication and follow-up care was evaluated with a yes/no question. The study included two groups: The HD group and the KT group.

Research results

The HD group was significantly older than the KT group. Additionally, the level of education was higher in the KT group than in the HD group. Patients in the two study groups had different concerns regarding the COVID-19 pandemic. The main concern with the highest intensity was the transmission of COVID-19 to family and friends in the HD group and the loss of caregiver and social support in the KT group. Concerns regarding financial hardship, loneliness, stigmatization, limited access to health care services, failure to find medical supplies, and transmission of COVID-19 to family and friends were more intense in the HD group. The levels of anxiety and depression were higher in the HD group than in the KT group, whereas the post-traumatic stress level was higher in the KT group. The rate of PTSD was significantly higher in the KT group as compared to HD group. The psychological resilience level was also higher in the KT group. In addition, in the KT group the reported non-compliance with treatment rate was significantly higher than in the HD group during the COVID-19 pandemic.

Research conclusions

ESRD is a chronic condition characterized by kidney failure that requires either dialysis or KT for survival. Among these two treatment options, KT provides the best outcome, although at a cost. KT recipients must adhere to complex immunosuppressive regimens and medical follow-up. HD, on the other hand, is a more demanding treatment that requires visiting a dialysis center three times per week, blood work-ups, and the risk of exposure to COVID-19 in confined and crowded dialysis centers. The present study aimed to determine the levels of stress, anxiety, and depression, as well as psychological resilience and the frequency of PTSD in HD patients and KT recipients. The present findings highlight the differences in the COVID 19-related concerns and major stressors in the participants in the HD and KT groups. The levels of anxiety and depression were significantly higher in the HD than in the KT group. On the other hand, PTSD and non-compliance with treatment were more common in the KT group. These findings should help clinicians tailor specific support and treatment for HD patients and KT recipients.

Research perspectives

Stress factors associated with the COVID-19 pandemic include fear of death, concerns about personal health and the health of loved ones, loneliness caused by social distancing mandates, concerns about the inability to access medical treatment, job loss, and financial hardship. The magnitude of these stressors and unknowns about COVID-19 and its treatment are likely to lead to PTSD in some individuals, and anxiety and depression set the stage for its development. ESRD patients constitute a vulnerable population, as the present findings show they have high levels of anxiety and depression and are prone to developing PTSD.

ACKNOWLEDGEMENTS

We would like to thank Cansu Çoban for her support in the conduction of this study.

FOOTNOTES

Author contributions: Gundogmus AG and Guler-Cimen S are the guarantors and designed the study; All authors participated in the acquisition, analysis, and interpretation of data and drafted the initial manuscript; Gundogmus

AG, Guler-Cimen S, and Ayli MD revised the article for important intellectual content.

Institutional review board statement: This study was conducted at Ankara Diskapi Yildirim Beyazit Research and Training Hospital, Transplantation and Nephrology Clinic, affiliated with the Saglik Bilimleri University of Turkey, Ankara, Turkey. The local ethics committee approved the study protocol, No. 10.08.2020-93/01. The study was carried out in accordance with the Declaration of Helsinki and the Declaration of Istanbul.

Informed consent statement: All study participants provided written informed consent.

Conflict-of-interest statement: Preliminary results of this clinical study were presented as an oral abstract at the European Society for Organ Transplantation meeting held in Milan in 2021.

Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at sanem.cimen@sbu.edu.tr.

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S-Editor: Li L
L-Editor: Filipodia
P-Editor: Li L

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3791-3801

DOI: 10.12998/wjcc.v11.i16.3791

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Incidence and peri-operative risk factors for development of acute kidney injury in patients after cardiac surgery: A prospective observational study

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Specialty type: Critical care medicine

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Eccher A, Italy; Glumac S, Croatia

Received: February 8, 2023
Peer-review started: February 8, 2023
First decision: March 14, 2023
Revised: March 28, 2023
Accepted: May 4, 2023
Article in press: May 4, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Patients admitted to intensive care unit (ICU) after cardiac surgery develop acute kidney injury (AKI) immediately post-operation. We hypothesized that AKI occurs mainly due to perioperative risk factors and may affect outcome.

AIM

To assess peri-operative risk factors for AKI post cardiac surgery and its relationship with clinical outcome.

METHODS

This was an observational single center, tertiary care setting study, which enrolled 206 consecutive patients, admitted to ICU after cardiac surgery. Patients were followed-up until ICU discharge or death, in order to determine the incidence of AKI, perioperative risk factors for AKI and its association with outcome. Univariate and multivariate logistic regression analysis was performed to assess predictor variables for AKI development.

RESULTS

After ICU admission, 55 patients (26.7%) developed AKI within 48 h. From the logistic regression analysis performed, high EuroScore II (OR: 1.18; 95%CI: 1.06-

1.31, *P* = 0.003), white blood cells (WBC) pre-operatively (OR: 1.0; 95%CI: 1.0-1.0, *P* = 0.002) and history of chronic kidney disease (OR: 2.82; 95%CI: 1.195-6.65, *P* = 0.018) emerged as independent predictors of AKI among univariate predictors. AKI that developed AKI had longer duration of mechanical ventilation [1113 (777–2195) *vs* 714 (511–1020) min, *P* = 0.0001] and ICU length of stay [70 (28–129) *vs* 26 (21–51) h, *P* = 0.0001], higher rate of ICU-acquired weakness (16.4% *vs* 5.3%, *P* = 0.015), reintubation (10.9% *vs* 1.3%, *P* = 0.005), dialysis (7% *vs* 0%, *P* = 0.005), delirium (36.4% *vs* 23.8%, *P* = 0.001) and mortality (3.6% *vs* 0.7%, *P* = 0.046).

CONCLUSION

Patients present frequently with AKI after cardiac surgery. EuroScore II, WBC count and chronic kidney disease are independent predictors of AKI development. The occurrence of AKI is associated with poor outcome.

Key Words: Acute kidney injury; Renal failure; Cardiac surgery; Predisposing factors; Prognosis; Outcome

Core Tip: Acute kidney injury (AKI) may develop in patients after cardiac surgery. In this observational study we assessed the incidence, the peri-operative risk factors for AKI occurrence and its association with outcome in patients after cardiac surgery post- intensive care unit (ICU) admission. The results of the study have shown that AKI occurs frequently after cardiac surgery. EuroScore II, history of chronic kidney disease and white blood cell count are independent predictors of AKI development. The presence of AKI was associated with poor outcome in terms of mechanical ventilation duration, ICU length of stay, rate of dialysis, reintubation, ICU-acquired weakness, delirium and mortality.

Citation: Dimopoulos S, Zagkotsis G, Kinti C, Rouvali N, Georgopoulou M, Mavraki M, Tasouli A, Lyberopoulou E, Roussakis A, Vasileiadis I, Nanas S, Karabinis A. Incidence and peri-operative risk factors for development of acute kidney injury in patients after cardiac surgery: A prospective observational study. *World J Clin Cases* 2023; 11(16): 3791-3801

URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3791.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3791

INTRODUCTION

Each year, more than 2 million cardiac surgeries are performed worldwide. Acute kidney injury (AKI) consists of a frequent and serious complication postoperatively. Cardiac surgery-associated acute kidney injury (CSA-AKI) has an incidence rate that varies from 5% to 42%. Apart from sepsis, it is the most common cause of AKI in the intensive care unit (ICU) setting. CSA-AKI is a major risk factor of death after cardiac surgery resulting to 3-8-fold increase in perioperative mortality, while it is associated with prolonged stay in the ICU and hospital and increased cost of care[1]. 10 years after cardiac surgery, long term mortality remains high, even for patients with complete recovery of renal function and regardless of other risk factors[2]. Many of the predisposing risk factors for AKI, such as advanced age, hypertension, smoking and chronic kidney disease, are non-modifiable[3]. However, the patho-physiological mechanisms that alter renal perfusion causing CSA-AKI appear to be multifactorial and are associated with the unique characteristics of cardiac surgery, highlighted by cardiopulmonary bypass (CPB), as well as with the perioperative and postoperative anesthetic and ICU management, mostly regarding fluid, vasopressor and blood product administration[1,3,4].

This study aimed to investigate the prevalence of AKI as well as to assess peri-operative risk factors for AKI post cardiac surgery and its relationship with clinical outcome.

We hypothesized that there is a high prevalence of AKI post cardiac surgery and perioperative risk factors play a major role for developing AKI in these patients.

MATERIALS AND METHODS

Study population

This prospective observational study was conducted at the Cardiac Surgery ICU of Onassis Cardiac Surgery Center during a 3-mo period. The research was approved by Ethics Committee of the Onassis Cardiac Surgery Center (Number Id: 663/12.12.19) with obtained patient`s informed consent and

carried out in accordance with the ethical standards set by the Declaration of Helsinki.

Inclusion criteria were consecutive adult (> 20 years old) patients following their admission in the Cardiac Surgery ICU within 24 h of cardiac surgery.

Participants with chronic renal failure requiring dialysis prior to cardiac surgery operation were excluded from the study. Moreover patients who were re-admitted to the ICU were not included twice in the study.

Study design

This was a prospective observational study conducted in a single center Cardiac Surgery ICU. All patients were enrolled consecutively to the study post cardiac surgery and they were followed-up until ICU discharge.

Demographic data and baseline clinical perioperative characteristics of all participants and according to AKI development within the first 48 h after cardiac surgery and post ICU admission were prospectively collected and are presented in Table 1. Chronic kidney disease (CKD) was defined by the presence of an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2, that was calculated preoperatively using the CKD-EPI equation[5].

The duration of mechanical ventilation, ICU length of stay, the incidence rate of ICU acquired weakness, delirium, reintubation and dialysis required as well as the ICU mortality outcome of enrolled patients were also recorded. (1) The primary endpoint of the present study was the incidence of AKI after cardiac surgery and the assessment of the perioperative risk factors for AKI development; and (2) The secondary endpoint was the association of AKI with clinical outcome.

The medical research council (MRC) scale was used to evaluate muscle strength. Patients proceeded to assessment as soon as were awake and cooperative. Evaluation included the measurement of six muscle groups bilaterally: shoulder abductors, elbow flexors and wrist dorsiflexors for the upper limbs as well as hip flexors, knee extensors and ankle dorsiflexors for the lower limbs. Test was performed in the same order each time. Each muscle group scored from 0, indicating no contraction, to 5, indicating normal power. Total maximum score was 60, whilst MRC score ≤ 48 was defined as ICU-acquired weakness.

The confusion assessment method for the intensive care unit (CAM-ICU) was used to assess delirium among patients during ICU stay.

AKI definition

AKI was defined according to the kidney disease: Improving global outcome (KDIGO) guidelines. For each patient, serum creatinine (sCr) levels were measured within 3 d prior to surgery (as baseline levels) and were monitored during the first 48 h postoperatively. AKI was defined as an absolute increase in sCr of 0.3 mg/dL within 48 h or a 1.5-fold increase from baseline[6].

Statistical analysis

Descriptive statistics analysis was performed to describe the baseline data. Distribution's normality was checked with Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean ± SD and non-normally distributed variables as median with interquartile range, and categorical variables as proportions with percentages and absolute numbers. To analyze continuous variables between patient groups, Mann Whitney test was used for those with non-normal distribution, *t* test for those with normal distribution and χ^2 test for categorical variables. Univariate logistic regression analysis was performed for all variables to assess risk factors for AKI development. A multivariate logistic regression analysis model (enter method) was then applied to detect independent predictors of AKI for those variables with statistical significance in the univariate analysis. A receiver operating characteristics (ROC) analysis was also performed to test predictor variables for AKI development. Level of significance was set at $P < 0.05$. All statistical analyses were performed with SPSS v.25 software.

RESULTS

Clinical characteristics

The present study enrolled 206 patients during a 3 mo period with a predominance of male gender (69.9%). The incidence of postoperative AKI, as defined by KDIGO guidelines, was 26.7%. The baseline demographic and clinical perioperative characteristics in the entire cohort and according to AKI status are presented in Table 1. We had all types of cardiac surgery including heart transplantation; however we did not have any case of beating heart surgery.

Patients that developed AKI were significantly older, had a higher rate of chronic kidney disease, greater EuroScore II and white blood cells, lower diastolic and mean blood pressure with higher rate of vasopressor and inotrope requirement at ICU admission than those patients without AKI. They had also greater extracorporeal circulation time and a trend to a greater cross-clamp time intra-operatively with longer duration of general anesthesia and ICU sedation than non-AKI patients.

Table 1 Baseline demographic and clinical characteristics in all patients and according to acute kidney injury status

Total population (%)	*N* = 206	AKI	No AKI	*P* value
	206 (100)	55 (26.7)	151 (73.3)	
Baseline pre-operative characteristics				
Gender, female	62 (30.1)	13 (23.6)	49 (32.5)	0.236
Age (yr)	70 (59-76)	74 (59–79)	68.5 (59–74)	0.039
BMI (kg/m^2)	27.8 (25.2-31.3)	27.0 (24.8–30.0)	28.1 (25.4–31.5)	0.308
EuroScore II (%)	1.7 (1.09-2.9)	2.54 (1.52–4.4)	1.54 (0.94–2.4)	0.0001
Hb (gr/dL)	10.3 (9.6-11)	10.3 (9.8–10.9)	10.2 (9.5–11.0)	0.603
WBC (×10^3/μL)	10.3 (7.9-13.1)	11.4 (8.9–13.7)	9.5 (7.5–12.8)	0.015
Creatinine (mg/dL)	0.9 (0.8-1.1)	1.0 (0.9–1.3)	0.9 (0.8–1.1)	0.009
CKD	50 (24.3)	22 (40)	28 (18.5)	0.003
eGFR (mL/min/1.73 m^2)	79.1 (60.2-89.9)	69.1 (52.3-84.2)	81.3 (63.1-90.8)	0.007
PPC	5 (2.4)	1 (1.8)	4 (2.6)	1.0
ICD	5 (2.4)	4 (7.3)	1 (0.7)	0.019
PAD	10 (4.9)	4 (7.3)	6 (4)	0.462
Thyroid disease	36 (17.5)	7 (12.7)	29 (19.2)	0.309
Stroke	3 (1.5)	1 (1.8)	2 (1.3)	1.0
Intraoperative characteristics				
CPB (Extracorporeal circulation)	198 (96.1)	51 (92.7)	147 (97.4)	0.214
Duration of CPB (min), N = 198	112 (84-145)	121 (104–171)	106 (80–141)	0.009
Aortic cross-clamp time (min), N = 193	89 (59-108)	87 (67–111)	77 (56–107)	0.067
Duration of general anesthesia in surgery (min)	240 (190-300)	273 (213–350)	229 (183–300)	0.016
CABG	116 (56.3)	29 (52.7)	87 (57.6)	0.634
Heart valve repair	7 (3.4)	1 (1.8)	6 (4)	0.678
Aortic valve replacement	71 (34.5)	20 (36.4)	51 (33.8)	0.743
Mitral valve replacement	15 (7.3)	4 (7.3)	11 (7.3)	1.0
Tricuspid valve replacement	7 (3.4)	2 (3.6)	5 (3.3)	1.0
Mixed valve replacement	10 (4.9)	2 (3.6)	8 (5.3)	1.0
Aneurysm repair	23 (11.2)	5 (9.1)	18 (11.9)	0.803
Acute aortic dissection	4 (1.9)	3 (5.5)	1 (0.7)	0.059
Heart transplant	4 (1.9)	3 (5.5)	1 (0.7)	0.059
Post-operative characteristics				
Duration of mechanical ventilation (min)	780 (591-1198)	1113 (777–2195)	714 (511–1020)	0.0001
Duration of sedation in ICU (min)	360 (250-600)	540 (300–810)	300 (240–480)	0.0001
Duration of sedation during and post surgery (min)	593 (480-842)	754 (540–1245)	570 (476–740)	0.0001
Fluid balance 24 h post surgery (mL)	722 (70-1418)	1090 (330–1862)	501 (11–1150)	0.001
Fluid balance 48 h post surgery (mL), (*N* = 146)	N (%); 146 (70.9)	46 (31.5)	100 (68.5)	0.526
	-202 [(-1146) - 377]	-163 [(-1186) – 531]	-248 [(-1099) – 296]	
Systolic blood pressure (mmHg)	119 (105-135)	116 (103 – 134)	120 (108–135)	0.162
Diastolic blood pressure (mmHg)	61 (55-70)	58 (54–65)	63 (55–70)	0.015

Mean arterial blood pressure (mmHg)	80 (71-88)	75 (68–84)	80 (74–89)	0.005
Vasopressors	65 (31.6)	27 (49.1)	38 (25.2)	0.002
Inotropes	130 (63.1)	41 (74.5)	89 (58.9)	0.05

AKI: Acute kidney injury; BMI: Body mass index, Hb: Hemoglobin, WBC: White blood cells; sCr: Serum creatinine, HTN: Hypertension; CKD: Chronic kidney disease defined as eGFR ≤ 60 mL/min/173 m^2; PPC: Permanent pacemaker; ICD: Implantable cardioverter defibrillator; PAD: Peripheral artery disease; CPB: Cardiopulmonary bypass, ICU: Intensive care unit. All continuous variables are presented as median (interquartile range) and categorical variables as absolute values (%). Statistical significance was set at *P* value less than 0.05.

Logistic regression analysis

The univariate logistic regression analysis is presented in Table 2. From the multivariate logistic regression analysis performed, high EuroScore II (OR: 1.18; 95%CI: 1.06-1.31, $P = 0.003$), white blood cells pre-operatively (OR: 1.0; 95%CI: 1.0-1.0, $P = 0.002$) and history of chronic kidney disease (OR: 2.82; 95%CI: 1.195-6.65, $P = 0.018$) were independent predictors of AKI (the multivariate analysis model included also univariate predictors such as mean arterial blood pressure, duration of cardiopulmonary bypass, ICU sedation time, duration of general anesthesia, use of vasopressors and inotropes and fluid balance at the 1st ICU day).

ROC analysis

Graphic results from ROC analysis are illustrated in Figure 1 and detailed data are reported in Table 3.

Outcome

There was a significant association of AKI development and clinical outcome. Patients with AKI had prolonged duration of mechanical ventilation and stay in ICU, higher rate of ICU-acquired weakness, reintubation, delirium, dialysis and mortality (Table 4).

DISCUSSION

By this study we have shown that there is a high incidence of AKI development in patients undergoing cardiac surgery. The main results of our study demonstrated also that the pre-operative assessment severity score EuroScore II, white blood cell count and chronic kidney disease were independent predictors of AKI development. Moreover, the occurrence of CSA-AKI was significantly associated with poor outcome. More specifically, patients that developed AKI after cardiac surgery had prolonged duration of mechanical ventilation and ICU stay, higher rate of re-intubation, dialysis and mortality, while they suffered more ICU-acquired weakness and delirium.

Our study results are in line with previous reports. A moderate to high incidence of AKI has been reported previously from other researchers with, however, a wide range of results. This wide range of incidence is partly explained by the differences in study populations and the non-uniform definition of AKI reported in the current literature[4]. Notably, over thirty different arbitrary definitions have been used over time for the diagnosis and staging of AKI. The Risk, Injury, Failure, Loss, and End stage kidney disease (RIFLE) classification criteria were introduced in 2004, defining AKI as an increase in sCr by 1.5 times compared to baseline (or 25% reduction in GFR) and urine output less than 0.5 mL/kg/h for at least 6 h, over a period of 7 d. The Acute Kidney Injury Network (AKIN) group suggested a revision of these criteria in 2007, where GFR was omitted, the period for the change in sCr was reduced to 48 h, while a small increase of 0.3 mg/dL in sCr was used as a cutoff to define AKI[7]. The KDIGO workshop proposed a synthesis of the RIFLE and AKIN criteria in 2012, defining AKI as an 50% increase in SCr in 7 d, increase in SCr over 0.3 mg/dL in 48 h, or oliguria (< 0.5 mL/kg/h for 6-12 h)[6]. The pooled incidence rate of AKI after cardiac surgery was reported to be 22.3% (95%CI: 19.8 to 25.1) by Hu *et al*[8] in a systematic review and meta-analysis of 91 observational studies with 320068 patients that defined AKI using RIFLE, AKIN or KDIGO criteria, an incidence rate similar to the one we report. Notably, the polled incidence rate in studies using KDIGO criteria was 24.2 % (95%CI: 17.5-32.5), while greater difference was reported in studies using RIFLE [18.9%, (95%CI: 15.7-22.5)] and AKIN criteria [28.0%, (95%CI: 23.6-32.8)]. We have used the KDIGO criteria that has become the new consensus for the definition of AKI as they demonstrate greater sensitivity to detect AKI and predict in-hospital mortality in critically ill patients[9].

Unfortunately, the implementation of the above criteria in patients who have undergone cardiac surgery remains problematic as they have important limitations. Fluid resuscitation and fluid loading from the pump during CPB is very common, resulting in sCr changes by haemodilution[1,2,4]. Taking into account that sCr concentrations may take up to 24-36 h to rise after the initial renal insult, this may lead to AKI being underdiagnosed[10]. Oliguria consist another pitfall in the assessment of AKI, as it typically occurs prior to sCr increase, but often is an appropriate response to intravascular hypovolemia

Table 2 Univariate logistic regression analysis for acute kidney injury development

Variable	Exp (B)	95%CI	*P* value
Preoperative characteristics			
Female sex	0.64	0.32–1.31	0.224
Age	1.02	0.99–1.05	0.125
BMI	0.98	0.92–1.05	0.601
EuroScore II	1.21	1.08–1.34	0.001
Hb	1.01	0.76–1.34	0.948
WBC	1.0	1.0–1.0	0.014
Creatinine	1.5	0.76–2.96	0.246
HTN	0.86	0.4–1.85	0.699
Diabetes	0.91	0.47–1.75	0.777
CKD	2.93	1.49–5.77	0.002
CAD	1.02	0.53–1.96	0.959
CHF	0.12	0.01–1.14	0.64
PCP	1.47	0.16–13.44	0.733
PAD	0.53	0.14–1.95	0.337
Thyroid disease	1.63	0.67–3.97	0.282
Stroke	0.73	0.06–8.16	0.794
Intraoperative characteristics			
Duration of CPB	1.01	1.0–1.01	0.044
Aortic cross-clamp time	1.01	1.0–1.01	0.222
Duration of general anesthesia in surgery	1.0	1.0–1.01	0.031
Postoperative characteristics			
Systolic blood pressure	0.99	0.97–1.01	0.181
Diastolic blood pressure	0.97	0.94–1.0	0.026
Mean arterial blood pressure	0.97	0.94–0.99	0.009
Duration of mechanical ventilation	1.043	1.02-1.066	< 0.001
Duration of sedation in ICU	1.0	1.0–1.0	0.004
Duration of sedation during and post surgery	1.0	1.0–1.0	0.003
Fluid balance 24 h post surgery	1.0	1.0–1.0	0.007
WBC	1.11	1.02–1.21	0.014
Vasopressors	0.35	0.18–0.67	0.001
Inotropes	0.49	0.25–0.98	0.042

AKI: Acute kidney injury; BMI: Body mass index; Hb: Hemoglobin; WBC: White blood cells; sCr: Serum creatinine; HTN: Hypertension; CAD: Coronary artery disease; CKD: Chronic kidney disease; CHF: Chronic heart failure; PPC: Permanent pacemaker; ICD: Implantable cardioverter defibrillator; PAD: Peripheral artery disease; CPB: Cardiopulmonary bypass; ICU: Intensive care unit. Statistical significance was set at *P* value less than 0.05.

[3]. Significant differences in the incidence of AKI have been reported in cardiac surgery patients by Lagny *et al*[11], who compared AKI diagnosed by oliguria criteria *vs* AKI diagnosed by sCr criteria (40.2% *vs* 9.7%). Given the fact that urine output documentation is frequently poor, clinicians often use sCr measurements alone to diagnose AKI[3]. The use of novel urinary biomarkers, such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin and interleukin 18 (IL-18), has been proposed for the early detection of AKI, prior to the increase of sCr levels. However, they require further validation before being routinely applied in the heterogeneous population of patients who have undergone cardiac surgery[1,10].

Table 3 Receiver operating characteristics curve analysis for major predictors of acute kidney injury development

Test result variable(s)	Area under curve	SE	*P* value	95%CI	
				Lower bound	Upper bound
CKD	0.602	0.050	0.036	0.504	0.699
EuroScore II percentage (%)	0.692	0.045	0.000	0.604	0.781
Duration of ECC (min)	0.618	0.044	0.015	0.532	0.704
Duration of GA (min)	0.607	0.047	0.028	0.515	0.699
Duration of ICU sedation (min)	0.625	0.051	0.010	0.526	0.724
White blood cell (k/uL)	0.643	0.046	0.003	0.554	0.733
Vasopressors	0.610	0.049	0.024	0.514	0.706
Inotropes	0.562	0.047	0.204	0.469	0.654
Fluid balance 1st day after cardiac surgery (mL)	0.634	0.050	0.006	0.537	0.731

ECC: Extracorporeal circulation; GA: General anesthesia. The statistical significance was set at *P* value less than 0.05.

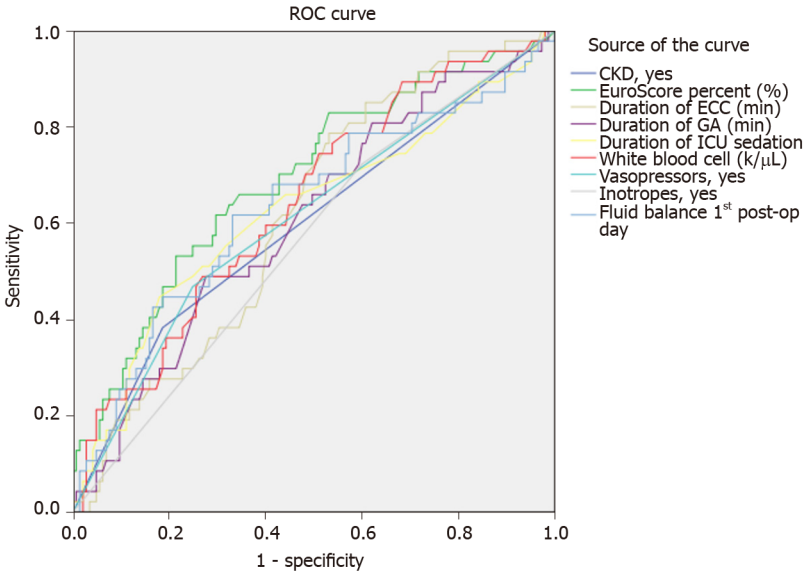
Table 4 Outcome characteristics of all patients and according acute kidney injury status

Outcome	AKI	No AKI	*P* value
Reintubation (*n*)	6 (10.9)	2 (1.3)	0.005
Dialysis (*n*)	4 (7)	0	0.005
Duration of mechanical ventilation (min)	1113 (777–2195)	714 (511–1020)	0.0001
Delirium (*n*)	20 (36.4)	36 (23.8)	0.001
ICU acquired weakness (*n*)	9 (16.4)	8 (5.3)	0.015
ICU length of stay (hours)	70 (28–129)	26 (21–51)	0.0001
Mortality (*n*)	2 (3.6)	1 (0.7)	0.046

AKI: Acute kidney injury; ICU: Intensive care unit.

In our study, CKD, preoperative elevated WBC count and EuroScore II were found as independent risk factors for the development of CSA-AKI. Chen *et al*[12], have reported the association between increased sCr and postoperative AKI in a prospective cohort study of 353 patients who received isolated CABG. Moreover, the presence of CKD has been also associated with the severity of AKI. In a retrospective observational study of 156 CKD patients who received valve surgery with CPB, performed by Fu *et al*[13], every +1 mg/dL increase in baseline sCr was found to result in 111% increase in the incidence of AKI stage 3. Apart from impaired intrarenal hemodynamics and accelerated atherosclerosis, CKD is characterized by a chronic inflammatory state due to proinflammatory cytokines, oxidative stress and uremia that predisposes to the development of AKI[14]. Preoperative WBC count may as well indicate subclinical inflammatory response or multi-organ dysfunction, predisposing to CSA-AKI or other postoperative complications. In a retrospective cohort study of 10979 cardiac surgery patients, excluding individuals with inflammatory syndromes like CKD or cancer, Mahmood *et al*[15], reported that leucocytosis (WBC > 11000/μL) was a significant predictor of medical complications, including AKI, although it was not associated with 30-day mortality. EuroScore II has been updated in 2011 and has been widely implemented to assess the mortality risk in patients undergoing cardiac surgery[16]. Since then, several studies has reported its association with the development of AKI and it has been included in preoperative scoring systems in order to predict major postoperative complications such as CSA-AKI[12,17].

The prolonged duration of CPB as well as the longer duration of sedation and mechanical ventilation support appeared to be major intra-operative risk factors for the development of CSA-AKI. These associations were confirmed in our study in univariate, but not in multivariate analysis. CPB induces AKI with complex, not completely understood mechanisms such as: (1) Low-flow, low-pressure non-pulsatile perfusion that leads to renal ischemia; (2) inflammation caused by the CPB pump and circuit resulting in formation of free radicals, complement activation and increase of proinflammatory cytokines; (3) intravascular hemolysis and free hemoglobin release causing renal tubular damage; (4)



DOI: 10.12998/wjcc.v11.i16.3791

Figure 1 Receiver operating characteristics analysis for acute kidney injury development for major peri-operative risk factors in patients undergoing cardiac surgery. CKD: Chronic kidney disease; ECC: Extracorporeal circulation; GA: General anesthesia; ICU: Intensive care unit; ROC: Receiver operating characteristic; WBC: White blood cell.

platelet activation resulting in renal ischemia from microemboli; and (5) reperfusion injury after CPB that exacerbates oxido-inflammatory stress[1,3,4,7,18]. The renoprotective effects of off-pump coronary artery bypass grafting (CABG) were evaluated as a secondary outcome in the CORONARY randomized trial, which included 4752 patients that were randomized to undergo CABG, either on-pump or off-pump. The use of off-pump CABG resulted in reduced incidence of AKI in the first 30 d (RR: 0.87, 95%CI: 0.80-0.96), but did not affect the incidence of AKI requiring dialysis[19]. In our study, there was a trend in the association between CSA-AKI and the duration of CPB, as it has been reported in previous studies[11,18]. A meta-analysis of 14 case-control studies that included 2157 patients undergoing cardiac surgery, reported that longer CPB time is associated with increased risk for CSA-AKI (OR: 33.78, 95%CI: 23.15–44.41)[18].

In our study a higher positive fluid balance (FB) 24 h post cardiac surgery was associated with increased incidence of CSA-AKI, but the association did not reach statistical significance. This correlation has been reported previously in several studies. A retrospective observational study performed by Chen *et al*[20], suggested that a positive FB over 5% was an independent predictor of AKI occurrence (OR: 3.976, $P < 0.001$). Fluid resuscitation is performed during and after cardiac surgery, in order to avoid volume depletion and hypoperfusion, especially in the case of low cardiac output syndrome. However, fluid overload leads to venous congestion that plays a major role in the development of congestive cardiorenal syndrome and AKI. Yang *et al*[21], showed that increased central venous pressure (CVP) after CPB operation is related with increased incidence of AKI, especially when CVP exceeds 10 cmH_2O, while it is also an independent factor for mortality. On the other hand, the benefit of negative FB is questionable, as its association with decreased incidence of AKI has been reported, in the previously mentioned study by Chen *et al*[20], as non-significant. Moreover, a "U"-shaped correlation was found between 48h accumulative FB and AKI progression, suggesting that an accumulative FB between -5% and 3% might be a possible safe target window 48 h post cardiac surgery. Fluid management remains challenging, "cut-off" values are difficult to be determined and clinical judgment plays an important role. Efforts for the implementation of "goal-directed therapies" have been made in order to guide fluid and vasoactive drug administration by achieving preset hemodynamic or perfusion goals. Some studies showed reduction in the incidence of CSA-AKI. However, the administered regimens, the monitored parameters and the strategies are not well established[22].

The development of AKI after cardiac surgery has been associated in several studies with worse outcomes, regarding mortality and morbidity. These associations have been confirmed in our study. In a meta-analysis performed by Hu *et al*[8], that included 57 observational studies, the presence of CSA-AKI resulted in increased short term mortality (unadjusted OR: 0.144, 95%CI: 0.108-0.192, $P < 0.001$), and in increased long term mortality (unadjusted OR: 0.342, 95%CI: 0.287-0.407 $P < 0.001$). Hobson *et al*[2] reported in a retrospective study that the impact of AKI on reduced short and long term survival was propoptional to its severity. AKI, as well as its severity, were also significantly associated with prolonged stay in ICU and in hospital. The association of CSA-AKI with other postoperative complications is a common finding in several studies. Patients with AKI is more likely to suffer prolonged mechanical ventilation support, compared with patients that did not develop AKI[23]. Moreover, CSA-

AKI has been reported to result in increased risk for reintubation in patients undergoing coronary artery bypass grafting[24] as well as for the development of neurological complications like delirium[25].

Limitations

This observational study, performed in "Onassis" Cardiac Surgery ICU, represents one of the first prospective studies conducted in Greece that investigate the incidence of AKI development and the peri-operative risk factors. The main limitation of this study is that, as an explorative study, its sample size was estimated based on feasibility for a predefined certain period. Hence, it might have been underpowered to demonstrate the association of AKI development during ICU and important perioperative risk factors such as CPB and cross-clamp duration. Despite the relative low sample size, we did find an important association of AKI development and clinical outcome in all outcome parameters assessed in the present study. Another limitation of the study was the cardiac surgery population included with different types of cardiac surgery which might have also underpowered the sample size.

CONCLUSION

In conclusion, patients undergoing cardiac surgery present frequently with AKI postoperatively. EuroScore II, white blood cell count and history of chronic kidney disease were independent predictors of AKI development. Importantly, AKI occurrence post cardiac surgery was found to be associated with poor outcome in terms of prolonged duration of mechanical ventilation and ICU stay, more ICU-acquired weakness and delirium and higher re-intubation, dialysis and mortality rate.

ARTICLE HIGHLIGHTS

Research background

Acute kidney injury (AKI) is a complication for patients undergoing cardiac surgery that might be associated with adverse outcome.

Research motivation

Perioperative targeted monitoring for possible AKI risk factors remains suboptimal and identification of patients at greater risk requires further investigation.

Research objectives

The study aimed to assess AKI presentation after cardiac surgery, to investigate prognostic factors for its development and its association with clinical outcome.

Research methods

This is a prospective observational single-center study that included 206 patients admitted in ICU post cardiac surgery followed-up until ICU discharge. Patients were divided in two groups, the AKI group that developed AKI within 48 h and the non-AKI group. Preoperative clinical characteristics, intra-operative factors and outcome were compared between two groups.

Research results

Patients presented frequently with AKI post cardiac surgery. High EuroScore II (P = 0.003), white blood cells (WBC) pre-operatively (P = 0.002) and history of kidney disease (P = 0.018) were independent predictors of AKI. AKI is associated with prolonged intensive care unit (ICU) stay, greater duration of mechanical ventilation and higher rate of dialysis, reintubation, ICU-acquired weakness, delirium and mortality.

Research conclusions

AKI is a frequent complication post cardiac surgery associated with poor outcome. Preoperative clinical characteristics, such as EuroScore II, preoperative WBC or presence of chronic kidney disease may help in early identification and appropriate management of patients in risk for AKI.

Research perspectives

Further investigation is necessary to assess preventive and optimal treatment strategy protocols for AKI presentation.

ACKNOWLEDGEMENTS

We would like to thank Aggeliki Dorkofiti, Professional English Translator and Editor for editing our manuscript. We would also like to thank all staff of Cardiac Surgery ICU, Onassis Cardiac Surgery Center for their continuous support throughout the study period.

FOOTNOTES

Author contributions: Dimopoulos S conceptualized and designed the study. Karabinis A supervised the study; Dimopoulos S, Zagkotsis G, Tasouli A, Vasileiadis I and Nanas S were involved in the data curation and analysis, projet administration and provided scientific review; Dimopoulos S, Kinti C, Rouvali N, Georgopoulou M, Mavraki M and Lyberopoulou E performed the research and collected the data; Dimopoulos S and Zagkotsis G wrote the paper, reviewed, edited and revised the final version of the manuscript. All authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by Ethics Committee of the Onassis Cardiac Surgery Center, Athens, Greece (Number Id: 663/12.12.19.

Informed consent statement: All study participants provided informed consent and the study was carried out in accordance with the ethical standards set by the Declaration of Helsinki.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

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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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3802-3812

DOI: 10.12998/wjcc.v11.i16.3802

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Randomized Controlled Trial

Coaxial radiography guided puncture technique for percutaneous transforaminal endoscopic lumbar discectomy: A randomized control trial

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Specialty type: Surgery

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

Peer-review model: Single-blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bakır M, Turkey; Xu B, China

Received: December 11, 2022
First decision: January 30, 2023
Revised: February 19, 2023
Accepted: April 19, 2023
Article in press: April 19, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

The coaxial radiography-guided puncture technique (CR-PT) is a novel technique for endoscopic lumbar discectomy. As the X-ray beam and the puncturing needle are maintained in a parallel and coaxial direction, the X-ray beam can be used to guide the trajectory angle, facilitating the choice of the puncture site and providing real-time guidance. This puncture technique offers numerous advantages over the conventional anterior-posterior and lateral radiography-guided puncture technique (AP-PT), especially in cases of herniated lumbar discs with a hypertrophied transverse process or articular process, high iliac crest, and narrowed intervertebral foramen.

AIM

To confirm whether CR-PT is a superior approach to percutaneous transforaminal endoscopic lumbar discectomy compared to AP-PT.

METHODS

In this parallel, controlled, randomized clinical trial, herniated lumbar disc patients appointed to receive percutaneous endoscopic lumbar discectomy treatment were recruited from the Pain Management Department of the Affiliated Hospital of Xuzhou Medical University and Nantong Hospital of Traditional

Chinese Medicine. Sixty-five participants were enrolled and divided into either a CR-PT group or an AP-PT group. The CR-PT group underwent CR-PT, and the AP-PT group underwent AP-PT. The number of fluoroscopies during puncturing, puncture duration (min), surgery duration (min), VAS score during puncturing, and puncture success rate were recorded.

RESULTS

Sixty-five participants were included, with 31 participants in the CR-PT group and 34 in the AP-PT group. One participant in the AP-PT group dropped out due to unsuccessful puncturing. The number of fluoroscopies [median (P25, P75)] was 12 (11, 14) in the CR-PT group *vs* 16 (12, 23) in the AP-PT group, while the puncture duration (mean ± SD) was 20.42 ± 5.78 *vs* 25.06 ± 5.46, respectively. The VAS score was 3 (2, 4) in the CR-PT group *vs* 3 (3, 4) in the AP-PT group. Further subgroup analysis was performed, considering only the participants with L5/S1 segment herniation: 9 patients underwent CR-PT, and 9 underwent AP-PT. The number of fluoroscopies was 11.56 ± 0.88 *vs* 25.22 ± 5.33; the puncture duration was 13.89 ± 1.45 *vs* 28.89 ± 3.76; the surgery duration was 105 (99.5, 120) *vs* 149 (125, 157.5); and the VAS score was 2.11 ± 0.93 *vs* 3.89 ± 0.6, respectively. All the above outcomes demonstrated statistical significance ($P < 0.05$), favoring the CR-PT treatment.

CONCLUSION

CR-PT is a novel and effective technique. As opposed to conventional AP-PT, this technique significantly improves puncture accuracy, shortens puncture time and operation time, and reduces pain intensity during puncturing.

Key Words: Herniated lumbar disc; Coaxial; Puncture; Anterior-posterior; L5/S1

Core Tip: Puncturing is the first step for percutaneous endoscopic lumbar discectomy. Compared with the anterior-posterior and lateral radiography-guided puncture technique (AP-PT), the coaxial radiography-guided puncture technique (CR-PT) has the advantage of guiding the trajectory angle, facilitating the choice of the puncture site, and also providing real-time guidance for puncturing. This study aimed to compare the two techniques. In this randomized controlled trial, the CR-PT technique demonstrated significantly better puncture accuracy, and shorter puncturing and operation duration. We argue that the CR-PT technique is an advisable option in percutaneous endoscopic lumbar discectomy, especially for unusual cases.

Citation: Chen LP, Wen BS, Xu H, Lu Z, Yan LJ, Deng H, Fu HB, Yuan HJ, Hu PP. Coaxial radiography guided puncture technique for percutaneous transforaminal endoscopic lumbar discectomy: A randomized control trial. *World J Clin Cases* 2023; 11(16): 3802-3812
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3802.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3802

INTRODUCTION

Percutaneous endoscopic lumbar discectomy (PELD) is a promising treatment for herniated lumbar disc (HLD). Its advantages over conventional surgery include less intraoperative bleeding, minimal paraspinal muscle injury, high clinical efficacy, and rapid functional recovery. Therefore, PELD has become a popular surgical method[1-8]. Furthermore, in PELD surgery, only a tiny part of the bone tissue is removed, which does not compromise spinal stability[9,10].

Despite its numerous advantages, PELD is technically challenging and has a steep learning curve[11,12]. Accurate puncturing and working channel intubation are required to create favorable conditions for endoscopic surgery[13,14]. However, the puncture technique is relatively difficult, especially in percutaneous transforaminal endoscopic lumbar discectomy (PTELD), which requires specific puncture angles to certain parts of the intervertebral foramen. In addition, for a L5/S1 segment HLD case with a hypertrophied L5 transverse process and articular process, high iliac crest, and narrowed intervertebral foramen, the puncturing is more difficult[15,16].

Conventionally, intermittent anteroposterior and lateral radiography is used for accurate puncturing. However, this process relies on the surgeon's experience to determine and adjust the trajectory angle and depth of the needle. Occasionally, an inappropriate puncture angle leads to failure of the

endoscopic surgery[17,18]. Repeated puncturing results in a prolonged operation and increased exposure to radiation[19,20]. Moreover, repeated puncturing increases the patient's pain perception.

This paper describes a novel coaxial radiography-guided puncture technique (CR-PT) that we developed in our clinical practice. This technique focuses on maintaining the X-ray beam and the puncturing needle in a parallel and coaxial direction[21,22]. With the coaxial technique, the X-ray beam can be used to facilitate puncture site selection and guide the trajectory angle while providing real-time guidance. We hypothesized that this new technique reduces the difficulty of the puncture process, reduces the number of Xray fluoroscopies, shortens the puncture duration, and increases the puncture accuracy. Therefore, the new puncture technique was compared with the conventional anterior-posterior and lateral radiography-guided puncture technique (AP-PT) in order to confirm its superiority.

MATERIALS AND METHODS

Study design

This is a parallel, controlled, single-blinded, randomized clinical trial. The participants were recruited from the Pain Management Department of the Affiliated Hospital of Xuzhou Medical University and Nantong Hospital of Traditional Chinese Medicine and were assigned to two parallel groups: CR-PT group and AP-PT group. The CR-PT group underwent CR-PT, and the AP-PT group underwent AP-PT. This study complied with The Declaration of Helsinki, and the trial was approved by the Institutional Ethics Committee of Clinical Research of Nantong Hospital of Traditional Chinese Medicine. The clinical trial was registered on the Chinese Clinical Trial Registry website (Registration number ChiCTR2200058894) and written informed consent was obtained from all the participants. No external funding was available for the trial.

Inclusion criterion: HLD patients appointed to receive PELD treatment.

Exclusion criteria: Patients with verbal communication disorders; patients with mental disorders; patients who underwent percutaneous inter-laminar endoscopic lumbar discectomy.

Randomization and masking

One researcher was in charge of the enrollment and allocation. The participants were allocated according to their year of birth. Participants with an odd-numbered birth year were assigned to the CR-PT group, while participants with an even-numbered birth year were assigned to the AP-PT Group. The participants were blinded to which group they were assigned.

Another researcher was assigned to evaluate the outcomes. The operations were performed by two surgeons in the two respective hospitals. They were not blinded to the allocation. Data processing and statistical analysis were performed by another researcher who was blinded to the allocation. The allocation method was revealed after the completion of the statistical analysis.

Outcomes

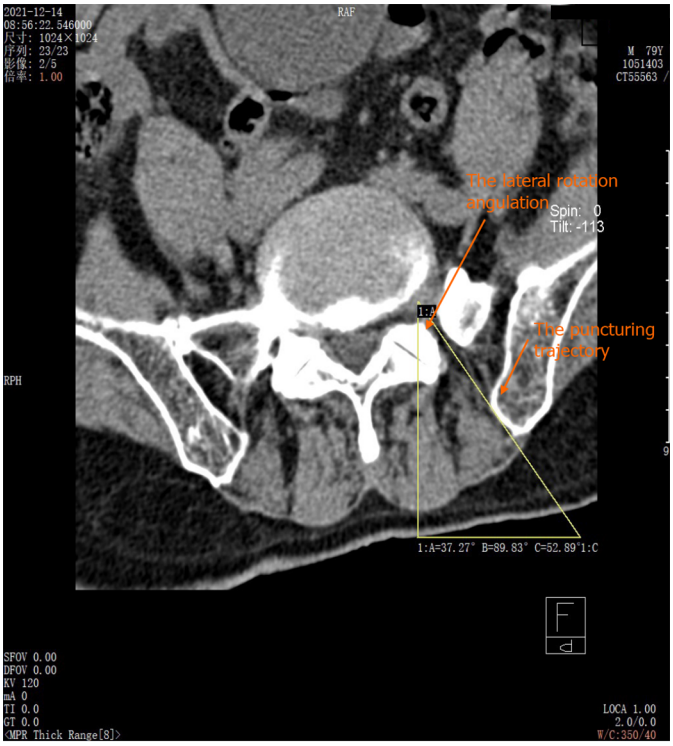
The primary outcomes included the number of fluoroscopies during puncturing and the puncture duration (min). The puncture duration was defined as the time taken from setting the operation position to the needle tip reaching the correct target. The secondary outcome was the surgery duration (min), which was defined as the time taken from setting the operation position to suturing. The VAS score during puncturing and the puncture success rate were also evaluated as secondary outcomes. Successful puncturing was defined as the needle tip reaching the correct target; otherwise, the puncture was deemed unsuccessful. The outcomes were recorded during and after the surgeries by a separate researcher.

Sample size

The sample size was set based on the number of fluoroscopies. According to the previous literature, the effect size was set to be 4 and the standard deviation was set to be 4.6, with $\alpha = 0.05$ and beta = 0.1. The sample size was 32 for each group. As no follow-up work was needed in the study, no dropout rate was considered. The sample size was calculated to be 64.

Interventions

CR-PT procedure: MRI or CT was performed before surgery, and the proper lateral and cranial tilt angle of the trajectory was measured (Figure 1). The participant was placed in the prone position, and a cushion was placed under the abdomen to reduce lumbar lordosis. Then, the C-arm was tilted to the predetermined lateral and cranial oblique angulation, and the superior part of the lateral border of the superior articular process (SAP), also known as the shoulder of the SAP, was identified as the target. In some circumstances, some modifications were made to the target selection. In L5/S1 segment cases, if the intervertebral foramina and the SAP were obstructed by the iliac crest, the C-arm was tilted cranially



DOI: 10.12998/wjcc.v11.i16.3802

Figure 1 Proper trajectory angle measured in computed tomography scan. For this far lateral type herniated lumbar disc case, a much smaller lateral tilt angulation of the trajectory was measured in the computed tomography scan beforehand.

and slightly medially until the intervertebral foramina and the SAP could be visualized. The radiopaque marker was then placed on the skin superimposing the target, which was marked, disinfected, and draped. Subsequently, the marked skin and subcutaneous tissues were anesthetized. A needle (17G, 15 cm) was inserted a short distance until it was seated in the subcutaneous tissues overlying the target, and the angle of the needle was adjusted until it was parallel to the X-ray axis. In this instance, the needle hub projected directly over the tip and was aligned with the target, as displayed in Figure 2. The needle was advanced while maintaining a parallel direction to the X-ray axis until contact with the shoulder of the SAP was made. Then, anteroposterior and lateral radiography was performed to confirm the needle placement.

In some cases, the SAP could not be visualized clearly despite setting the C-arm to the predetermined angulation, and mild angulation adjustments were made to allow for proper visualization. This situation occurred when the lateral oblique angle of the C-arm was very large. In such cases, a guiding needle was utilized in addition to the puncturing needle (Figure 3).

First, the radiopaque marker was placed and the skin was prepared for puncture as described above. The guiding needle (20G, 15 cm) was inserted sagittally under X-ray guidance until contact was made with the SAP, and the needle was repositioned and advanced slightly along the lateral border of the SAP. The needle was further advanced slightly to ensure that the needle tip was situated near the ventral margin of the SAP, and the anteroposterior and lateral view was taken to confirm the position (Figure 4). Then, the tip of the guiding needle was set as the puncturing target, and the coaxial technique was performed as described above (Figure 5).

AP-PT procedure

The C-arm was set at the correct alignment to achieve a standard lumbar anteroposterior radiography. This process ensured that the X-ray beam was parallel to the disc and that the endplate was displayed as a straight line. Subsequently, the center longitudinal line of the lumbar spine and an oblique line passing through the shoulder of the SAP were marked. For the L5/S1 Lumbar disc, the oblique line should reach above the peak point of the iliac crest. Then, a longitudinal line parallel and 10-14 cm lateral to the center line was drawn. The intersection of the lateral longitudinal line and the oblique line was defined as the puncture point (Figure 6). After disinfection, draping, and anesthesia, a needle was inserted. During the procedure, anteroposterior and lateral views were taken every 1 cm of needle advancement, confirming that the needle was oriented to the shoulder of the SAP (Figure 7). Slight modifications in direction were performed as necessary. When the needle tip touched the SAP, anteroposterior and lateral radiographs were taken to confirm the needle position.

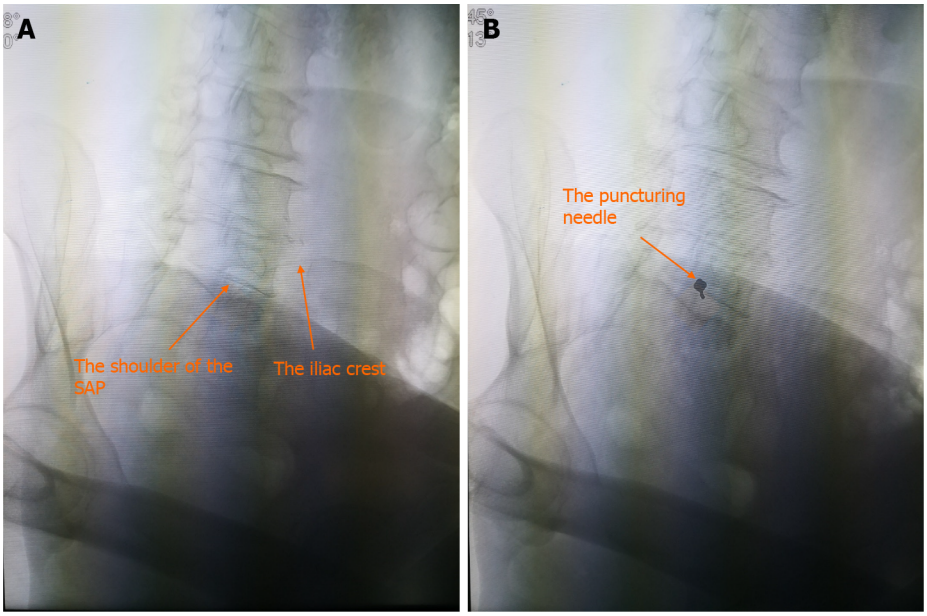


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Figure 2 X-ray films of the coaxial radiography-guided puncture technique. A: For the coaxial radiography-guided puncture technique, the target should be identified first, which is usually the shoulder of the superior articular process; B: The needle was maintained coaxial to the X-ray beam and parallel to the X-ray axis. In this instance, the needle hub projected directly over the tip and aligned with the target, and the needle appeared as a dot instead of a line. SAP: Superior articular process.

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Figure 3 Picture of the coaxial radiography-guided puncture technique with an additional guiding needle. If the superior articular process could not be visualized clearly, a guiding needle was used in addition to the puncturing needle. This usually occurred when the lateral oblique angle of the C-arm was very large.

Statistics

Quantitative variables with a normal distribution are presented as the mean ± SD, while non-normally distributed variables are reported as the median (P25, P75). An independent *t*-test was performed to analyze normally distributed data with homogeneity of variance. A separate variance estimated *t*-test was performed to analyze normally distributed data without homogeneity of variance. The remaining quantitative data were statistically analyzed by the Wilcoxon rank sum test. For qualitative variables, Fisher's exact test and Pearson chi-square test were applied. In this study, $P < 0.05$ was considered statistically significant. SPSS version 26 was utilized for statistical analyses. Moreover, a subgroup analysis of the patients with L5/S1 HLD was performed using the same statistical methodology.

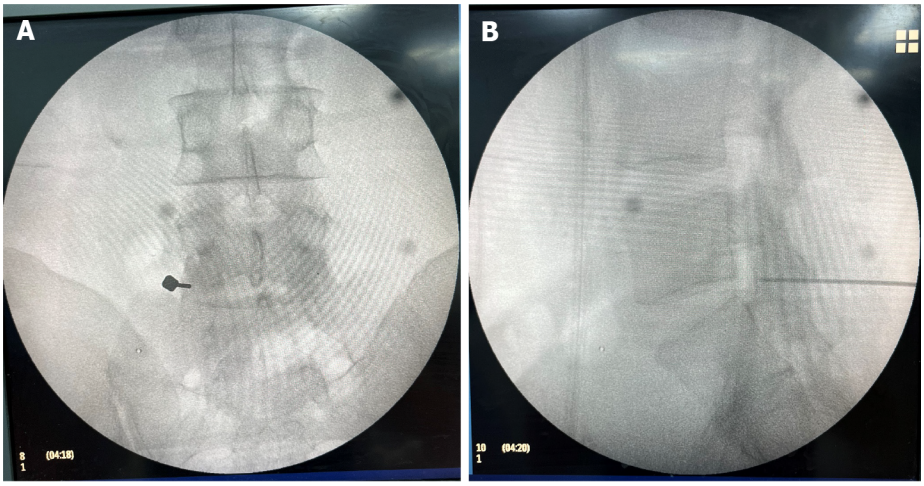

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Figure 4 X-ray films of a successful puncturing of a guiding needle. The anteroposterior and lateral views confirmed the needle tip placement near the ventral margin of the superior articular process.

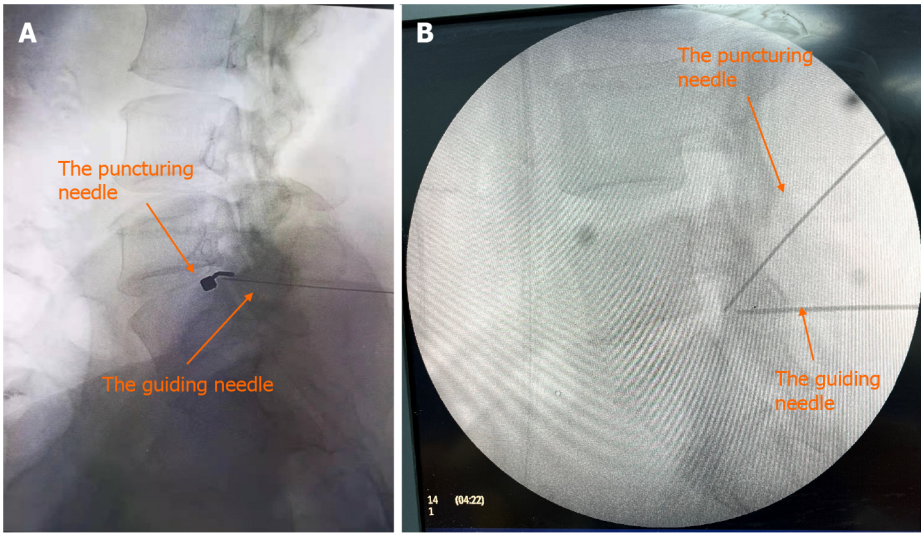

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Figure 5 X-ray films of a successful puncturing with an additional guiding needle. A: The C-arm was set at the coaxial position and puncture was performed under coaxial radiography guidance. In this position, the puncturing needle was shown as a dot rather than a line; B: The lateral view shows that the puncturing needle has reached the tip of the guiding needle, indicating a successful puncture.

RESULTS

In total, 86 participants were evaluated from April 2022 to May 2023, and 65 participants were enrolled in the trial. Among the enrolled participants, 16 were from the Nantong Hospital of Traditional Hospital, and 49 were from the Affiliated Hospital of Xuzhou Medical University. One participant in the AP-PT group dropped out due to AP-PT failure and eventually underwent CR-PT. Therefore, statistical analysis was performed for 64 participants, with 31 participants in the CR-PT group and 33 in the AP-PT group.

The demographic characteristics of the patients showed no statistically significant difference between the two groups, as displayed in Table 1.

The number of fluoroscopies [median (P25, P75)] was 12 (11, 14) in the CR-PT group *vs* 16 (12, 23) in the AP-PT group, while the puncture duration (mean ± SD) was 20.42 ± 5.78 *vs* 25.06 ± 5.46, respectively. All the variables demonstrated statistically significant differences ($P < 0.05$), as displayed in Table 2.

Furthermore, a subgroup analysis of the clinical outcomes was performed on the participants who underwent L5/S1 segment surgery. In total, 15 participants were included in the subgroup analysis, with 7 patients from the CR-PT subgroup and 8 from the AP-PT subgroup. The number of fluoroscopies was 11.56 ± 0.88 *vs* 25.22 ± 5.33, and the puncture duration was 13.89 ± 1.45 *vs* 28.89 ± 3.76, respectively. All the variables demonstrated statistically significant differences ($P < 0.05$), as displayed in Table 3.

Table 1 Demographic data of patients included in the two groups

	CR-PT group (31)	AP-PT group (34)	*P* value
Sex (male:female)	19:12	18:16	0.5
Height (cm)	168.29 ± 7.99	167.53 ± 8.18	0.71
Weight (kg)	66 (62, 75)	69 (60, 80)	0.17
BMI (kg/cm^2)	25.3 (22.63, 28.04)	27.25 (23.19, 33.35)	0.15
Age	55 (41, 65)	58 (38, 66)	0.5
Surgical segment			
L1/L2	0	2	0.57
L2/L3	1	0	
L3/L4	1	3	
L4/L5	20	19	
L5/S1	9	10	
Laterality (left:right)	18:13	12:22	0.07
Pain duration (mo)	6 (1, 24)	6 (2, 24)	0.64

Normally distributed data are presented as the mean ± SD; non-normally distributed data are presented as the median (P25, P75). AP-PT: Radiography-guided puncture technique; CR-PT: Coaxial radiography-guided puncture technique.

Table 2 Clinical outcomes of the two groups

	CR-PT group (31)	AP-PT group (33)	*P* value
Number of fluoroscopies	12 (11, 14)	16 (12, 23)	0.002
Puncture duration	20.42 ± 5.78	25.06 ± 5.46	0.002
Surgery duration	115 (107, 124)	123 (92, 148.5)	0.173
VAS score during puncturing	3 (2, 4)	3 (3, 4)	0.021
Puncture success rate (34 participants included for AP-PT group)	100%	97.06%	1

AP-PT: Radiography-guided puncture technique; CR-PT: Coaxial radiography-guided puncture technique.

Table 3 Clinical outcomes of the two groups in the L5/S1 segment

	CR-PT subgroup (9)	AP-PT subgroup (9)	*P* value
Number of fluoroscopies	11.56 ± 0.88	25.22 ± 5.33	0
Puncture duration	13.89 ± 1.45	28.89 ± 3.76	0
Surgery duration	105 (99.5, 120)	149 (125, 157.5)	0
VAS score during puncturing	2.11 ± 0.93	3.89 ± 0.6	0

AP-PT: Radiography-guided puncture technique; CR-PT: Coaxial radiography-guided puncture technique.

No complications were reported in the trial.

DISCUSSION

This clinical trial was carried out to compare the two puncturing techniques. The aim of the study was to confirm whether CR-PT is a superior approach to percutaneous transforaminal endoscopic lumbar discectomy compared to AP-PT. The number of fluoroscopies during puncturing, puncture duration,

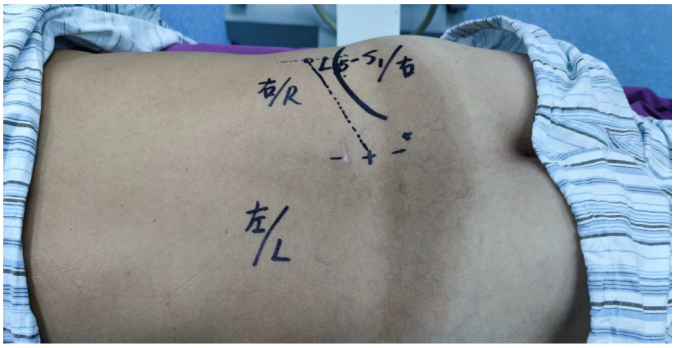

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Figure 6 Picture of puncturing direction in the radiography-guided puncture technique marked in the skin. A lateral longitudinal line parallel to the center longitudinal line was drawn, about 10-14 cm from the center line, and the intersection of the lateral longitudinal line and the oblique line passing through the tip of the superior articular process was chosen as the puncture point.

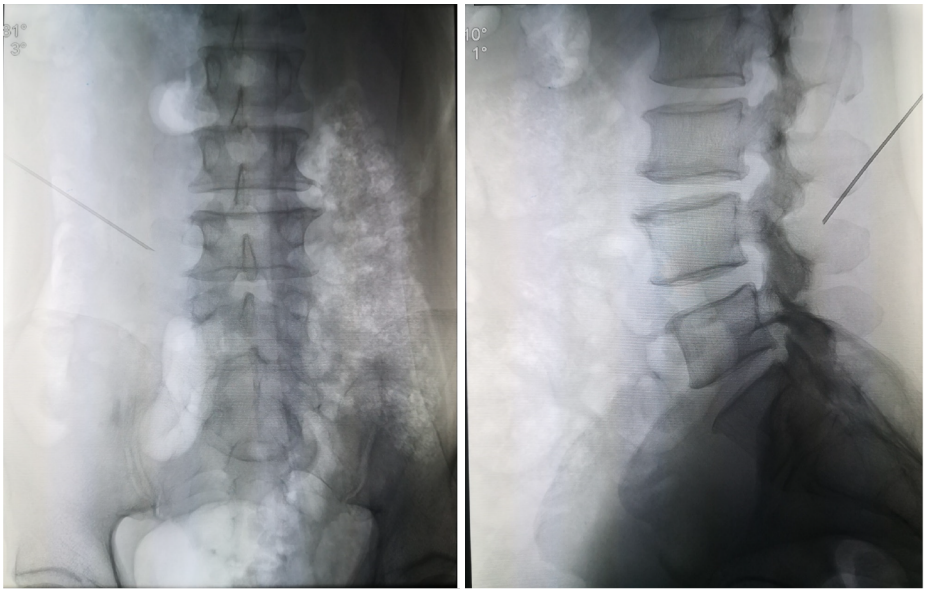

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Figure 7 X-ray films of the radiography-guided puncture technique. The needle should be oriented to the shoulder of the superior articular process under both the anteroposterior and lateral views.

surgery duration, VAS score during puncturing, and puncture success rate were recorded.

One participant with L5/S1 segment HLD dropped out due to an unsuccessful AP-PT procedure. All the clinical outcomes demonstrated superiority with statistical significance favoring the CR-PT group except the surgery duration. Additionally, a subgroup analysis was performed, focusing on L5/S1 segment participants. All the clinical outcomes demonstrated statistically significant superiority in the CR-PT subgroup compared to the AP-PT subgroup. The superiority was more obvious in the subgroup analysis.

The superiority of CR-PT over AP-PT may be attributed to the following points. In the coaxial puncturing technique, the puncturing needle and X-ray beam share a common axis, which is easier to observe on radiography and allows for less needle repositioning. Additionally, as opposed to AP-PT, this novel puncturing technique does not require shifting the C-arm machine between the lateral position and the anteroposterior position repeatedly. The working cannula tilt angulation is crucial for PTELD, as it should be accurate and individualized. For example, a central-type disc herniation requires a larger lateral oblique angulation, whereas a small lateral oblique angulation is warranted in a foraminal type or far lateral type HLD case. Similarly, caudal hernia prolapses require a larger cranial tilt angulation, otherwise minor cranial tilt angulation is necessary. In the coaxial technique, the individualized puncturing angle and the individualized puncturing spot can be predetermined and guaranteed by setting the C-arm angulation beforehand. Hence, the angulation of the working cannula intubation can be optimized, which facilitates subsequent endoscopic surgery. However, for AP-PT, selecting the optimal puncture point and puncturing angulation depends on the surgeon's expertise,

which is much less accurate.

Our research demonstrated a more obvious superiority of CR-PT in HLD of the L5/S1 segment, which may be due to the following reasons. First, L5/S1 segments typically require a smaller lateral rotation angle, allowing easy visualization of the SAP. Therefore no guiding needle is required, which shortens puncturing time. Second, in the coaxial technique, the iliac crest is relatively easily avoided due to the more accurate angulation. Therefore, we believe that CR-PT is far more advantageous in L5/S1 cases.

Other innovative puncturing techniques have been reported for PELD. Zeng *et al*[14] reported a novel targeted puncture technique using a lumbar disc herniation target collimator, indicating superiority over the conventional free-hand injection method. Fan *et al*[23] applied a so-called HELLO system, which consisted of a self-made surface locator and a puncture-assisted device to guide the percutaneous puncturing process. The report also indicated improved puncturing accuracy and reduced fluoroscopic duration, as well as preoperative location duration. Moreover, C-arm navigation and 3D printing technologies have been applied in multiple studies. Qin *et al*[13] reported that using the C-arm navigation system could dramatically reduce the number of fluoroscopies and puncture attempts compared with the conventional method. Erken *et al*[24] reported the use of a collimation device to facilitate puncturing in PELD. However, all these methods require additional equipment and could increase the cost of the procedure. In contrast, our method requires no additional device and provides a more convenient and practical approach.

Nevertheless, the limitations of this study should be acknowledged. The sample size was small. Thus, further clinical research with a larger sample size is required. Second, the puncturing technique relies on personal expertise and surgeons have their personal preferences, and our result can only provide an alternative reference.

CONCLUSION

CR-PT in PTELD is a novel and effective technique. It enables individualized cranial and lateral tilt angulation during puncturing, accurate identification of the puncturing location, fewer needle direction adjustments, and no need for repeated C-arm angulation shifting. This technique significantly improves puncture accuracy, shortens puncture time and operation time, and reduces pain during puncturing. Therefore, CR-PT could be an advisable option in PTELD.

ARTICLE HIGHLIGHTS

Research background

As a conventional puncture technique in endoscopic discectomy, anterior-posterior and lateral radiography-guided puncture technique (AP-PT) has limitations, such as repeated intermittent radiographs and inaccurate needle angulation. Although some innovative puncturing techniques have been reported, most of them require additional equipment. This paper describes an innovative coaxial radiography-guided puncture technique (CR-PT) and verifies its feasibility and superiority compared to the traditional AP-PT technique.

Research motivation

The coaxial radiography-guided puncture technique (CR-PT) is commonly applied in conventional procedures; however, we applied this technique in endoscopic lumbar discectomies. For some difficult cases, a guiding needle was used and the tip of the guiding needle was set as the target, which subsequently enabled the coaxial puncture technique to be performed.

Research objectives

The aim of the research was to verify the superiority of CR-PT over AP-PT in endoscopic lumbar discectomies.

Research methods

This is an RCT trial. The participants were assigned to either a CR-PT group or an AP-PT group. The number of fluoroscopies during puncturing, puncture duration (min), surgery duration (min), VAS score during puncturing, and puncture success rate were recorded and compared.

Research results

The trial verified the superiority of CR-PT over AP-PT in terms of puncture duration, puncture accuracy, and VAS score during puncturing.

Research conclusions

The CR-PT technique is a novel and effective technique. This technique significantly improves puncture accuracy and shortens puncture duration. Therefore, CR-PT could be an advisable option in endoscopic discectomy.

Research perspectives

This study lays a foundation for further research on the CR-PT technique in trans-interlaminar endoscopic lumbar discectomies and endoscopic cervical discectomies.

FOOTNOTES

Author contributions: Yuan HJ, Chen LP, and Xu H designed the research study; Yuan HJ and Chen LP performed the procedure; Hu PP, Fu HB, and Xu H recorded the outcomes; Wen BS, Deng H, and Lu Z did the statistical work, Wen BS, Yan LJ, and Yuan HJ wrote the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: This study complied with The Declaration of Helsinki, and the trial was approved by the Institutional Ethics Committee of Clinical Research of Nantong Hospital of Traditional Chinese Medicine (Approval No. 20221230-5).

Clinical trial registration statement: The clinical trial was registered on the Chinese Clinical Trial Registry website (Registration number ChiCTR2200058894).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare no potential conflicting interests related to this paper.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

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S-Editor: Liu JH
L-Editor: Wang TQ
P-Editor: Wu RR

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3813-3821

DOI: 10.12998/wjcc.v11.i16.3813

ISSN 2307-8960 (online)

CASE REPORT

Blood typing and transfusion therapy in a patient with A2 subtype acute myeloid leukemia M2: A case report

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Specialty type: Hematology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Adepoju VA, Nigeria; Sultana N, Bangladesh

Received: October 10, 2022
Peer-review started: October 10, 2022
First decision: January 12, 2023
Revised: February 25, 2023
Accepted: April 20, 2023
Article in press: April 20, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Acute myeloid leukemia (AML) is one of the most common types of leukemia in adults. However, AML is relatively rare in the population overall, accounting for only about 1 percent of all cancers. Treatment for AML can be very effective for some patients, yet it leaves others with serious and even life-threatening side effects. Chemotherapy is still the primary treatment for most AML, but over time, leukemia cells become resistant to chemotherapy drugs. In addition, stem cell transplantation, targeted therapy, and immunotherapy are currently available. At the same time, with the progression of the disease, the patient may have corresponding complications, such as coagulation dysfunction, anemia, granulocytopenia, and repeated infection, so transfusion supportive therapy will be involved in the overall treatment regime. To date, few articles have reported on blood transfusion treatment options for patients with ABO subtypes AML-M2. Blood transfusion therapy is an important supportive treatment for AML-M2, and accurate determination of patients' blood type is one of the most important steps in the treatment process. In this study, we explored blood typing and supportive treatment strategies for a patient with A2 subtype AML-M2 to provide the basis for treatment for all patients.

CASE SUMMARY

In order to determine the blood type of the patient, serological and molecular biological methods were used for reference tests, and the genetic background was studied to determine the patient's final blood type and select the appropriate blood products for infusion treatment. According to the results obtained by serological and molecular biological methods, the blood type of the patient was A2 subtype; the genotype was A02/001; the irregular antibody screening was

negative, and anti-A1 was found in the plasma. According to the overall treatment plan, active anti-infection, elevated cells, component blood transfusion support, and other rescue and supportive treatments were given, and the patient successfully passed the stage of myelosuppression after chemotherapy. Re-examination of bone marrow smears showed that AL was in complete remission of bone marrow signs, and minimal residual leukemia lesions suggested no cells with obvious abnormal immunophenotype (residual leukemia cells < 10^{-4}).

CONCLUSION

The infusion of patients with A2 subtype AML-M2 with A irradiated platelets and O washing red blood cells can meet the needs of clinical treatment.

Key Words: ABO blood-group system; A2 subtypes; Blood grouping and crossmatching; Blood transfusion; Acute myeloid leukemia; Atypical blood transfusion

Core Tip: There has always been a debate on the large-scale transfusion therapy for acute myeloid leukemia (AML). This study provides strong and favorable evidence for the clinical treatment of blood transfusion. There are few specific reports in the literature on the treatment of blood transfusion for patients with AML-M2 blood type A2, and this study provides a protocol and precedent for the treatment of blood transfusion for patients with rare subtype AML. The study can provide clinical reference data for supporting transfusion therapy in patients with clinically rare blood type leukemia.

Citation: Kuang XC, Zhang SH, Cen YJ, Zhang JB, Liu YS. Blood typing and transfusion therapy in a patient with A2 subtype acute myeloid leukemia M2: A case report. *World J Clin Cases* 2023; 11(16): 3813-3821
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3813.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3813

INTRODUCTION

Acute myeloid leukemia (AML) is a malignant clone of myeloid progenitor cells in the hematopoietic system, mainly treated by chemotherapy and hematopoietic stem cell transplantation[1]. Anemia and thrombocytopenia are the main clinical manifestations of patients with AML, and blood transfusion is the most important treatment strategy for anemia and thrombocytopenia caused by chemotherapy in AML. However, blood transfusions have been associated with immunosuppression and can bring a large number of foreign antigens to the patient. It has been repeatedly reported that 55% of patients with type A, B, or AB blood with myeloid malignancies have a proportion of red cells with decreased expression of A or B antigens[2,3].

It has also been noted that AML restricted blood transfusion treatment could more effectively reduce the risk of infection and improve the prognosis of patients than free blood transfusion treatment[4]. As a result, when clinicians treat patients with type AML-M2, it is not enough to simply improve the hemoglobin content of patients, but rather, it is vital that patients have longer remission, and that treatment reduces the chance of infection, strengthens organ protection, relieves pain, and ultimately, the patient has improved quality of life. It is well known that subtype A is the most common human ABO blood type, and the main subtypes A1 and A2 account for 99.9% of all blood types. Because the A antigen is only present on the red blood cells of the A2 subtype, there is a small number of anti-antibodies in the serum, apart from the anti-B antibody. In practice, when the traditional serological method is used to identify the A2 subtype, subtype O can easily be mistaken for subtype A2. After the infusion of abnormal blood products, the infusion is invalid in mild cases. However, severe hemolytic transfusion reaction may occur, leading to shock, disseminated intravascular coagulation, and acute renal failure. Subtype A, A1, and A2 are the most common, while A1 and A antigens have been found on A1 cells, but only A antigens on A2 cells. A2 and A2B individuals account for less than 1% of A and AB individuals because of the fewer A2 sites and lower glycosyltransferase activity compared to A1. Among these sites, 1%-8% of A2 and 22%-35% of A2B have resistance to A1. Therefore, clinically, blood typing of patients with AML is particularly important during extensive long-term transfusion support therapy. The cases of weak ABO antigen frequently appear in male AML patients. Further, the DNA methylation level of the *ABO* gene promoter in patients with weak ABO antigens are significantly higher than that in patients with normal ABO antigens[5].

Over recent years, the hematology of patients in need of long-term transfusions has been extensively studied. New genomics approaches provide the ability to routinely select donor units that match the receptor antigen for the first time, rather than ABO/Rh blood group system (RHD), thus helping to reduce non-hemolytic fever, allergic reactions, and occurrence of hemolytic reaction complications[6]. So far, the main techniques used in laboratory identification of ABO subtypes have been polymerase chain reaction sequence-specific primer (PCR-SSP)[7], gene sequencing[8], and similar. However, there are few large-scale laboratories in China for such typing, and the routine serological antibody method is still predominantly used[6]. Accordingly, the existing methods must be used to accurately identify blood type and to more precisely guide appropriately patient treatment. To date, few articles have reported on blood transfusion treatment options for patients with ABO subtypes AML-M2. In this study, we explored blood typing and supportive treatment strategies for a patient with A2 subtype AML-M2.

CASE PRESENTATION

Chief complaints

A 44-year-old male patient with a 2-mo course of disease of was treated at the Department of Hematology of the Sichuan Academy of Medical Sciences in the Eastern Branch of Sichuan Provincial People's Hospital (Sichuan Institute of Hematology). He came to our hospital in August 2019 due to systemic fatigue and abdominal distension without an obvious cause.

History of present illness

The patient suffered from weight loss and high skin temperature but was not excessively sweating. He had pale conjunctiva, no yellow sclera, no bilateral pupil constriction, and large and round pupils that were sensitive to light reflection. His superficial lymph nodes were non-palpable and enlarged. No rales were detected in the lungs. The patient had arrhythmias, with 132 beats/min, and no murmurs. He was ABO positive and the negative stereotypes of the patient were not related to the disease.

History of past illness

He had no history of prior treatment or chemotherapy.

Personal and family history

The patient had no family history of genetic diseases.

Physical examination

A physical examination showed a temperature of 37°C, pulse of 132 beats/min, a respiratory rate of 20 breaths/min, and blood pressure of 91/58 mmHg.

Laboratory examinations

The laboratory blood test results indicated the following: White blood cells: 13.75 × 10^9/L [reference range: (3.50–9.50) × 10^9/L], neutrophils: 4.54 × 10^9/L, monocytes: 7.01 × 10^9/L [reference range: (0.10–0.60) × 10^9/L], lymphocytes: 1.38 × 10^9/L, red blood cell count: 2.71 × 10^{12}/L [reference range: (4.30–5.80) × 10^{12}/L], hemoglobin: 96 g/L (reference range: 130–175 g/L), platelet count: 17 × 10^9/L [reference range: (85–303) × 10^9/L], reticulocyte percentage: 2.84% (reference range: 0.67%-1.92%), mirror inspection: primitive + naive cells: 76%, Auer bodies present. Biochemical results indicated the following: Liver function: Blood sugar: 6.31 mmol/L (reference range: 3.90–6.10 mmol/L), alanine aminotransferase 59 U/L (reference range: 9–50 U/L), total albumin: 68.2 g/L, albumin: 39.7 g/L, lactate dehydrogenase: 1629 U/L (reference range: 120–250 U/L), renal function and electrolytes: Normal. Immune results indicated the following: Hepatitis C virus IgG antibody: Positive (consider AML-M2) (reference range: Negative); the results of flow cytometry showed that the leukemia was a partially mature type, and the leukocyte differentiation antigens, CD34, CD117, CD13, CD33, and myeloperoxidase were positive, while CD10, CD19, CD7, CD20, and CD14 were negative; karyotype analysis indicated the following: 46, XY, del(9)(q22)[5]/46, XY[9], the fusion gene was normal. Comprehensive clinical manifestations and laboratory findings were diagnosed as acute M2 Leukemia.

Imaging examinations

Imaging was not included in this case.

Instruments and reagents

The following experimental instruments were used: ORTHOVISION Max automatic blood group analyzer, Orsondor Medical Equipment Trading (China) Co., Ltd., Shanghai, China; Microlab STAR Line automatic blood group analyzer, Changchun Boxun Biotechnology Co., Ltd., Changchun, China; SLAN-96P Real-time fluorescent quantitative PCR, Shanghai Hongshi Medical Technology Co., Ltd., Shanghai, China; and American Bio-Rad 3130 gene sequencer, Bó Lè Life Medical Products (Shanghai)

Co., Ltd., Shanghai, China.

The following experimental reagents were used: ORTHO ABO positive and negative typing and RhD blood typing reagent card (column agglutination method) (lot number: ABR207J), Orsendo Medical Equipment Trading (China) Co., Ltd., Shanghai, China; Changchun Boxun ABO, RhD blood type testing microcolumn card: (Lot No.: 20200904), ABO blood group anti-typing reagent: Changchun Boxun (Lot No.: 2017040201); Changchun Boxun Irregular Antibody Screening Cells (Lot No.: 20201001); Changchun Boxun Biotechnology Co., Ltd., Changchun, China; ALBA Company RhD (IgM) blood typing reagent (monoclonal antibody) (batch number: v177217), British Alba Biotechnology Co., Ltd.; Beijing Jinhao anti-A, anti-B reagent (batch number: 2016083003), Beijing Jinhao Pharmaceutical Co., Ltd. Company, Beijing, China; and Human anti-A and anti-B serums were made by our laboratory.

ABO blood typing and irregular antibody screening

ABO blood typing: A 2 mL of whole venous blood, with EDTA-K2 for anticoagulation, was taken from patient's wife, parents, and a daughter; 1000 g were centrifuged for 5 min to do a serological pedigree investigation. ABO blood group was identified by the gel microcolumn method, an immunological method for the agglutination of erythrocyte antigen and corresponding antibody in the gel microcolumn medium. After adding reagents and specimens, the results were directly observed by the naked eye or analyzed by blood group meter after centrifugation with special centrifuge or card blood matching system. This method has standardized operation and quantitative sample to ensure the accuracy of the results. Two kinds of ABO blood types were tested by Changchun and Johnson according to the reagents' instructions, and the Jinhao blood typing reagent was used to test positive and negative ABO blood types.

Irregular antibody screening

Irregular antibody, also known as accidental antibody, refers to the anti-A and anti-B antibodies of other blood groups in the serum. Irregular antibodies in other blood group systems can lead to transfusion reactions. Mild cases can cause chills and fever, which can affect the therapeutic effect of the treatment. In severe cases, the incoherent red blood cells will be destroyed, or their life will be shortened, resulting in hemolytic transfusion reactions and endangering the patient's life. Therefore, irregular antibody detection is necessary. A variety of erythrocyte antigens present on screening cells are used to react with the tested serum. If there is agglutination, there is irregular antibody in the serum. Changchun Boxin and Johnson reagent screening was used for irregular antibody screening.

Anti-H test

A test tube was used to detect the surface H red blood cell membrane.

Test of salivary, blood type and substance and absorption and release

The patient's saliva was collected and tested according to the National Clinical Laboratory Procedures [10], and the plasma and red blood cells of the patient were also absorbed and released according to the National Clinical Laboratory Procedures[10].

Options of blood transfusion

As there is still no unified standard for blood transfusion strategies for ABO subtypes in China, the principle of homotypic or compatible infusion is usually followed. According to the relevant provisions of Technical Specifications for Clinical Transfusion and combined with the characteristics of patients with subtype A AML, HB < 60 g/L was injected into suspended red blood cells, PLT < 20 × 10^9/L was injected into platelets. The process was completed while avoiding the infusion of red blood cell antigens corresponding to the antibodies in the plasma of the recipient and red blood cell antibodies corresponding to the antigens of the red blood cell, thus minimizing the input of the antigens of the abnormal red blood cells to prevent the production of alloantibodies due to the immune reaction. Considering the difficulty in obtaining type A2 blood, the patient was given an infusion of type O washed of red blood cells, and the monitoring during transfusion was strengthened to actively prevent the occurrence of adverse reactions. During the course of the disease, the patient received a total of 32 blood transfusions, including 16 (34 U) infusions of type O washed of red blood cells and 16 (16 U) infusions of type A platelets. The experimental data and clinical manifestations after blood transfusion suggested that the expected therapeutic effect of blood transfusion was achieved, and adverse blood transfusion reactions such as chills and fever after blood transfusion were not likely to occur. In the later treatment, the blood group serological test results were compared with those before transfusion, and anti-A1 was not detected. After the blood transfusion, the patient's hemoglobin was maintained at about 90 g/L, and platelet increased to more than 50 × 10^9/L.

The patient's blood transfusion process was smooth, with no rash, fever, lumbago, soy-colored urination, chills or other symptoms. After the infusion, the patient's fatigue, soft limbs, tired and tightness of the heart were significantly relieved, the complexion and mucosa were rosy, the hemoglobin was significantly increased, monitoring showed no significant increase in the reexamination of the reticulata, bilirubin was normal, urochologen was negative, and the lactate dehydrogenase did

not decrease.

ABO blood group identification is extremely important in clinical transfusion practice. Blood group identification errors lead to incorrect transfusion of blood products and often serious transfusion reactions. Therefore, in the case of inconsistency between positive and negative serotypes, it is suggested to further improve the detection method and recommend the supplementation of molecular biological methods to avoid blood group identification errors as often as possible, to ensure the safety of transfusion.

ABO gene amplification and sequencing

For exons 6, 7 of ABO genes, partial 5 and 6 introns were amplified and sequenced[11]. First, DNA was extracted from the samples (DNA concentration between 30–50 ng/mL with A260/A280 values ranging from 1.8 to 2.0). The PCR instrument was amplified, and the amplified products were purified and sequenced according to the instructions of the kit.

Cross-matching test

Since a low titer anti-A1 was found in the patient, O washing red blood cells were used for cross-matching test.

Results

The results of the ABO blood typing serological test showed that the ABO of the patient was not consistent, the erythrocyte and anti-A, anti-AB were agglutinated, the plasma and A1 erythrocyte were weakly agglutinated, and the B cells were agglutinated. The ABO blood type and anti-H results of the patient's parents, wife, and daughter were normal (Table 1). Two reagent irregular antibody screening for antigen spectra response in three cells was negative (Table 2).

Test of salivary, blood type and substance and absorption and release of the patient

The results showed secretory substances A in the patient's saliva substance (Table 3).

ABO gene test results of the patient

The results of the ABO testing indicated that the individual was A 02/O01 genotype. In sequencing ABO exons 6 and 7, we found that the changes were single base substitution (C/T) at 467 and C deletion at 1061 (467C>T, 1061del C).

FINAL DIAGNOSIS

Acute myeloid leukemia M2.

TREATMENT

In addition to conventional chemotherapy, O-type washed red blood cells and isotype irradiated platelets were used as adjuvant therapy.

After admission, the pathological *in vitro* antitumor drug sensitivity assaybioluminescence assay was conducted; after which, the daunorubicin combined with cytarabine to induce remission for AML (DA) regimen chemotherapy (daunorubicin 100mg qd d1-d3, cytarabine 200mg qd d1-d7) was started, simultaneously with the symptomatic treatments such as esomeprazole gastric, liver, and heart protection, hydration, and alkalization.

On September 9, 2019, the bone marrow morphology was reexamined, revealing complete remission. On September 12, 2019, lumbar puncture and intrasheath injection were performed, and cerebrospinal fluid flow indicated no abnormality. The patient had long myelosuppression, heavy infection, and difficulty in blood transfusion after the previous chemotherapy, so the reduction of dosage was given in this consolidation chemotherapy regimen. CD14 was not expressed, and the patient was treated with cytarabine 1g q12h d1, d3, and d5 on September 13, 2019. After two chemotherapy treatments, the patient developed grade IV myelosuppression, granulocytopenia, recurrent high fever, severe lung infection, and cardiac insufficiency. After active treatment, the patient's condition gradually improved and was discharged with medication.

OUTCOME AND FOLLOW-UP

Supportive care brought the patient's condition into remission. The patient's condition was stable throughout the maintenance treatment period, which provided a basic reference for follow-up stem cell

Table 1 ABO blood group serological test results of the patient and his family members

		Blood typing (column coagulation)		Blood typing (test tube)		Blood typing of father	Blood typing of mother	Blood typing of wife	Blood typing of daughter
		Johnson Biological	Changchun Boxun	At 4℃	At normal temperature				
Positive typing	Anti-A	2+	1+	2+	1+	4+	0	4+	4+
	Anti-B	0	0	0	0	0	4+	4+	4+
	Anti-AB	3+	2+	2+	1+	4+	4+	4+	4+
Negative typing	Anti-H	3+	3+	3+	3+	0	0	0	0
	Ac	2+	1+	1+	1+	0	4+	0	0
	Bc	4+	4+	4+	4+	4+	0	4+	4+
	Oc	0	0	0	0	0	0	0	0
	Self-control	/	/	0	0	0	0	0	0
Blood typing test results		A_2	A_2	A_2	A_2	A	B	A	A

0: Negative; 1+: Most of the agglutinated red blood cells remained in the lower part of the column, where some red blood cells were visible; 2+: The agglutinated red blood cells were distributed throughout the column, and a small number of cells were visible at the bottom of the column; 3+: Most of the red blood cells that agglutinate remained in the upper part of the glass column; 4+: Red blood cells agglutinated above the column and formed a ring band.

transplantation.

DISCUSSION

There are currently few international reports on ABO subtype patients with blood diseases. It is generally accepted that the phenomenon of ABO antigen weakening occurs occasionally in patients with leukemia, which is likely to lead to inconsistent positive and negative stereotypes in blood group identification. It is undoubtedly the best choice for blood donors of ABO subtype patients, but it is difficult to do in practice. When considering transfusion treatment for ABO subtype leukemia patients, we should avoid importing red blood cells containing red blood cell antigens corresponding to antibodies in the plasma and plasma containing antibodies corresponding to red blood cell group antigens and choose type O washing red blood cells and normal plasma corresponding to subtype, cryoprecipitate and platelets for cross matching[12,13]. This case report illustrated that the blood typing of patients with subtype A AML should follow the principle that positive and negative typing results should be consistent, and the specimens should be tested for molecular biology if they are not. Patients for whom it is difficult to obtain type ABO blood type and need blood transfusion treatment should be strictly treated according to the blood transfusion regulations to ensure efficacy and avoid adverse reactions. However, few articles report on blood transfusion treatment options for patients with ABO subtypes AML-M2. As for treatment strategies for patients, it is necessary to ensure that before deciding on the treatment, the blood type of the patient is determined to exclude any correlation with the disease or chemotherapy that could reduce the content of antibodies in the blood. If a patient has anti-A1 with A2 AML-M2, he or she should not be treated with regular homotypic infusion, as the infusion of the same type of red blood cell suspension or washing of red blood cells in the presence of anti-A1 antibodies in the patient's body can only aggravate the patient's condition. Consequently, it is very challenging to achieve the routine infusion for this subtype. If the symptoms are mild, a patient might also experience fever and chills, and in severe cases, this may lead to hemolytic transfusion reactions, or could lead to death.

Presently, there are 39 blood type systems reported by International Blood Transfusion Association [14]; among these, ABO are of great significance in the field of genetic research, clinical blood transfusion, and transplant immunity. The most important subtypes of the ABO blood type system are the A1 and A2 subtypes, which do not belong to any specific blood type. The identification of subtypes of ABO blood type in clinical laboratories in China is still mainly based on the traditional serological methods, considering such an approach is economical, fast, and easy to standardize. However, the agglutination intensity of antigens and antibodies tends to change in different subtypes, easily leading

Table 2 Experimental results of irregular antibody test in the patient

Serial number		O_I	O_{II}	O_{III}
Rh-hr	D	+	+	+
	C	+	-	+
	E	-	+	+
	c	-	+	+
	e	+	-	+
Kidd	J k^a	+	-	+
	J k^b	+	+	+
MNS	M	-	+	-
	N	+	+	+
	S	-	-	-
	s	+	+	+
Duffy	F y^a	+	+	+
	F y^b	-	-	+
Kell	K	-	-	-
	k	+	+	+
Lewis	L e^a	+	-	-
	L e^b	-	+	+
P	P_1	-	+	-
Test results (Johnson & Johnson)		0	0	0
Test results (Boxun)		0	0	0

The antigens of the Duffy blood group are named after the last two letters of Duffy: Fy, and there are two main antigens: Fy^a and Fy^b; Le^a and Le^b are two of the six antigens in the Lewis blood group system.

Table 3 Results of the patient's salivary, blood type and substance and absorption test and release of the patient

	Ac	Bc	Oc	Results
Red blood cells + human-derived plasma	1+	0	0	A
Plasma + standard ABO cells	0.5+	3+	0	A
Saliva of patients	0	3+	0	A

Ac: A cells, Bc: B cells, Oc: O cells.

to missed tests or false identification. The perfect matching of patient and donor blood type is achieved by genotyping, which makes up for the standard that traditional serology cannot reach, but it is difficult to popularize on a large scale due to high cost and technical issues. Although this method increases the patient's expenditure to a certain extent, it has many advantages for the patients' long-term prognosis.

The use of serological methods to identify ABO subtypes should be based on the agglutination intensity between red blood cells and anti-A, anti-A1, anti-B, anti-AB, and anti-H, the presence of anti-A1 in plasma and the A, B, and H substances in the saliva of secreted human[15]. In our practical clinical work, subtype blood types are generally found in ABO blood group identification. When the positive and negative stereotyping results are inconsistent, or the agglutination intensity is weak, methods other than routine tests should be carried out for identification, such as anti-H, anti-A1, anti-A, and anti-B serums that are increased in positive stereotyping; increase O cells, A1 cells, A2 cells, absorption and release tests, and saliva blood group substances detection[16]. Accurate identification of blood type is an important prerequisite for blood transfusion therapy for patients with AML-M2. Based on the correct blood group and the patient's own body antibodies, the homotypic transfusion of suspended red blood cells or washing of red blood cells can be excluded, and the best scheme selected. In the present study,

the transfusion plan for the patient with A2 subtype (M2) included infusion of O-type scrubber red blood cells and irradiated platelets of the same blood type (A-type), which achieved satisfactory symptom relief effect.

The main treatment for patients with A2 subtypes AML-M2 is still chemotherapy, whose main disadvantages are long duration and serious side effects. Blood transfusion is the main treatment for addressing anemia caused by chemotherapy and an important measure for prolonging the patient's life. Hence, ABO blood typing is of crucial importance. In this study, we selected O washing of red blood cells as the transfusion red blood cells of patients to avoid the existence of antibodies corresponding to red blood cell antigens and antibodies corresponding to red blood cell blood group antigens in plasma. We selected homo-irradiated platelets for transfusion to prevent the occurrence of incompatibilities between antibodies in plasma or ABO antigen on platelets and the recipient.

The pre-transfusion test of patients with A2 subtype AML-M2 should follow the principle that the positive and negative results of blood typing must be the same, and the different samples should be tested by molecular biology. For patients with difficult ABO blood type setting and in need of blood transfusion treatment, the treatment should be carried out strictly according to the relevant regulations of blood transfusion to ensure the curative effect and avoid adverse reactions. Consequently, when making a clinical blood transfusion plan, it is necessary to consider all kinds of blood type systems, diseases, physical quality, blood safety problems, and similar. In any possible case, the treatment should be local to improve the future treatment plan[17].

CONCLUSION

The infusion of patients with A2 subtype AML-M2 with A irradiated platelets and O washing red blood cells can meet the needs of clinical treatment. With ABO blood typing, it is necessary to uphold the principle of consistency between positive and negative results, while molecular biological methods should also be used to test specimens that do not conform to this principle. For patients who may be affected by the weakening of antigens due to ABO blood diseases and who require blood transfusion before the ABO blood group is determined, the strictest standards for blood transfusion therapy should be adopted to ensure the efficacy of blood transfusion and to avoid the occurrence of accidental antibodies that may affect subsequent blood transfusion therapies. In clinical practice, homotype infusion is ideal, but in clinical practice, it is difficult to meet the homotype transfusion blood products for patients with this subtype. In the case of limited conditions, and to avoid hemolysis reaction, isoantibody production, and heterosexual blood transfusion whenever possible, it is best to transfuse O-type red blood cells or blood products corresponding to the same subtype for cross-matching blood. All of the above treatment presupposes that we can accurately determine the current blood type of the patient, so assessment of the accurate blood type becomes particularly important. Using molecular biological sequencing or PCR-SSP to identify the patients' blood type will gradually become the consensus of clinicians and transfusion doctors. This consensus could lead to safer treatment strategies for ABO subtype leukemia patients.

FOOTNOTES

Author contributions: Kuang XC and Zhang SH designed research; Liu YS performed research; Zhang JB and Liu YS contributed new reagents or analytic tools; Cen YJ analyzed data; Kuang XC and Zhang SH wrote the paper; Kuang XC and Zhang SH have contributed equally to the study.

Informed consent statement: This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by the Ethics Committee, Hematology Department, Sichuan Provincial People's Hospital [Lun Sheng (Research Institute) No. 549, 2021], and all participants provided written informed consent.

Conflict-of-interest statement: 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).

Country/Territory of origin: China

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Wu RR

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3822-3829

DOI: 10.12998/wjcc.v11.i16.3822

ISSN 2307-8960 (online)

CASE REPORT

Valve repair after infective endocarditis secondary to perforation caused by *Streptococcus gordonii*: 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 scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gravina AG, Italy; Karcioglu Ö, Turkey

Received: November 26, 2022
Peer-review started: November 26, 2022
First decision: February 7, 2023
Revised: February 24, 2023
Accepted: April 27, 2023
Article in press: April 27, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

We report a case of infective endocarditis (IE) in a patient with congenital heart valve lesions accompanied by IE, which was diagnosed based on blood culture analysis that revealed the presence of a gram-negative bacterium, *Streptococcus gordonii*.

CASE SUMMARY

The patient had a history of precordial valve disease diagnosed by cardiac ultrasound, as well as a 4-mo history of fever. He was subjected to comprehensive anti-infection and anti-heart failure treatment in the internal medicine department. Further examination revealed sudden dislodgement from and perforation through the aortic valve by the superfluous organisms, as well as occurrence of bacterial emboli dislodgement, which caused bacteremia and infectious shock. He recovered and was discharged from the hospital after surgical and postoperative anti-infection treatments.

CONCLUSION

We review the treatment process and highlight inspirations and reflections from this case; suggest possible future changes in treatment modalities.

Key Words: Bacteremia; Comprehensive medical and surgical treatment; *Streptococcus gordonii*; Infective endocarditis; Case report

Core Tip: Infective endocarditis is caused by pathogenic bacteria that infect the heart *via* the bloodstream. It is most common in heart valves but also in atrioventricular walls, tendons and other structures. Congenital heart disease is common in heart structures near the abnormal intracardiac shunt low-pressure cavities, and serious cases can be accompanied by abscesses, fistulas and other cardiac complications. The fallen flap or leaflet can cause embolism of various organs throughout the body, has a high mortality rate, and there are no specific clinical manifestations. It is very easy to misdiagnose, and missed diagnoses are common. The search for sensitive diagnostic methods and timely treatment are particularly important.

Citation: Qu YF, Yang J, Wang JY, Wei B, Ye XH, Li YX, Han SL. Valve repair after infective endocarditis secondary to perforation caused by *Streptococcus gordonii*: A case report. *World J Clin Cases* 2023; 11(16): 3822-3829
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3822.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3822

INTRODUCTION

Infective endocarditis (IE) is a life-threatening cardiovascular disease with an annual incidence of 1.5/100000-15/100000 and a mortality rate of 20%-25%[1]. The disease is caused by a pathogenic microorganism that directly infects heart valves, the endocardium of the ventricular wall or the endocardium of the adjacent aorta *via* the bloodstream, often leading to superfluous organisms. Subacute IE is characterized by an insidious and slow onset, with a long course that usually lasts between 6 wk and 3 mo[2]. These patients mostly experience cardiac problems. Due to the insidious site of infection, notably, IE patients have diverse and nonspecific clinical manifestations, which subsequently lead to missed diagnoses and misdiagnoses that result in serious adverse consequences that threaten quality of life[3]. Therefore, early diagnosis coupled with timely treatment is crucial for management of the disease. In the present study, we report on a case of IE caused by *Streptococcus gordonii*, with fever as the main manifestation, at our hospital.

CASE PRESENTATION

Chief complaints

A 61-year-old man presented at our hospital with intermittent fever and malaise for 4 mo.

History of present illness

Four months before the visit, he had developed a fever (up to 40 C), mostly in the afternoon and at night, accompanied by chills and malaise. Although his body temperature normalized after 3 d of anti-infection treatment *via* self-treatment, the fever reappeared after stopping the treatment. The disease progressively worsened, and his blood pressure decreased and was accompanied by an increased heart rate. The patient was diagnosed with infectious shock and was subsequently transferred to our hospital for further treatment.

History of past illness

The patient was previously in good health.

Personal and family history

He was previously healthy and had no family history of disease.

Physical examination

Physical examination revealed slightly pale skin and mucous membranes, with no enlargement of the jugular vein, but there was enlargement of the cardiac border to the left. There was also evidence of a grade III-IV diastolic murmur in the aortic valve area and peripheral vascular signs (+).

Laboratory examinations

Laboratory test results revealed normal leukocytes and neutrophils, the patient had C-reactive protein and calcitonin levels of 53.1 mg/L and 2.66 ng/mL, respectively, as well as liver and renal function tests that were within normal limits. The Tuberculin purified protein derivative test results were negative. Paired blood cultures (asymmetric limbs, *e.g.*, left upper limb and right lower limb) on 3 consecutive days showed gram-positive cocci. Macrogen next generation sequencing technology showed *Strepto-*

coccus gordonii.

Imaging examinations

Cardiac ultrasonography showed an ejection fraction of 52% and aortic valve leaflet thickening and echogenic enhancement, a moderate regurgitant signal under the aortic valve in diastole, a small amount of regurgitant signal on the left atrial side of the mitral valve in systole, a small amount of regurgitant signal on the right atrial side of the tricuspid valve in systole, an ascending aortic internal diameter of 46 mm, an aortic valve Vmax of 2.2 m/s, an enlarged left atrium, aortic valve calcification with moderate regurgitation, and mild regurgitation of the second and tricuspid valves (Figure 1). The cardiac magnetic resonance imaging results were consistent with dilated cardiomyopathy changes, left heart insufficiency, a significantly reduced systolic function, aortic valve thickening and stenosis, incomplete closure of the mitral valve and tricuspid valve, a small amount of pericardial effusion, pericardial inflammatory changes, and a small amount of bilateral pleural effusion.

Bone marrow aspiration and serum test

Flow cytometry showed an increase in the proportion of granulocytes and nucleated red cells and a mild decrease in the proportion of lymphocytes. The phenotype was not abnormal. Abnormal immunoglobulins and identification of multiple myeloma: Immunofixation electrophoresis (IFE) results showed that there was no “M protein” detected within the serum polyclonal immunoglobulins; there were no kap and lam light chain "M protein" detected in the urine. Serum protein and IFE revealed no significant "M protein", a reduction in albumin levels, and elevated levels of α1 and γ globulins. The serum immunoglobulin (Ig)G, IgA, IgM and kap, as well as lam light chain levels, were normal, but the IgE levels were high. We also found a moderate increase in the level of urine kap light chain and 24-h urine protein levels. Protein electrophoresis revealed no specific band in the urine. No light chain type "M protein" was detected in the urine *via* IFE, This result excluded abnormal immunoglobulinemia and multiple myeloma (Table 1).

FINAL DIAGNOSIS

Infective endocarditis.

TREATMENT

The patient's prolonged unexplained fever, coupled with blood culture and echocardiographic results, made us strongly suspect a subacute infection. The patient’s fever subsided after 9 d of continuous treatment, and his infection index was under control. Consequently, aortic valve replacement was recommended following anti-infection treatment. The patient then developed a preoperative sudden onset of chest and abdominal pain with profuse sweating and an emergency transesophageal ultrasonography was performed. The results are presented in Figure 2. In summary, we found evidence of aortic valve redundancy with perforation, while the emergency CTA results revealed moderate stenosis of the lumen at the beginning of the abdominal trunk. The possibility of bacterial esophageal involvement and visible penetrating ulcers was considered (Figure 3). Consequently, the surgical approach was changed from simple aortic valve replacement to aortic valve replacement surgery and aortic valvuloplasty. The intraoperative examination findings were as follows: Moderate levels of yellowish pericardial fluid were present, there was marked widening of the ascending aorta, marked malformation of the aortic bicuspid valve, leaflet destruction with perforation and massive regurgitation, complete leaflet removal, and compression of the artificial vessel to wrap the ascending aorta, and placement of aortic valve bioprosthesis was performed. The operation was successfully completed. Postoperative pathological analysis revealed fibrous connective tissue hyperplasia with focal glassy and mucinous degeneration, localized fibrin deposition, and evidence of calcified foci in the valve tissue.

OUTCOME AND FOLLOW-UP

The patient received anti-infection treatment for 1 mo after surgery. Reexamination revealed that his liver, kidney and cardiac functions had been restored back to normal.

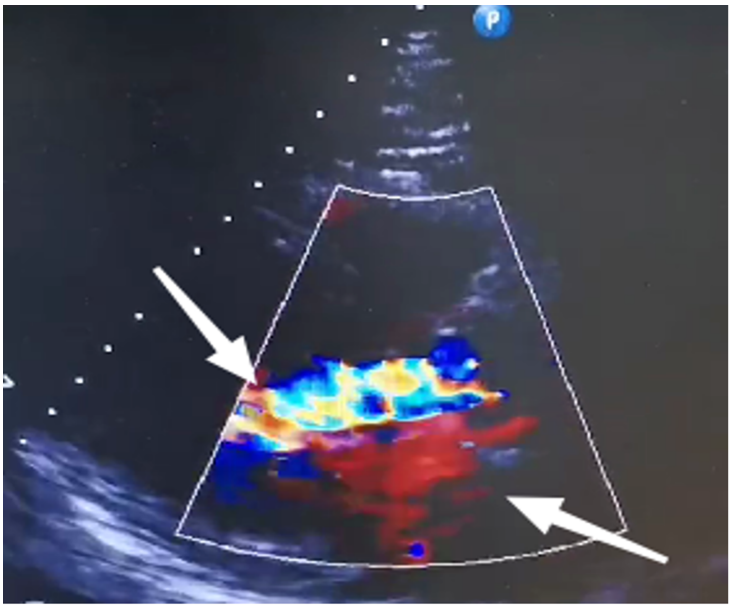
DISCUSSION

In 2016, the American Association for Thoracic Surgery (AATS) published an expert consensus on the

Table 1 Report of abnormal immunoglobulinemia and multiple myeloma identification the results showed no abnormalities

Name	Value	Rang	Unit
IgG	1500	751-1560	mg/dL
IgE	126	0-100	IU/mL
Urine kaP	2.1	< 1.9	mg/dL
Stray lam	38.2	8.3-27.0	mg/L
Lamlight chain	704	313-723	mg/dL
IgA	243	82-453	mg/dL
Urine lam	< 0.5	< 5.0	mg/dL
FLC k/L	0.56	0.13-1.56	mg
IgM	57.5	46-304	mg/dL
24-h urine protein	1900	1000-2000	mg
Stray kap	21.4	6.7-22.4	mg/L
Kaplight chain	1310	629-1350	mg/dL

Ig: Immunoglobulin; FLC: Free light chain.



DOI: 10.12998/wjcc.v11.i16.3822

Figure 1 Bidirectional regurgitation of the aortic valve (shown by the arrows).

surgical management of IE, the most recent guiding document for the management of this condition. The AATS expert consensus indicates that the current DUKE criteria, which are based on the diagnostic criteria proposed in 1994 and have subsequently been modified several times, are the most practical for the diagnosis of IE[4]. The most common clinical IE manifestation is fever, with an insidious onset in subacute cases, and it can be associated with relatively mild toxic symptoms that may range from weeks to months. Although IE is a common cause of unexplained fever, only 18.6%-20.3% of patients present with typical manifestations described in the DUKE criteria, such as skin petechiae, emboli, splenomegaly, and Osler nodules. Approximately 30% of IE patients do not exhibit an obvious heart murmur during the early stages of disease development or during the course of treatment. The doctors who treated the patient in the present study before he came to our hospital thought that the heart murmur could be explained by mitral regurgitation and did not consider the possibility of IE. Notably, they were satisfied with improvement of his clinical symptoms and did not follow up on the disease change, a phenomenon that resulted in a delay of treatment of the disease.

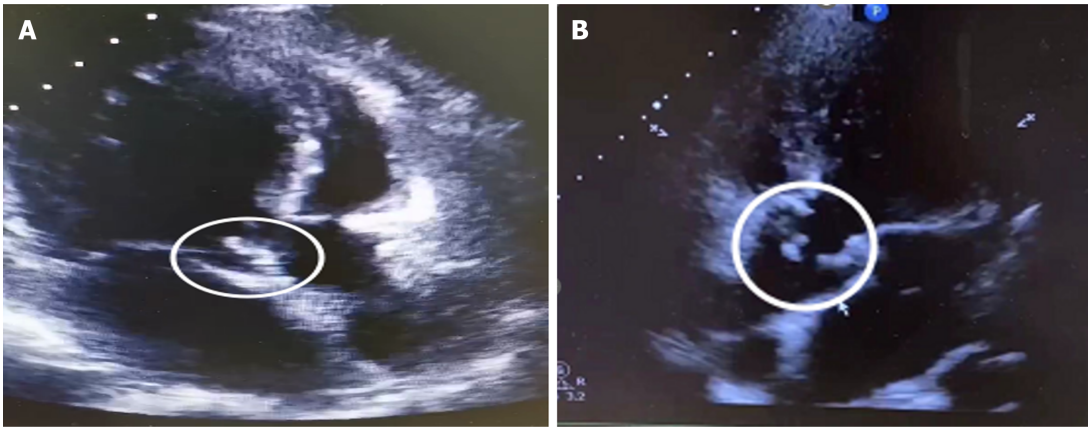


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Figure 2 Aortic valve. A: Aortic valve bulge (shown in circle); B: Aortic valve redundancy detached with perforation (shown in circle).

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Figure 3 Computed tomography angiography examination results. A: moderate stenosis of the lumen at the beginning of the abdominal trunk, with possible bacteriophage involvement; B: Visible penetrating ulcers can be seen.

Bacteremia, caused by pathogenic microorganisms in the blood, is the basis for the development of IE. Blood culture tests have diagnostic value and can help guide the selection of anti-infective drugs. The main pathogens and major routes of infection in IE have changed in recent years. Notably, virulent and drug-resistant staphylococci are the most common organisms and are more likely to occur in elderly patients, as well as in those with nosocomial chronic disease and intracardiac implants. In the present study, the blood culture results suggested that this patient had a *Streptococcus gordonii* infection. This pathogen belongs to the Gram-stain-positive retarded streptococcal group and is a partly anaerobic α-haemolytic streptococcus (VGS). Recent studies have shown that community-acquired autologous valvular endocarditis caused by VGS is also common in IE patients, particularly in developing countries [5], and many of them are caused by *Streptococcus gordonii*. Generally, *Streptococcus gordonii* colonizes the oral cavity and upper respiratory tract and is mainly involved in the composition of dental plaque; it is a conditional pathogen that is usually not pathogenic. In recent years, many cases of *Streptococcus gordonii* infections have been reported in China and abroad, and these cases include cases of sepsis, IE, splenic abscess and septic arthritis. These infections have subsequently been associated with poor oral hygiene, loose teeth, dental surgery and other invasive procedures. The patient in the present study exhibited upper respiratory tract infection symptoms, such as a sore and dry throat, 1 wk before the onset of fever. However, he did not pay attention to these symptoms and experienced overexertion during the same period[6]. It is worth noting that the patient's medical history is imperative to obtain an adequate disease diagnosis.

Echocardiography is a key procedure for confirming an IE diagnosis[7] because it can not only detect superfluous organisms at an early stage but also accurately measure their sizes, thereby facilitating assessment of the disease severity, can be used to assess cardiac function, and can detect cardiac complications, among other factors[8]. However, echocardiography is influenced by subjective factors. In the present case, the initial echocardiography failed to detect superfluous organisms in this patient's heart valve and relaxed our vigilance. We attributed this to the fact that the location and size of the flap

were not easily detectable by the ultrasound beam and because of the physician's inexperience. Transesophageal echocardiography can detect redundant organisms with a diameter of 1-1.5 mm and directly reveal the relationship between the redundant organisms and the valve from the posterior left atrium, achieving a positive detection rate of up to 90%. However, echocardiography is not an ideal detection tool for patients with severe valvular lesions, bulging valves < 2 mm, prolapsed valves, or valves without bulging valves. Based on this, a negative result does not completely exclude IE.

Successful IE treatment depends on the efficient removal of pathogenic microorganisms and surgery has shown promise in successfully eradicating these pathogens in patients[9]. Previous studies have shown that to reduce morbidity and mortality, 20%-50% of patients require cardiac surgery to remove infected tissue and restore valve function[10-12]. In fact, timely surgery is the only hope for saving a patient's life in a case of severe IE. Internal medicine and surgery have their own advantages and shortcomings during IE treatment. Although internal medicine-based treatments can clear most of the microorganisms, it was not efficacious with the patient in this case. The use of anti-infection treatment not only caused an impairment of his cardiac function but also resulted in hemodynamic abnormalities due to the destruction of the intracardiac structures and the emergence of dislodged bacterial emboli. Therefore, internal medicine treatment alone cannot prevent the occurrence of superfluous events, necessitating the application of surgical treatment that corrects congenital valve malformation and restores the heart valve. The patient in the current study was subjected to surgical treatment, which corrected his congenital valve malformation, restored his heart valve function, and improved his heart failure. The patient recovered. Choosing the right time for surgery is the key to effective surgical treatment. It is generally believed that patients with heart failure or hemodynamic disorders, persistent infections, uncontrolled intracardiac local infections, refractory microbial infections, persistent floppy biology > 10 mm with embolism or valve dysfunction should undergo surgery as soon as possible[13]. The echocardiography results of the patient in the present study revealed a floppy biology measuring 1.2 cm × 1.2 cm, with indications for surgery. There are also physicians who believe that surgical intervention is not appropriate in the acute phase due to the possibility of an increased occurrence of complications and high surgical risks and believe in conservative therapy. Notably, controversy still surrounds the timing and indications for surgery, necessitating further research explorations with large randomized controlled clinical trials. Although the application of cardiac surgery for the treatment of active IE is only a century old, recent advances in surgical techniques and perioperative management have made it the cornerstone of IE treatment. Moreover, there is no uniform standard for the indication, timing, and risk assessment of surgery in active IE due to the complexity and variable nature of the disease[14]. Therefore, clinical decision-making in complex cases must be fully individualized, taking into account the patient's demographic characteristics, comorbidities, disease severity, and stage, to determine whether and when to perform surgical intervention and to prepare for foreseeable risks after surgery. There is a need to consult hospitals with multidisciplinary teams specializing in IE in cases of complex IE. Given the large number of IE patients in China, there is a need for concerted efforts across clinical research to standardize IE treatment strategies by focusing on unresolved international issues. Since the population and pathogenic spectrum of IE patients in China are different from those in Europe and the United States, there is a need to develop active IE surgery strategies for the Chinese population through research on treatment and prospects.

IE is a very serious infectious disease which has an increasing incidence every year. The current treatment modalities are: (1) Antibiotic treatment; and (2) Surgical treatment. Antibiotic therapy is administered intravenously for a long period of time, usually 4-6 wk, depending on whether the pathogenic organism is cleared and whether the infection is in the primary or prosthetic valve. Currently, a randomized controlled trial in Denmark investigated the need for a full course of intravenous antibiotic therapy during the treatment of IE[15]. That study randomized patients with IE infected with Staphylococcus, Streptococcus, or Escherichia coli (infection controlled) to two groups, one group received continuing intravenous antibiotic therapy and the other group received oral antibiotic therapy. The results showed that the oral antibiotic treatment group did not have a higher incidence of death, embolism, bacteremia, and unplanned cardiac surgery than the full IV group, and the results were statistically significant. This finding may lead to future changes in the IE treatment guidelines, where the vast majority of patients with largely controlled infections can be transitioned to outpatient oral drug therapy due to the option of combination therapy, which means fewer hospital days and therefore potentially fewer hospital-acquired complications, and this may reduce financial stress for patients. In the next 5-10 years, more randomized clinical trials are planned to be completed to validate the feasibility of combination therapy[16]

CONCLUSION

IE is characterized by an insidious onset, a difficult diagnosis, an aggressive condition and susceptibility to floppy dislodgement events. Therefore, patients with recurrent fever of unknown origin need to be monitored closely.

There is a need for clinicians to raise awareness of IE, especially by performing comprehensive physical examinations and analysis. Clinicians should highly consider IE in patients with unexplained fever, especially those with underlying cardiac disease conditions.

Patients, who are suspected of having IE but who have negative results on echocardiogram should be retested or ultrasounded by a senior ultrasonographer. In cases where transthoracic echocardiogram suggests indirect hints, such as valve prolapse, incomplete closure, or septic lesions, transesophageal echocardiogram should be performed promptly to improve the detection rate.

The disease course in patients with active IE is often complex and variable. Although international guidelines have somewhat standardized the indications and timing of surgery in active IE patients, there is still a need for concerted efforts from an IE-specific multidisciplinary team during decision-making for specific patients. In fact, the discussion on the indication and timing of surgery is a game of risk *vs* expected benefit. Therefore, assessment of the risk of surgery in active IE patients is imperative for effective management of the disease.

ACKNOWLEDGEMENTS

I am grateful to Dr. Jun Yang and Dr. Jun-Yu Wang for inspiring me about the treatment of infective endocarditis and establishing a sound examination idea. I am grateful to Bing Wei, Si-Lu Han, Yi-Xuan Li, and Xing-Hua Ye for organizing the case contents and providing helpful examination results.

FOOTNOTES

Author contributions: Qu YF and Yang J contributed equally to this work; Qu YF, Yang J, Wang JY, and Wei B designed the research study; Han SL, Li YX, and Ye XH provided the medical records and obtained patient consent; All authors have read and approved the final manuscript.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report having 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).

Country/Territory of origin: China

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S-Editor: Cai YX
L-Editor: Filipodia
P-Editor: Cai YX

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3830-3836

DOI: 10.12998/wjcc.v11.i16.3830

ISSN 2307-8960 (online)

CASE REPORT

Prevotella oris-caused meningitis and spinal canal infection: 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 scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Beran RG, Australia; Mora DJ, Brazil;

Received: January 7, 2023
Peer-review started: January 7, 2023
First decision: March 10, 2023
Revised: March 16, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Prevotella oris-induced meningitis and *Prevotella oris*-induced meningitis concomitant with spinal canal infection are extremely rare. To the best of our knowledge, only 1 case of *Prevotella oris*-induced central system infection has been reported. This is the second report on meningitis combined with spinal canal infection due to *Prevotella oris*.

CASE SUMMARY

We report a case of a 9-year-old boy suffering from meningitis and spinal canal infection. The patient presented to the neurosurgery department with lumbosacral pain for 1 mo and headache and vomiting for 1 d. He had been treated with cephalosporin and nonsteroidal anti-inflammatory drugs for fever, otalgia and pharyngalgia in a local hospital 2 mo prior to this admission. During hospitalization, magnetic resonance imaging suggested meningitis and L3-S1 lumbosacral dural sac infection. The cerebrospinal fluid and blood cultures were negative, but the cerebrospinal fluid specimen indicated the presence of *Prevotella oris* by metagenomic next-generation sequencing. Previous cases of *Prevotella oris* infection were retrieved from PubMed to characterize the clinicopathological features and identify the prognostic factors and related antimicrobial treatment of infection due to *Prevotella oris*.

CONCLUSION

This report shed light on the characteristics of *Prevotella oris* infection and highlighted the role of metagenomic next-generation sequencing in pathogen detection.

Key Words: *Prevotella oris*; Meningitis; Spinal canal infection; Metagenomic next-

generation sequencing; Central nervous system infection; Case report

Core Tip: *Prevotella oris* is an anaerobic, Gram-negative, nonpigmented bacterium that rarely results in central nervous system infection. To date, only 1 case has been reported of *Prevotella oris* causing central nervous system infection. We report a patient who suffered from meningitis and spinal canal infection due to *Prevotella oris*. Metagenomic next-generation sequencing identified the pathogen, although the cerebrospinal fluid and blood cultures were negative. Early detection of pathogens is crucial for patient survival and prognosis. We analyzed the characteristics of *Prevotella oris*-induced infection and found that all patients were male; the most commonly used antimicrobial agent was metronidazole.

Citation: Zhang WW, Ai C, Mao CT, Liu DK, Guo Y. *Prevotella oris*-caused meningitis and spinal canal infection: A case report. *World J Clin Cases* 2023; 11(16): 3830-3836
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3830.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3830

INTRODUCTION

Bacterial meningitis and spinal canal infection are not common but can be deadly. They may result in permanent disabilities such as cognitive impairment and learning disabilities, which pose a threat to public health[1,2]. The leading pathogens of bacterial meningitis and spinal canal infection are mainly *Streptococcus pneumoniae* and *Neisseria meningitidis*[3]. *Prevotella oris* is rarely the cause of meningitis and spinal canal infections. There was only one documented case of cervical spinal epidural abscess and meningitis caused by *Prevotella oris* and *Peptostreptococcus micros*[4]. More references are warranted to understand the characteristics of *Prevotella oris*-induced central nervous system (CNS) infection. We presented a case of a 9-year-old male with *Prevotella oris*-induced meningitis and spinal canal infection whose symptoms were relieved significantly after targeted antimicrobial therapy.

CASE PRESENTATION

Chief complaints

A 9-year-old Chinese male presented to the neurosurgery clinic with a complaint of headache and vomiting for 1 d.

History of present illness

The patient had lumbosacral pain for 1 mo prior to this presentation.

History of past illness

Three months prior to admission, the patient presented with fever, otalgia and pharyngalgia and was admitted to a local hospital with a diagnosis of otitis media. He was treated with cephalosporin and nonsteroidal anti-inflammatory drugs (the specific agents and dosages are unknown), and the symptoms were alleviated temporarily. One month later, he had a fever and bilateral muscle pain in the thighs. The pain spread to the whole lumbosacral region. He began to vomit and experienced a progressive headache.

Personal and family history

The patient's personal and family history were not significant.

Physical examination

Physical examination showed that his body temperature was 38 °C, pulse rate was 110 beats per min, respiratory rate was 19 breaths per min and blood pressure was 120/62 mmHg. His consciousness was clear but exhibited despondency. Neurological examinations revealed that his meningeal irritation sign was negative and other functions were normal.

Laboratory examinations

A routine blood examination revealed 12990 leukocytes/μL (79% neutrophils) and procalcitonin was

0.099 ng/mL. The cerebral spinal fluid (CSF) was colorless and clear, and the leukocyte count was 985 cells/μL with 89% polymorphonuclear leukocytes. The CSF glucose was 2.33 mmol/L, the CSF chloride was 114 mmol/L, and the total protein was 962 mg/L. The CSF and blood cultures were negative.

Imaging examinations

Brain magnetic resonance imaging (MRI) revealed hydrocephalus, and there were multiple intracranial meningeal thickening areas and mastoiditis on the left side (Figure 1). In addition, spinal MRI showed that the dura in the thoracolumbosacral spinal canal (mainly in the lumbar segment) was unevenly thickened, and there were scattered small nodular hypointense foci in the spinal canal at the level of the L3-S1 vertebral body, with the largest being approximately 5 mm (Figure 2).

FURTHER DIAGNOSTIC WORK-UP

To investigate the pathogenic microorganisms, a CSF specimen was tested using metagenomic next-generation sequencing (mNGS). The results showed the presence of *Prevotella oris* with a sequence number of 630 copies and a relative abundance of 1.81%.

FINAL DIAGNOSIS

The patient was diagnosed with meningitis and L3-S1 lumbosacral dural sac infection.

TREATMENT

Initially, the patient was empirically treated with intravenous vancomycin (40 mg/kg/d in two divided doses) and meropenem (40 mg/kg every 8 h). He also underwent a puncture and external drainage of the right ventricle and was given intracranial pressure-decreasing agents and systemic nutritional support. His symptoms did not improve. After the mNGS results indicated the presence of *Prevotella oris* , antibiotic therapy was changed to intravenous metronidazole (15 mg/kg every 6 h) and meropenem (40 mg/kg every 8 h) for 2 wk, followed by meropenem (40 mg/kg every 8 h) for another 2 mo due to the patient experiencing a metronidazole-induced gastrointestinal reaction.

OUTCOME AND FOLLOW-UP

The patient's temperature returned to normal, and his symptoms improved significantly with targeted antimicrobial therapy. After 1 mo of treatment, the routine blood examination showed that the leukocyte count and the percentage of neutrophil granulocytes returned to normal. The leukocyte count in the CSF was 66 cells/μL with 33% polymorphonuclear leukocytes. The CSF glucose was 3.11 mmol/L, the CSF chloride was 117 mmol/L, and the total protein was 560 mg/L. Brain and spinal MRI showed that the thickening of the intracranial and lumbosacral dura mater was greatly resolved. The ventricular drainage catheter was pulled out. The patient was continuously treated for another month and followed up for 2 mo without recurrence.

DISCUSSION

CNS infections are potentially devastating and disabling infectious diseases worldwide. They include meningitis, encephalitis, spinal and cranial abscesses, discitis and other complications. It is estimated that the global incidence of CNS infections was 389/100000 between 1990 and 2016[5]. Although CNS infections are not common in developed countries, they remain a public health problem in developing countries[5,6]. Bacterial infections are one type of CNS infection and can be frequently caused by *Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis,* Group B strep and *Listeria monocytogenes* in children[7].

Prevotella oris, a nonpigmented, anaerobic, Gram-negative, rod-shaped bacterium, is a periodontopathogen and frequently detected in periodontal diseases[8]. We retrieved and reviewed previous cases of *Prevotella oris* causing extraoral infection from the PubMed database (Table 1). *Prevotella oris* was reported as a pathogen in pleural infection, bacteremia, hepatic abscess, pericarditis, mediastinitis, sepsis and empyema. Only 1 case reported cervical spinal epidural abscess and meningitis due to *Prevotella oris* and *Peptostreptococcus micros* after retropharyngeal surgery in 2004[4]. Upon review, we found that the patients all reported cases were male, and 2 of the 7 cases were initially diagnosed as a

Table 1 Characteristics of infections caused by *Prevotella oris*

Ref.	Age/Sex	Initial symptoms	Infection site	Pathogens	Initial diagnosis	Final diagnosis	Antimicrobial treatment	Outcome
Viswanath *et al*[14], 2022	51/M	Right-sided chest pain	Pleura	*Prevotella oris*	Pulmonary tuberculosis	Pleural infection	Metronidazole (500 mg) IV twice a day initially and then continued for 5 d	Improved
Cobo *et al* [15], 2022	70/M	Fever, dyspnea and general malaise	Blood and liver	*Prevotella oris*	COVID-19 infection	Bacteremia, hepatic abscess	Initially, piperacillin-tazobactam (1 g/8 h/IV) and levofloxacin (500 mg/12 h/IV); subsequently, piperacillin-tazobactam (1 g/8 h/IV) and metronidazole (500 mg/8 h/IV) for 10 d	Recovered
Carmack *et al*[16], 2021	34/M	Cough, fever and night sweats	Pericardium	*Prevotella oris* and *Fusobacterium nucleatum*	Tuberculosis pericarditis	Pericarditis secondary to *Prevotella oris* and *Fusobacterium nucleatum*	Initially, rifampin, isoniazid, pyrazinamide, ethambutol (RIPE) and prednisone, then ceftriaxone and doxycycline; subsequently, ampicillin/sulbactam 3 g every 6 h	Improved
Duan *et al* [17], 2021	64/M	Unconsciousness, dyspnea and swelling in the mandible and neck	Mediastinum	*Prevotella oris; Prevotella denticola; Streptococcus anginosus; Peptostreptococcus stomatis; Fusobacterium nucleatum; Alloprevotella tannerae*	Acute purulent mediastinitis	Descending necrotizing mediastinitis	Initially, vancomycin, imipenem; subsequently, piperacillin/tazobactam and tinidazole; finally, levaquin and piperacillin/tazobactam	Improved
Bein *et al* [18], 2003	NA	Acute unconsciousness due to spontaneous intracerebral bleeding in the cerebellar region	Blood	*Prevotella oris*	Spontaneous intracerebral bleeding	Bacteremia and sepsis due to *Prevotella oris* from dentoalveolar abscesses	Initially, imipenem *via* central venous catheter; subsequently, metronidazole IV	Improved
Abufaied *et al*[19], 2020	42/M	Left-sided pleuritic chest pain and acute onset of left upper limb weakness	Chest	*Prevotella oris*	Empyema necessitans	Empyema necessitans	14 d of IV ertapenem and later 14 d of oral ciprofloxacin 500 mg two times daily and amoxicillin/clavulanic acid 625 mg three times daily at the time of discharge	Improved
Frat *et al*[4], 2004	61/M	Right hemiparesis and bilateral Babinski's sign	Cervical spinal epidural space and meninges	*Prevotella oris* and *Peptostreptococcus micros*	Meningoencephalitis	Cervical spinal epidural abscess and meningitis	Initially, ceftriaxone, amoxicillin and cotrimoxazole; subsequently, fosfomycine, ceftriaxone and metronidazole for 3 wk, followed by 8 wk of oral metronidazole	Improved

COVID-19: Coronavirus disease 2019; IV: Intravenous; NA: Not available; M: Male.

tuberculosis infection, which indicated that the symptoms of *Prevotella oris*-induced infection may not be specific and may be similar to tuberculosis infection.

In this case, the patient did not show significant meningitis or spinal infection symptoms. His meningeal irritation sign was negative, and the glucose level of the CSF was in the normal range. Both his blood and CSF cultures were negative. All these factors make pathogen identification more difficult. To investigate the pathogen, we used mNGS, a promising and clinically validated test for CNS infections[9].

Traditional blood and CSF bacterial cultures are essential laboratory tests in meningitis and spinal canal infection. They rarely detect pathogens effectively and in a timely manner under certain circumstances, such as infections caused by oral flora[10]. Compared to traditional methods, mNGS can improve the detection of pathogens to aid clinicians with a timely diagnosis. Some researchers have

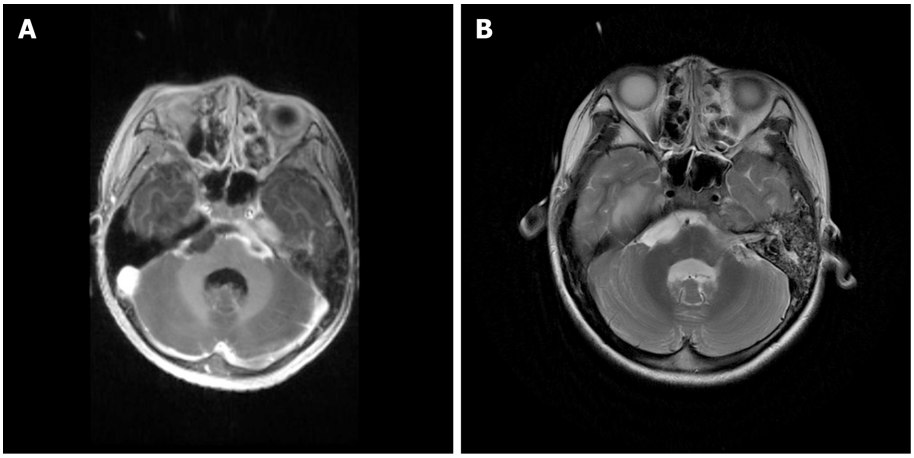

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Figure 1 Brain magnetic resonance imaging sequences of the patient. A: Contrast-enhanced T1-weighted imaging; and B: T2-weighted imaging.

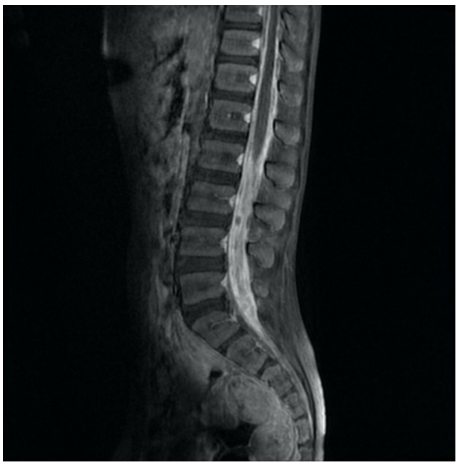

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Figure 2 Spinal magnetic resonance imaging sequences of contrast-enhanced T1-weighted imaging of the patient.

validated the effects of mNGS in CNS infections[11,12]. It can also provide guidance for clinicians in choosing appropriate antimicrobial regimens.

To date, antimicrobial treatment recommendations have been lacking for *Prevotella oris*-induced nervous system infection. By reviewing previous case reports, we found that the most commonly used antibiotic for treating *Prevotella oris*-induced infection was metronidazole, while other antibiotics included piperacillin-tazobactam, ampicillin/sulbactam, levaquin, ertapenem, ciprofloxacin and ceftriaxone. For the documented *Prevotella oris*-induced and *Peptostreptococcus micros*-induced cervical spinal epidural abscess and meningitis cases, fosfomycin, ceftriaxone and metronidazole were used for targeted therapy (Table 1). According to the European Committee of Antimicrobial Susceptibility Testing guidelines, *Prevotella oris* was susceptible to metronidazole, imipenem, chloramphenicol and cefoxitin discs[13]. For this patient, we used metronidazole and meropenem to treat the infection after we found that the effect of empirical antimicrobial therapy was unsatisfactory. The infection was controlled in a timely and effective manner.

CONCLUSION

To the best of our knowledge, this is the second report of meningitis combined with spinal canal infection due to *Prevotella oris*. Despite its rareness, *Prevotella oris* may cause meningitis and spinal canal infection. The symptoms of this kind of infection may not be typical, and conventional culture tests have difficulty detecting pathogens. mNGS is a promising technique to identify pathogens under such circumstances. Clinicians should be aware of this possibility and treat it with rapid imaging, neurosurgical intervention and targeted antibiotics.

FOOTNOTES

Author contributions: Zhang WW contributed to manuscript writing and editing; Ai C, Liu DK and Mao CT contributed to data collection and analysis; Guo Y contributed to conceptualization and supervision; All authors read and approved the final manuscript.

Informed consent statement: The patient's legal guardian provided informed written consent to publish this case report and any accompanying images.

Conflict-of-interest statement: All authors report no having 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: Liu XF
L-Editor: Filipodia
P-Editor: Zhang YL

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World J Clin Cases 2023 June 6; 11(16): 3837-3846

DOI: 10.12998/wjcc.v11.i16.3837

ISSN 2307-8960 (online)

CASE REPORT

Severe liver trauma with complex portal and common bile duct avulsion: A case report and review of the literature

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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 scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ghimire R, Nepal; Govindarajan KK, India; He YH, China

Received: February 9, 2023
Peer-review started: February 9, 2023
First decision: March 28, 2023
Revised: April 2, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Given its size and location, the liver is the third most injured organ by abdominal trauma. Thanks to recent advances, it is unanimously accepted that the non-operative management is the current mainstay of treatment for hemodynamically stable patients. However, those patients with hemodynamic instability that generally present with severe liver trauma associated with major vascular lesions will require surgical management. Moreover, an associated injury of the main bile ducts makes surgery compulsory even in the case of hemodynamic stability, thereby imposing therapeutic challenges in the tertiary referral hepato-bilio-pancreatic centers' setting.

CASE SUMMARY

We present the case of a 38-year-old male patient with The American Association for the Surgery of Trauma grade V liver injury and an associated right branch of portal vein and common bile duct avulsion, due to a crush polytrauma. The patient was referred to the nearest emergency hospital and because of the hemorrhagic shock, damage control surgery was performed by means of ligation of the right portal vein branch and right hepatic artery, and hemostatic packing. Afterwards, the patient was referred immediately to our tertiary hepato-bilio-pancreatic center. We performed depacking, a right hepatectomy and Roux-en-Y hepaticojejunostomy. On the 9th postoperative day, the patient developed a high output anastomotic bile leak that required a redo of the cholangiojejunostomy. The postoperative period was marked by a surgical incision site of incomplete evisceration that was managed non-operatively by negative wound pressure. The follow-up was optimal, with no complications at 55 mo.

CONCLUSION

In conclusion, the current case clearly supports that a favorable outcome in severe liver trauma with associated vascular and biliary injuries is achieved thru proper therapeutic management, conducted in a tertiary referral hepato-bilio-pancreatic center, where a stepwise and complex surgical approach is mandatory.

Key Words: Severe; Liver; Trauma; Avulsion; Right portal vein; Common bile duct; Case report

Core Tip: This paper analyzes a rare and difficult case of a 38-year-old male patient that presented to the nearest emergency hospital for polytrauma secondary to a crush injury, which mainly resulted in a severe liver trauma associated with vascular and biliary injury (grade V liver trauma with severe laceration involving more than 75% of the right hemiliver with injury of the right portal vein and common bile duct). Its management consisted in emergency damage control surgery for hemostasis by vascular ligation and packing in a primary trauma center. This was followed by a major liver resection (right hepatectomy) and biliary reconstruction in a tertiary hepato-bilio-pancreatic (HBP) center. The patient recovered well with no long-term complications and had a follow-up ultrasound that showed no issues. Currently, the overall survival is 55 mo. In conclusion, the current case clearly supports that a favorable outcome in severe liver trauma with associated vascular and biliary injuries is achieved thru proper therapeutic management, conducted in a tertiary referral HBP center, where stepwise and complex surgical approach is mandatory.

Citation: Mitricof B, Kraft A, Anton F, Barcu A, Barzan D, Haiducu C, Brasoveanu V, Popescu I, Moldovan CA, Botea F. Severe liver trauma with complex portal and common bile duct avulsion: A case report and review of the literature. *World J Clin Cases* 2023; 11(16): 3837-3846
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3837.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3837

INTRODUCTION

The general term "liver trauma" covers blunt or penetrating abdominal trauma that causes parenchymal hepatic injury and could involve a wide spectrum of intra and/or extra-parenchymal vascular structures and bile ducts[1]; the liver is the third most injured organ, given its size and anterior location[2]. Other associated organ lesions are found in up to 30% of the cases, usually involving the spleen, the pancreas or the kidneys[3,4].

The American Association for the Surgery of Trauma (AAST) classification, based on morphologic and imaging criteria, is scaled from I to VI, from the least injury to the most severe, and according to the anatomic disruption characteristics of the liver lesions. Grades from I to V are compatible with survival and represent increasingly complex injuries. Grade VI consists of a destructive lesion, usually incompatible with survival. This classification facilitates the comparison of an equivalent injury that is manageable by several therapeutic conducts[3]. The consecutive severity is based on the potential threat to the patient's life. In clinical practice, 80%-90% of the encountered liver lesions are minor and moderate[5]. Advances of the last decades have shifted the mainstay of treatment from exploratory laparotomy to non-operative management (NOM) by multidisciplinary teams in experienced centers[6,7].

The hemodynamic status, anatomic lesion, as well as associated injuries must be analyzed when deciding upon the optimal management plan[3]. NOM is the first choice of treatment in all hemody-

namically stable patients with AAST grade I-V injuries, showing no sign of peritonitis or other lesions requiring surgery[8,9].

However, in clinical practice it is generally admitted that patients with severe liver trauma graded ≥ III who present hemodynamic instability after initial fluid resuscitation must undergo an emergency laparotomy aimed at prompt bleeding control[10]. Thus, hemodynamically unstable patients should undergo operative management (OM), with major resections only to be considered in subsequent surgical interventions, and not upon the primary surgery setting – that should solely control the hemorrhage and restrict the bile leak[3].

AAST grade V-VI injuries are associated with vascular avulsion and higher mortality rates[11]. Vascular avulsion secondary to trauma is very rare and represents a challenge for surgeons who need to perform damage control surgery and can include the ligation of the injured vessels[12]. Post-traumatic bile duct injuries represent another entity that poses a high risk to major complications such as choleperitoneum and biliary fistulas[10].

The computed tomography (CT) scan is the gold standard investigation for diagnosing post-traumatic abdominal lesions and has a key role in selecting the treatment strategy[13]. However, bile duct lesions pose great diagnostic issues in the post-traumatic setting; literature data suggest that the clinical diagnosis is extremely difficult and stand-alone CT scanning does not hold an adequate sensitivity for detecting biliary leaks[14]; moreover, high morbidity rates are related to a delayed diagnosis thereby making the early diagnosis crucial[10].

The existing literature offers few studies that report the association between severe liver trauma, right portal vein branch, and common bile duct avulsion, and therefore the present paper is aimed at filling the gaps of knowledge by presenting the management of such a challenging injury.

CASE PRESENTATION

Chief complaints

We present the case of a 38-year-old male patient who was taken to the nearest emergency room with polytrauma due to a crush injury which presented with hemorrhagic shock due to a grade V liver trauma with severe laceration involving more than 75% of the right hemiliver, avulsion of the right portal vein and common bile duct, with massive hemoperitoneum, right hemopneumothorax, pulmonary contusions, right renal hematoma, II-X rib fractures and a left clavicle fracture.

History of present illness

Emergency laparotomy was performed, consisting with ligation and suture of the right portal vein, intentional ligation of the right hepatic artery for hemostasis, drainage of the total biliary fistula (the biliary reconstruction was not considered at this time), and perihepatic packing. Right pleurostomy and closed reduction and immobilization of the left clavicle were also performed. The pulmonary contusions and the right renal hematoma were treated conservatively.

History of past illness

The patient had no significant medical history.

Personal and family history

The patient had no significant personal or family medical history.

Physical examination

The patient was then referred 24 h later to our tertiary hepato-bilio-pancreatic (HBP) center for subsequent treatment.

Laboratory examinations

A high-output biliary fistula which drained externally was recorded.

Imaging examinations

The CT scan showed no contrast uptake of the right hemiliver in the portal phase, no intrahepatic bile ducts dilatation, no peritoneal liquid and a mild right renal contusion (Figure 1). A high-output biliary fistula which drained externally was recorded.

FINAL DIAGNOSIS

Grade V liver trauma with severe laceration involving more than 75% of the right hemiliver, avulsion of the right portal vein and common bile duct, with massive hemoperitoneum, right hemopneumothorax,

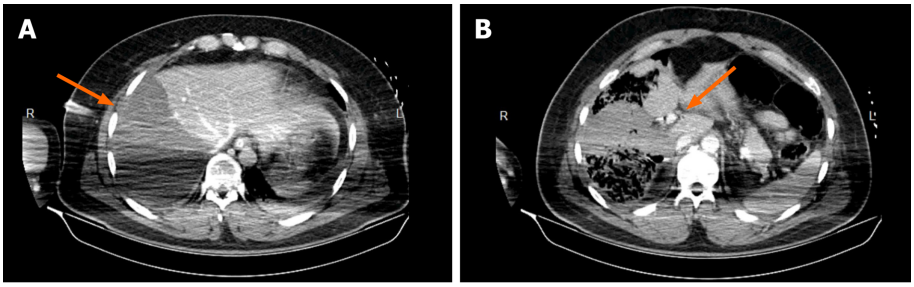

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Figure 1 Preoperative computed tomography scan image performed upon admission in our tertiary hepato-bilio-pancreatic referral center. A: Ischemic right hemiliver post-right hepatic pedicle ligation upon damage control surgery; B: Right hepatic pedicle ligated proximally.

pulmonary contusions, right renal hematoma, II-X rib fractures and left clavicle fracture.

TREATMENT

One day after the primary surgical intervention the second operation was performed, consisting of depacking, a right hepatectomy and Roux-en-Y hepatico-jejunostomy (using the stump of the common hepatic duct) protected by Wietzel external biliary drainage (Figures 2 and 3). The postoperative CT scan performed in postoperative day (POD) 6 showed the normal aspect of the remnant liver (Figure 4).

On POD 4, the onset of bile output through the subhepatic surgical drain was recorded and had increased progressively to 700 mL/d in POD 9. On POD 10, surgical reintervention was urged for high output anastomotic leakage. Intraoperatively, we diagnosed an anastomotic leakage and dubious vitality of the common bile duct stump. Therefore, we performed a redo cholangio-jejunostomy (using the left bile duct), protected by Wietzel external biliary drainage.

The intensive care unit stay had a total length of 4 d, as follows: 1 d in the emergency trauma center and 3 d in our center (2 d following the operation for right hemihepatectomy, 1 d following the intervention for biliary leakage). The patient was administered Piperacillin/tazobactam and Colistin. Blood products were used prior to and during the first operation performed in the primary emergency trauma center because the patient was admitted in hemorrhagic shock. Only 1 unit of blood was used in our tertiary referral center during the operation for right hemihepatectomy, and no blood products were used during the operation for biliary leakage.

The postoperative period was marked by a surgical incisional site incomplete evisceration that was managed non-operatively by means of negative pressure wound therapy (NPWT). The patient was discharged on POD 30, after a remaining uneventful course, with outcare NPWT, until the complete healing of the surgical wound after 4 mo postoperatively (Figure 5).

OUTCOME AND FOLLOW-UP

A follow-up ultrasound was performed at 1, 3, and 6 mo, showing no complications; the external biliary drainage was removed after 6 mo prior to cholangiography control. The patient fully recovered, as there were no other long-term complications encountered; currently the overall survival is 55 mo.

DISCUSSION

Although most liver traumas are successfully treated by NOM, which reduced the morbidity and mortality rates of these patients, interventional therapy still has a role in the management of complex liver injuries.

However, cases of severe blunt liver injury that associate hemodynamic instability after initial fluid resuscitation carry a high risk of hypovolemic shock and death, especially when other abdominal or thoracic lesions coexist; therefore, the current therapeutic conduct in such cases is the OM[3,5,10]. In this regard, the main goal of the primary surgery conducted in an emergency setting should be to secure efficient hemostasis by damage control surgery[15]. In the absence of major bleeding sites, it is usually suitable to employ techniques such as: compression, electrocautery, bipolar devices or suturing the liver parenchyma[16,17]. Major hemorrhage, however, may impose techniques such as: hepatic packing, direct vessel repair under vascular control, vessel ligation, shunting maneuvers, balloon tamponade or hepatic vascular isolation or exclusion[18]. Literature data clearly emphasizes that major resections

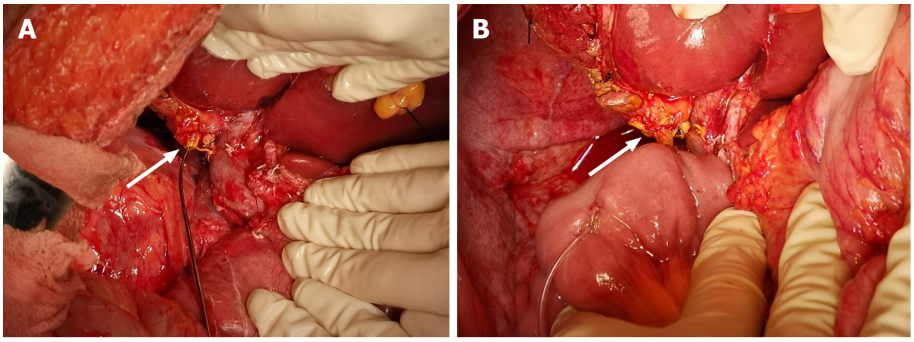

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Figure 2 Intraoperative aspect. A: Sectioned common hepatic duct, prepared for the hepaticojejunostomy; B: Finished hepaticojejunostomy.

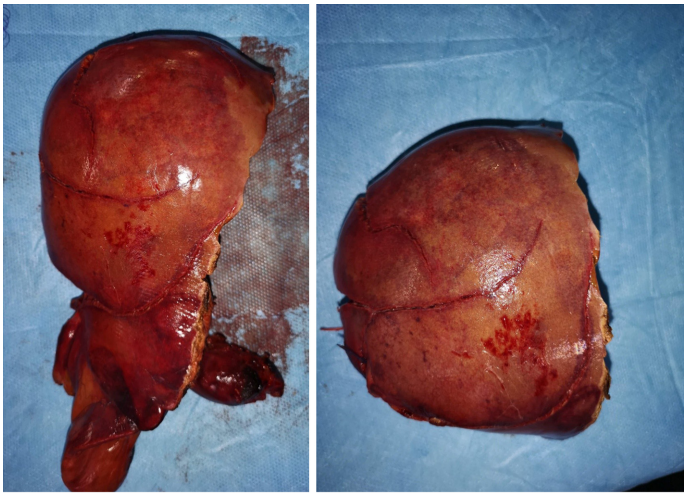

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Figure 3 Gross pathology of the resected right hemiliver.

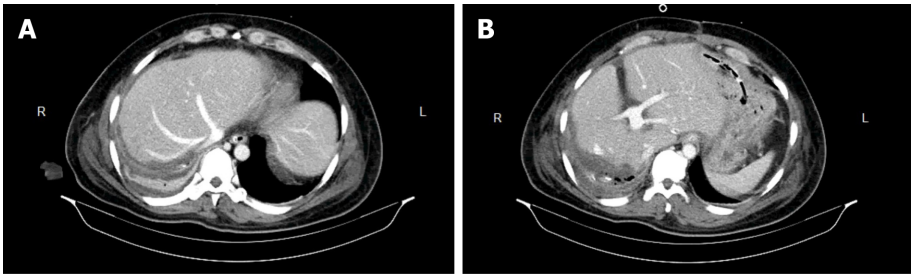

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Figure 4 Postresection computed tomography scan image. A: Remnant left hemiliver showing no ischemic regions; B: Image showing the left portal vein branches.

should be avoided whenever possible upon this primary surgical intervention[4].

Studies that have investigated the outcomes of damage control surgery came to the conclusion that the packing procedure is part of a whole "damage control" strategy[19]. Even after a well conducted perihepatic packing procedure, some patients present active hemorrhage generated from deep injured vessels. In such cases, these patients are managed in the multidisciplinary setting, by selective angioembolization techniques performed by the interventional radiologists[3]. Some severe patients that still present with active bleeding following the aforementioned procedures are quickly subjected to a second packing procedure, because time is of essence in order to avoid the onset of the mortality associated "lethal triad" (*i.e.*, acidosis, hypothermia and coagulopathy)[19]. The efficient perihepatic packing cannot be defined using an optimal number of gauzes[20]; it is important to avoid excessive packing in order to prevent abdominal compartment syndrome[19]. It is generally considered that packing is best removed after 48 h[21].

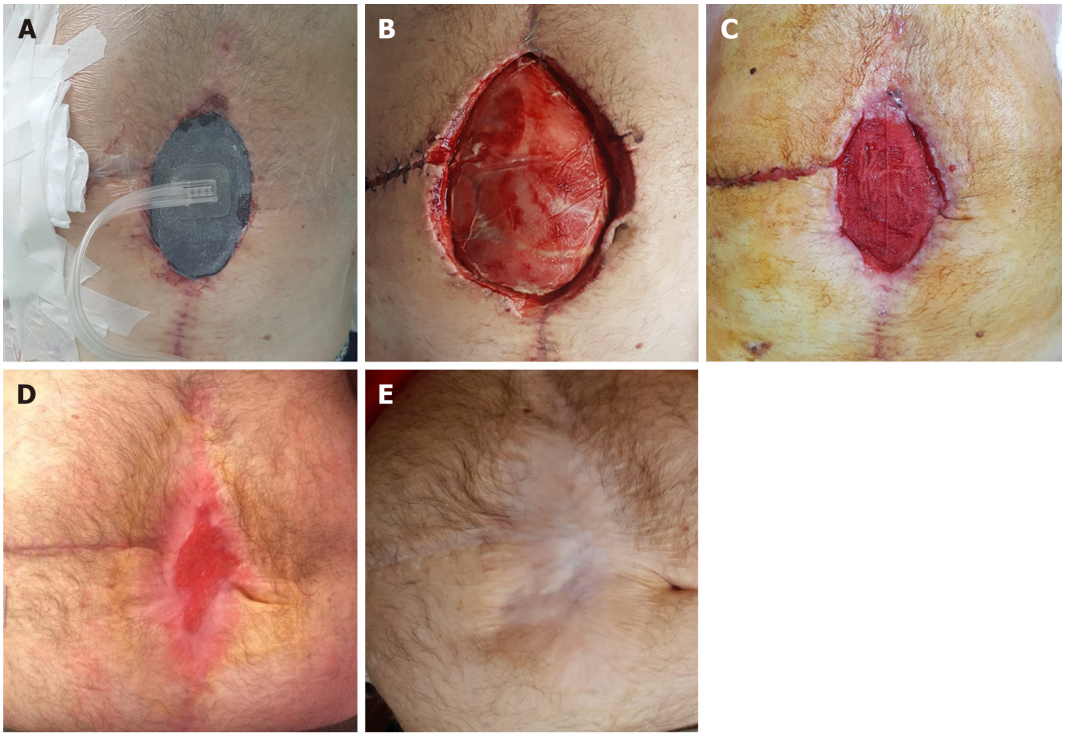

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Figure 5 Postoperative aspect. A: The surgical incisional site evisceration managed by negative-pressure wound therapy on the 48th postoperative day (POD); B: 18th POD aspect showing the surgical incisional site evisceration; C: 48th POD aspect showing the surgical incisional site evisceration managed by negative-pressure wound therapy; D: 4 mo postoperative aspect showing the chronological evolution of the surgical incisional site evisceration managed by negative-pressure wound therapy; E: 55 mo postoperative aspect showing the chronological evolution of the surgical incisional site evisceration following negative-pressure wound therapy.

When vascular avulsion is present, it is vital to identify the injured vessels. In the case of hepatic artery injury, selective ligation is suitable whenever the repair of the vessel is not feasible. If the right hepatic artery needs to be ligated, cholecystectomy is recommended in order to avoid necrosis of the gallbladder[22,23]; this was not the case with our patient, as he had previously undergone cholecystectomy prior to trauma. When there are injuries of the portal vein, packing or liver resection are preferred to ligation when only segmental branches are affected[17]. In our case, the right portal vein was severely injured, imposing its ligation in the setting of damage control surgery, followed by right hepatectomy in the referral HBP center, leaving a sufficient functional liver remnant.

In the case of extensive parenchymal damage with insufficient liver remnant, liver transplant is to be considered[23]. Liver transplantation completes the therapeutic armamentum, and should be considered the last therapeutic alternative when the previously mentioned procedures prove unsuccessful in achieving hemodynamic stability, and complete hepatectomy is the last resort in bleeding control[1]. Literature data on this topic are very scarce[24]; nonetheless, the generally accepted indications are: Uncontrollable hemorrhage following damage control surgery, extensive and complex hepatic injuries not correctable by surgical procedures, unrepairable injuries of the portal vein, hepatic veins or bile ducts, trauma related acute liver failure due to trauma, and hepatic necrosis[25]. The liver transplantation decision should be thoroughly evaluated and implies the identification of those patients unfit for transplant, that present severe sepsis, multiple system organ failure, or associated severe organ injuries[24,25].

Liver trauma leads to a great variety of intra- and/or extrahepatic bile duct injuries; unfortunately, few studies have evaluated the management of bile leakage according to the location of the injured bile duct; therefore, the therapeutic management is controversial[10]. Literature states that the moment of detection raises issues of great importance. Because of the vague symptoms at presentation, delayed diagnosis can often occur, leading to high mortality and morbidity rates, through bacterial or fungal peritonitis, intractable bile leakage, haemobilia, pseudoaneurysms, or biliocutaneous fistula, and septic shock[10,14]. Thus, great importance must be given to early detection and proper management of bile leakage following liver trauma[14].

As stated earlier, due to the patient's hemodynamic instability, the goal of the above mentioned primary emergency damage control surgery is to rapidly control the hemorrhage. Studies show that if a bile duct injury is diagnosed upon this primary procedure, the risks of performing extensive procedures such as liver resection and/or bile duct reconstruction are greater than the provided benefits, therefore it is generally accepted that the management of the injured bile ducts will be postponed and conducted

at a later time[10].

Recent literature data consider applying adequate therapeutic management according to the extent of the injury and to the bile duct's location. Certain studies have reported promising results following the nonoperative management of peripheral bile duct injuries by using percutaneous drainage procedures and early endoscopic biliary stenting, thus providing a safe alternative and avoiding open surgery[10,14,26,27]. Some of the major drawbacks are: the difficulty in performing early Endoscopic retrograde cholangiopancreatography (ERCP) and internal stenting in hemodynamically unstable patients, and post-ERCP cholangitis, resulting in hepatic abscess and consecutive liver rupture[28]. In an attempt to overcome these shortcomings, some centers avoided ERCP stenting and stent removal procedures, and adopted first-line percutaneous intraperitoneal drainage; their updated experience shows comparable outcomes[10,14]. Previous studies reporting the setting of severe liver trauma show that peripheral bile duct injuries can be managed by the above mentioned nonoperative treatments. However, the appropriate timing and the choice of therapeutic management are still subject of debate[10,26,29,30].

Recent studies also show that post-traumatic sections of a *central* bile duct are rare and often difficult to diagnose preoperatively[30]. The attempt to determine the degree of the bile duct injury with massive fluid collection by means of preoperative CT or magnetic resonance cholangiopancreatography (MRCP) scan is close to impossible[10]; therefore, as a diagnostic alternative, some authors promote the use of technetium-99 m trimethylbromoimino-diacetic acid scan for early detection on post-traumatic days 5 to 7[14]. Nonetheless, some studies suggest that a preoperative CT exam shows a strong correlation between the minimal distance measured from the portal pedicle to the parenchymal traumatic injury and the existence of a bile duct injury[14].

Given the emergency setting scenario of the case under discussion, the MPCR exam was not taken into consideration due to long delays in both waiting list times and performance of examination. In addition, properly conducted perihepatic packing can cause artefacts and major anatomic distortions that render the MRCP exam inconclusive. We considered that intraoperative exploration of the bile ducts combined with intraoperative cholangiography, whenever deemed necessary, is optimal for this type of case with severe hepato-biliary trauma managed with emergency packing as a first step of the surgical treatment. For example, we did not perform intraoperative cholangiography, as the surgical exploration of the bile ducts with a malleable metal probe was considered enough.

On the other hand, a central bile duct injury will require aggressive surgical treatment, performed once the patient's condition is stable; however, currently, there is no consensual therapeutic conduct available in the literature regarding central bile duct injuries; consequently, the management of such an injury must be tailored[10]. Literature data report successful outcomes after techniques, such as, liver resection, reconstruction of the injured bile ducts by Roux-en-Y hepaticojejunostomy[31], and /or primary repair of the injured duct with T-tube insertion[32]. Biliary leakage by anastomotic fistula is a possible complication, as shown by the current case – *i.e.*, the hepaticojejunostomy was redone in a subsequent intervention. There are also reports available on central bile duct injuries repaired by primary suture and complemented by ERCP and internal stenting as an option for biliary decompression. Due to the extent of the bile duct injury, the concepts of NOM were not applicable in the case in question. In addition, even if in retrospect a hepatico-jejunostomy would have been a better therapeutic option, there was no way of knowing this in advance, because the stump of the common bile duct seemed properly vascularized at the time of the first surgical intervention performed in our tertiary referral center. Therefore, at that time, an anastomosis performed on the left hepatic duct seemed like an excessive treatment measure.

Given the complexity of the encountered lesions, we did not consider it appropriate to adopt any other therapeutic approach. A reconstruction of the right portal vein and right hepatic artery was not considered feasible, because a significant portion of the right portal vein was missing (due to associated trauma and to surgical hemostasis during the damage control surgery), because of the long ischemic time of the right hemiliver, and finally because the parenchyma of the right hemiliver was almost completely damaged by trauma.

Of note, the ligation of the right hepatic artery performed upon the damage control laparotomy was considered mandatory due to remanent significant parenchymal bleeding despite right portal vein ligation. Moreover, the right hemiliver was already compromised by the laceration and associated right portal vein avulsion. Therefore, right hepatectomy would have been needed even in the absence of the right hepatic artery ligation.

NPWT facilitates healing by reducing edema, draining excess fluids, and eliminating barriers to cellular proliferation[33,34]. NPWT can successfully promote the healing of infected wounds, diabetic foot wounds, laparotomy incisions, as well as other chronic conditions[35,36]. In our case, it successfully facilitated the closure of the surgical incisional site evisceration allowing for complete healing, thus avoiding the need for additional surgery and exposing the patient to fewer risks.

CONCLUSION

This case clearly supports that a favorable outcome in severe liver trauma with associated vascular and

biliary injuries is achieved thru proper therapeutic management, conducted in a tertiary referral HBP center, where stepwise and complex surgical approach is mandatory.

ACKNOWLEDGEMENTS

The present study is included in a wider retrospective research entitled "Liver Trauma", as part of a doctoral dissertation, developed by Bianca Mitricof, Ph D student at "Titu Maiorescu" Doctoral School of Medicine, Bucharest, Romania with Irinel Popescu as thesis coordinator. The authors would like to thank Luiza-Anca Kraft, Associate Professor in "Carol I" National Defense University, Bucharest, Romania, for the language editing work.

FOOTNOTES

Author contributions: Mitricof B, Kraft A, Botea F, Moldovan C and Popescu I provided conceptualization; Botea F, Moldovan C and Popescu I designed the methodology and performed validation; Kraft A, Botea F, Moldovan C and Popescu I provided formal analysis; Mitricof B, Kraft A, Anton F, Bârcu A, Bârzan D, Haiducu C and Braşoveanu V were responsible for investigation; Mitricof B, Kraft A, Anton F, Bârcu A, Bârzan D, Haiducu C, Braşoveanu V and Popescu I performed data curation; Mitricof B, Kraft A, Anton F, Bârcu A and Haiducu C provided writing and original draft preparation; Braşoveanu V, Popescu I, Botea F and Moldovan C performed final review and editing; Popescu I and Braşoveanu V were in charge of supervision; Botea F and Moldovan C were responsible for project administration; All authors have read and agreed to the published version of the manuscript.

Informed consent statement: Informed consent was obtained from the subject involved in the study.

Conflict-of-interest statement: All the authors report having 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: Liu XF
L-Editor: Filipodia
P-Editor: Zhang YL

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3847-3851

DOI: 10.12998/wjcc.v11.i16.3847

ISSN 2307-8960 (online)

CASE REPORT

TACC diagnosed by transoesophageal endoscopic ultrasonography: A case report

Xiao-Xin Pu, Qin-Wei Xu, Bao-Yi Liu

Specialty type: Oncology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gokce E, Turkey; Zharikov YO, Russia

Received: February 10, 2023
Peer-review started: February 10, 2023
First decision: April 10, 2023
Revised: April 14, 2023
Accepted: May 6, 2023
Article in press: May 6, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Primary adenoid cystic carcinoma in the trachea (TACC) is a rare tumour. Tracheal bronchoscopy is always chosen as a routine approach to obtain a pathological diagnosis, but it can be associated with an increased risk of asphyxia.

CASE SUMMARY

We describe a case of TACC in a patient evaluated by chest computed tomography (CT) with three-dimensional reconstruction imaging and diagnosed by transoesophageal endoscopic ultrasonography. The pathological diagnosis confirmed tracheal adenoid cystic carcinoma.

CONCLUSION

We highlight the importance of CT and provide a successful exploration of transoesophageal biopsy as a safe alternative approach.

Key Words: Adenoid cystic carcinoma; Tracheal obstruction; Transoesophageal endoscopic ultrasonography; Three-dimensional computed tomography reconstruction; Case report

Core Tip: For large tracheal masses, tracheal bronchoscopy has certain limitations. This case highlights the importance of chest computed tomography for radiological assessment and provides a successful exploration of transoesophageal endoscopic ultrasound biopsy as a safe alternative biopsy approach.

Citation: Pu XX, Xu QW, Liu BY. TACC diagnosed by transoesophageal endoscopic ultrasonography: A case report. *World J Clin Cases* 2023; 11(16): 3847-3851
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3847.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3847

INTRODUCTION

Adenoid cystic carcinoma (ACC) is a rare malignant tumour of the salivary gland, especially in the trachea. In tracheal tumours, the incidence is secondary to squamous cell carcinoma[1], which is mostly located in the distal trachea, while ACC is usually located in the proximal trachea[2]. ACC is slow growing and locally aggressive with a propensity for perineural invasion and haematogenous spread. Surgery is often the first choice unless the difficulty and risk of surgery are assessed to be high.

CASE PRESENTATION

Chief complaints

A 64-year-old male was admitted to our hospital with the chief complaint of paroxysmal cough for more than 10 mo.

History of present illness

The main clinical manifestations of this patient with no smoking history were paroxysmal without sputum production and wheezing for more than 10 mo.

Physical examination

Physical examination showed no abnormalities.

Laboratory examinations

Laboratory examinations showed no abnormalities.

Imaging examinations

The chest X-ray showed no abnormal signs. Then, we performed a chest computed tomography (CT), which revealed airway occupation (Figure 1A). After a multidisciplinary consultation, we performed CT with three-dimensional (3D) airway reconstruction (Figure 1B) and completed tracheal bronchoscopy. However, bronchoscopy (Figure 2) showed that in the upper part of the trachea, the tumour protruded into the lumen from the membrane and extended to the carina, and the bronchoscope could barely pass through. The left and right main bronchi were unobstructed. As shown by bronchoscopy, the surface of the mass showed abundant vascularity.

MULTIDISCIPLINARY EXPERT CONSULTATION

Considering bleeding and the possibility of asphyxia, we decided to perform transoesophageal endoscopic ultrasonography after multidisciplinary treatment. A mucous eminence lesion was found on the right side of the oesophagus 25 cm away from the incisor. An ultrasound scan (Figure 3) revealed an extranuclear medium- and low-echo mass with an unclear boundary and uneven internal echo, with a size of 3.7 cm × 5.4 cm. Colour Doppler flow imaging showed few blood flow signals in this part of the mass, and a 22G puncture needle was used to repeatedly puncture the mass under ultrasound guidance. Finally, the tissue was successfully obtained.

FINAL DIAGNOSIS

Cytological examination of the tracheal tumours (Figure 4A) showed small lamellar cells arranged in sacs and follicles containing myxoid substances and a few eosinophilic epithelioid cells forming tubules, which were considered salivary gland epithelial-myoepithelial tumours. Histological findings (Figure 4B) of the tracheal tumours revealed that the tumour cells arranged in the puncture tissue were microcystic, contained thin mucus and were surrounded by eosinophilic tubules. Morphological and immunomarker results supported epithelial-myoepithelial-derived tumours, which tend to be adenoid cystic carcinoma. Combined with CT scans, the diagnosis confirmed adenoid cystic carcinoma of the

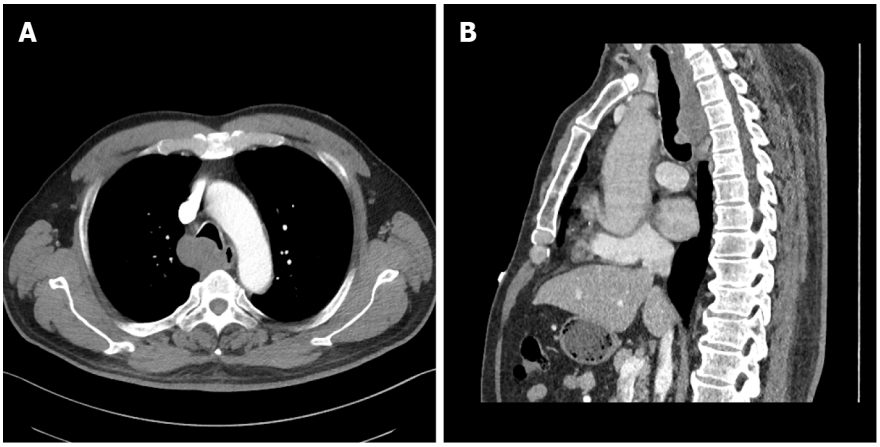

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Figure 1 Computed tomography scan of the airway occupation. A: Chest Computed tomography (CT); B: CT with three-dimensional airway reconstruction.

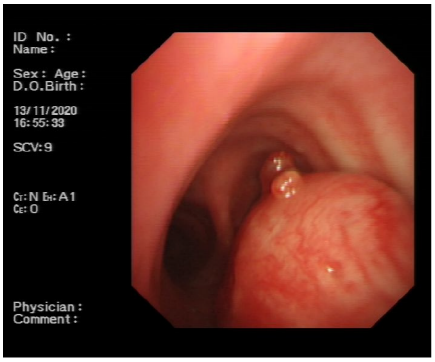

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Figure 2 Tracheal bronchoscopy. The masses originated from the trachea with expansive growth.

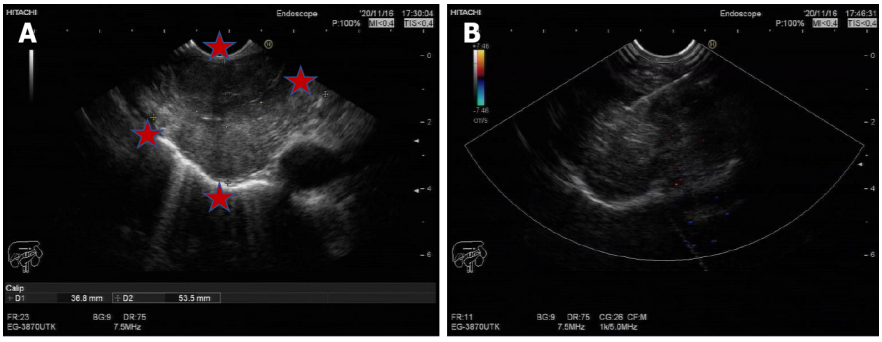

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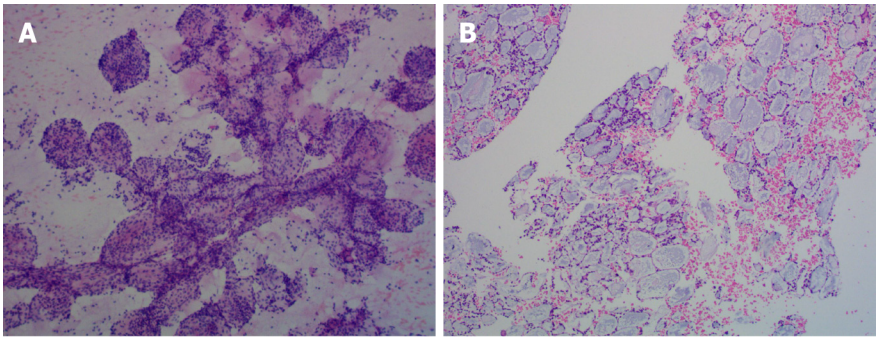
Figure 3 Ultrasound scan. A and B: A mass with an unclear boundary.

trachea.

TREATMENT

Considering that aggressive resection of tracheal lesions may cause fatal complications and that the tumour was slow growing, after consulting other medical institutions, our patient received local radiotherapy in another hospital.



DOI: 10.12998/wjcc.v11.i16.3847

Figure 4 Pathology (100 ×) of the tumour. A: Cytological pathology; B: Tissue pathology.

OUTCOME AND FOLLOW-UP

Our patient lost contact one year later.

DISCUSSION

Tracheal adenoid cystic carcinoma (TACC), originating in the tracheal submucous gland, is relatively rare[3,4]. The low incidence of TACC may be due to the vigorous cough reflex and the cleaning action of airway cilia. TACC is low-grade malignant, grows slowly, and can be polypoid or nodular and protrude into the trachea with a broad base. TACC can also invade the trachea and cause a soft tissue mass inside and outside the lumen, cause stenosis and obstruction of the lumen, and grow along the long axis of the tubular wall.

Microscopically, the tumour tissues show similar sieve and tubular structures, and the tumour cells are small and consistent, with little cytoplasm, an increased ratio of nucleus to cytoplasm, hyperchromatic nuclei, and rare mitosis. Pink-stained basement membrane-like substances can be seen in some lumens, blue-stained mucin-like substances can be seen in some lumens, and both substances can be found in some lumens[5]. Differential diagnoses includes squamous cell carcinoma, carcinoid, mucoepidermoid carcinoma, nonsquamous bronchial carcinoma, lymphoma, *etc.*[6].

The diagnosis is often delayed and early diagnosis is not obtained because of the absence of specific symptoms until the mass occludes most of the luminal diameter, and the tumour may cause symptoms such as cough, wheezing and exertional dyspnoea. TACC is often misdiagnosed as chronic obstructive pulmonary disease, asthma or airway inflammation. It is often difficult to detect lumps or eminences of the track on chest X-ray. Our case may be a good example. At the beginning, the patient presented with only a mild cough, and our community doctors thought it was bronchitis after completing the chest X-ray. Ten months later, we found the mass *via* a chest CT scan. Therefore, CT is particularly important [7]. In particular, CT with 3D reconstruction was used to assess airway involvement, and a combined enhancement scan was used to assess infiltration.

To obtain a pathological diagnosis and provide a better follow-up assessment, tissue biopsy was necessary. Tracheal bronchoscopy is always chosen as a routine approach to achieve this aim. The site can be confirmed visually, and enough prior information can be provided, including the appropriate size and position of the endotracheal intubation once asphyxia occurs. Conversely, the risk of asphyxia can be increased due to bleeding and mucosal oedema, especially when the tumour already causes almost 50% central airway obstruction; therefore, the bronchial approach may not be suitable. TEUS may be a safe alternative approach.

Surgical resection is the main treatment method at present, local mass resection is the main principle of radical treatment, and postoperative radiotherapy can reduce the recurrence rate[8]. However, due to the special location of the trachea, it is difficult to perform extended or complete resection, and aggressive resections may cause unpredictable and even fatal consequences, such as tracheoesophageal leakage. Therefore, partial resections with adjuvant therapy may help these patients obtain a promising prognosis. In addition to conventional radiation therapy, other treatment approaches have been attempted, such as radiotherapy with photons and hadron irradiation with carbon ions (C^{12})[9]. After consulting other medical institutions, the patient chose radiation therapy instead of a palliative operation.

There are several limitations in our report. First, rigid bronchoscopy may have been an alternative treatment option, but our team had limited experience with this approach. Second, our patient may have benefitted from undergoing palliative operation to treat the mass. Furthermore, we only provided short-term follow-up, and more detailed follow-up is needed.

CONCLUSION

In summary, we report a case of TACC. For tracheal masses, tracheal-bronchial biopsy is routine, but for large tracheal masses, tracheal bronchoscopy has certain limitations. This case highlights the importance of chest CT for radiological assessment and provides a successful exploration of transoesophageal endoscopic ultrasound biopsy as a safe alternative biopsy approach.

FOOTNOTES

Author contributions: Pu XX and Xu QW contributed to the data collection of the manuscript; Pu XX contributed to the writing of the manuscript; Liu BY helped shape the manuscript.

Informed consent statement: The patient provided informed written consent for his tissue samples to be used in this experimental research.

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

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).

Country/Territory of origin: China

ORCID number: Xiao-Xin Pu 0000-0003-2995-6586.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3852-3857

DOI: 10.12998/wjcc.v11.i16.3852

ISSN 2307-8960 (online)

CASE REPORT

Ruptured teratoma mimicking a pelvic inflammatory disease and ovarian malignancy: A case report

Pei-Hsuan Lai, Dah-Ching Ding

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Exbrayat JM, France; Martín Del Olmo JC, Spain

Received: February 16, 2023
Peer-review started: February 16, 2023
First decision: April 19, 2023
Revised: April 20, 2023
Accepted: May 6, 2023
Article in press: May 6, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

We report a case of ruptured ovarian teratoma mimicking pelvic inflammatory disease (PID) and ovarian malignancy. The case indicates the need for reviewing the information on ovarian teratomas, as the symptoms are vague, and, therefore, diagnosis and treatment had to be structured accordingly.

CASE SUMMARY

A 60-year-old woman was admitted to the emergency department with acute lower abdominal pain. She experienced weight loss and increased abdominal girth. Pelvic ultrasound and computed tomography revealed a 14-cm pelvic tumor. Laboratory examination revealed leukocytosis (white blood cell count: 12620/μL, segment: 87.7%) and high levels of C-reactive protein (18.2 mg/dL). Elevated levels of the tumor marker cancer antigen 19-9 (367.8 U/mL, normal value < 35 U/mL) were also noted. Due to the impression of a ruptured tubo-ovarian abscess or a tumor with malignancy, she immediately underwent an exploratory laparotomy. A ruptured ovarian tumor with fat balls, hair strands, cartilage, and yellowish fluid was observed on the right side. Right salpingo-oophorectomy was performed. A pathological examination revealed a mature cystic teratoma. The patient recovered after surgery and was discharged on post-operative day three. No antibiotics were administered.

CONCLUSION

This case illustrates the differential diagnosis of an ovarian tumor. Therefore, surgery is the mainstay for treating a ruptured teratoma.

Key Words: Teratoma; Ovarian cancer; Pelvic inflammatory disease; Ruptured; Peritonitis; Case report

Core Tip: We report a case of a ruptured ovarian teratoma mimicking pelvic inflammatory disease and malignancy. We updated the information on ovarian teratomas regarding symptoms, signs, diagnosis, and treatment. Because of the vague symptoms of ovarian teratoma, we provided a strategy to diagnose and treat this ovarian teratoma.

Citation: Lai PH, Ding DC. Ruptured teratoma mimicking a pelvic inflammatory disease and ovarian malignancy: A case report. *World J Clin Cases* 2023; 11(16): 3852-3857
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3852.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3852

INTRODUCTION

Mature cystic teratoma of the ovary constitutes 10%–20% of ovarian tumors[1]. Another report in Taiwan showed that the incidence of teratomas was 33%[2]. The most common symptom of teratomas is abdominal pain, which was observed in 48% of cases[2]. Other complications included torsion (9.2%), concurrent pregnancy (3.5%), and malignant transformation (0.7%)[2]. Abdominal pain is also a possible symptom following a ruptured teratoma[3].

We report a case of a 60-year-old woman with ruptured teratoma mimicking pelvic inflammatory disease (PID) and ovarian malignancy that was managed *via* an emergent right salpingo-oophorectomy (RSO).

CASE PRESENTATION

Chief complaints

A 60-year-old woman presented with aggravated abdominal pain and was admitted to the emergency department.

History of present illness

According to the patient's statement, she had suffered from general abdominal bloating and distension since August 2022. Since October 2022, the discomfort had developed into non-remitting dull pain, accompanied by occasional stabbing pain in the right lower quadrant. The pain, initially eased by over-the-counter analgesics, progressed to become intolerable, and she could barely walk and sleep for days. She also suffered from lower urinary tract symptoms characterized by obstructive etiology, including intermittent urinary flow, hesitancy, need for straining, incomplete emptying, and frequency. Her body weight had decreased substantially from 59 kg in August to 54 kg at the time of recording, while the abdominal circumference increased. No fever or unstable vital signs were noted.

History of past illness

Her body mass index was 22.2 kg/m^2 without remarkable gynecologic disorders or chronic illness. Menopause onset was at 54 years. Sexual activity and use of exogenous hormones were both ruled out.

Personal and family history

Personal and family history was unremarkable.

Physical examination

A detailed physical examination revealed diffuse abdominal tenderness and equivocal rebound tenderness. An ovoid enlarged abdominal surface with a protruding mass on the right was observed.

Laboratory examinations

The blood test yielded leukocytosis with left shift (white blood cell count: 12620/μL, segment: 87.7%) and a high C-reactive protein level (CRP 18.2 mg/dL), indicating an active systemic inflammatory status. The levels of tumor markers, including cancer antigen 125 (17.6 U/mL) and carcinoembryonic antigen (0.8 ng/mL), were within the normal ranges; however, cancer antigen 19-9 (CA 19-9 367.8 U/mL, normal value < 35 U/mL) was elevated. Post-operative cultures of the abdominal contents collected during surgery showed no microbial growth.

Imaging examinations

Contrast-enhanced computed tomography revealed a 14-cm cystic tumor occupying the pelvic cavity

and lower abdomen (Figure 1A-C). The tumor probably originated from the adnexa, contained a few septations, had a mixed density of fluid and fat components, and lacked an enhancing mural nodule. Bilateral hydronephrosis might be a consequence of the compression effect of the tumor. Notably, a small amount of mildly turbid ascites was observed in the cul-de-sac. Based on the imaging findings, tubo-ovarian abscess was the primary impression, while ovarian torsion, ovarian tumor of either benign or malignant nature, or pyometra required differentiation. The computed tomography (CT) findings were echoed by the transabdominal ultrasound images, revealing a heterogeneous tumor with hyperechoic hair strand-like materials and papillary growth, which mimicked ovarian cancer (Figure 1D and E).

FINAL DIAGNOSIS

Due to absence of any sexual history, a diagnosis of the tubo-ovarian abscess was less likely. Considering the rapid growth of the tumor and the prominent symptoms, an exploratory laparotomy was performed the following day under the suspicion of adnexal malignancy.

TREATMENT

A right ovarian tumor with yellowish fluid accumulation and without a malodorous smell was found in the peritoneal cavity. Aerobic and anaerobic cultures were performed. RSO was performed. Grossly, the tumor contained hair strands, ball-like fat tissues, and cartilage within the tumor (Figure 2). Intraoperative frozen sections showed a teratoma. The histopathological study of paraffin-embedded tissue was found to be a mature cystic teratoma (Figure 3). As was expected, the diagnosis was revised to a mature cystic teratoma complicated with chemical peritonitis, which contributed to severe abdominal pain and inflammatory status.

OUTCOME AND FOLLOW-UP

After surgery, no antibiotics were administered for non-infectious pathogenesis. The surgical drain at the cul-de-sac drained only minimal serosanguinous fluid; therefore, it was removed. The patient recovered soon after the procedure and was discharged on postoperative day three. Follow-up at the outpatient department could have been more uneventful.

DISCUSSION

We report a case of a ruptured teratoma managed *via* emergent RSO. The presurgical impression of this teratoma mimicked pelvic inflammatory disease and ovarian malignancy. Peritoneal signs, leukocytosis, and left shift showed a high likelihood of PID. A complex tumor ultrasound and high CA 19-9 Levels led to the suspicion of ovarian malignancy. Finally, the teratoma was managed by RSO.

Diffuse abdominal pain, leukocytosis, and elevated CRP levels may be caused by a ruptured ovarian teratoma[3]. Other teratoma complications include torsion, infection, rupture, and malignant transformation[4]. The evaluated case also presented these symptoms and signs.

Spontaneous rupture of teratomas can occur, but are rare, due to thick cystic walls, with the possibility of occurrence ranging between 0.3%-0.7%. The cause of teratoma rupture is unknown. Torsion with infarction, direct trauma, prolonged pressure during pregnancy, malignant transformation, and increased internal pressure from rapid growth may be rupture factors[5]. After the teratoma ruptures, leakage or spillage of contents may cause chemical peritonitis (aseptic inflammatory peritoneal reaction). During surgery, the incidence of chemical peritonitis caused by tumor content has been reported to be less than 1%[6]. In the presented case, abdominal pain caused by a teratoma rupture was suspected and confirmed during laparotomy.

Ultrasonography is an easy and effective tool for diagnosing ovarian teratomas[7]. The characteristics of ultrasound findings include dermoid mesh, tip of the iceberg sign, and Rokitansky nodule. Dermoid mesh indicates hyperechogenic lines reflecting that of hair[8]. Rokitansky nodule is a cystic lesion with echogenic tubercles projecting into the cystic lumen. To differentiate between benign and malignant tumors, the typical morphology for ovarian malignancy includes intratumor separation, papillary projection, vascular support to the lesion, heterogeneous echogenicity, and an ovarian volume of more than 20 cm^3[9]. In the presented case, ultrasound showed a heterogeneous tumor with hyperechoic hair strand-like materials and papillary growth.

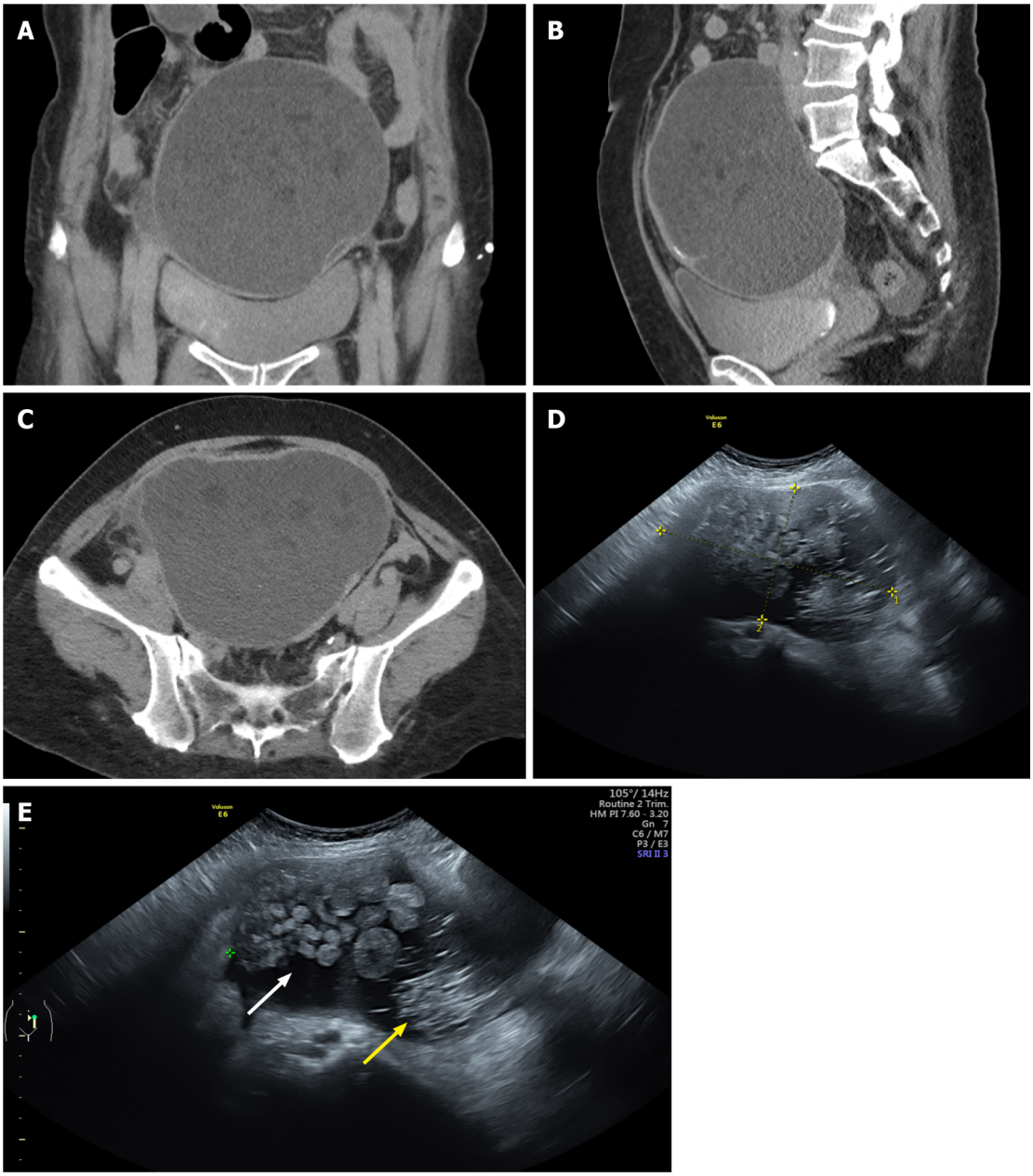

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Figure 1 Image studies of the tumor. A computer tomography scan showing a large tumor with septa in the abdominal cavity. A: Coronary view; B: Sagittal view; C: Axial view; D and E: Pelvic ultrasound showing a tumor with a size of 14.5 cm × 8.6 cm. Hair-strand-like materials (yellow arrow) and papillary-like growth (white arrow) were noted in the tumor.

A teratoma, a heterogeneous adnexal mass with calcification and fatty components, can be noted on a CT scan[3]. Ruptured teratoma can be suspected when a CT scan shows a fatty nodule on the lesion and ascites with a peritoneal thickening layer[3]. The CT scan of ovarian cancer may show the size, location, and extent of primary ovarian carcinoma[10]. Ovarian cancer can show a cystic lesion with a portion of a solid tumor within it and may have a papillary projection[11]. The CT scan of the presented case showed a heterogeneous tumor with hyperechoic hair strand-like materials and papillary growth. Papillary growth may be similar to ovarian malignancy.

Teratomas are usually located in the ovaries. However, teratomas can occur anywhere in the body. Eight to fifteen percent of teratomas can occur bilaterally[12]. Multiple teratomas on the same side can also occur[13]. The most commonly observed side of teratoma occurrence varies in different studies[14].

Surgical treatment for ovarian teratomas includes cystectomy and oophorectomy[15]. Laparoscopic management is the gold standard. For young adults, cystectomy can be performed[16]. Ovarian teratoma can occur in pregnant women. For suspected malignancy or postmenopausal women, an oophorectomy could be performed[15]. When doing cystectomy, content spillage and possible chemical peritonitis may be encountered. However, this event can decrease complications through rigorous fluid flushing[16]. The presented case underwent an oophorectomy due to the suspicion of malignancy and to

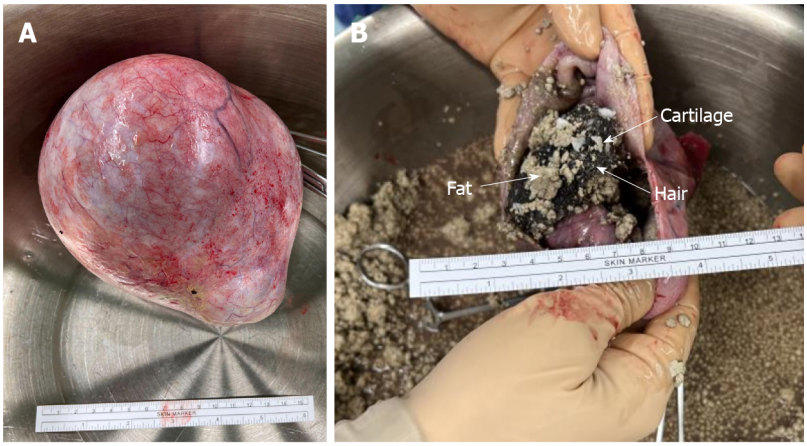

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Figure 2 Surgical image of the tumor. A: Gross picture of the tumor; B: After incising the tumor, the content showed hair-like small ball-like adipose tissues, and cartilage.

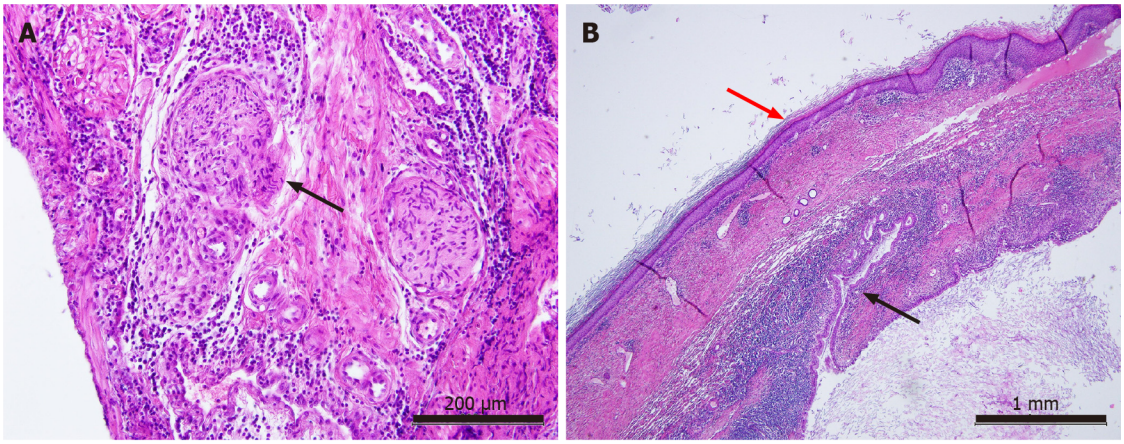

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Figure 3 Histopathological study of the tumor (hematoxylin-eosin staining). A: Nerve fiber (black arrow), scale bar = 200 μm; B: Squamous epithelium (red arrow) and columnar epithelium (intestine, black arrow), scale bar = 1 mm.

avoid content spillage. The choice of surgical method can be considered individually.

This report illustrates one case. The results of this report may not be applicable to another case of ruptured teratoma. Therefore, these results should be interpreted with caution.

CONCLUSION

We report a rare case of a ruptured teratoma causing symptoms, such as pelvic inflammatory disease and ovarian malignancy. Ultrasound and CT scan images cannot differentiate the actual tumor characteristics. After surgical exploration, a ruptured teratoma was diagnosed. This case illustrates the differential diagnosis of an ovarian tumor. Surgery is the mainstay for treating a ruptured teratoma.

ACKNOWLEDGEMENTS

We thank Dr. Ming-Hsun Li for his assistance with the pathological pictures.

FOOTNOTES

Author contributions: Ding DC and Lai PH contributed to conceptualization; Lai PH contributed to data curation;

Ding DC and Lai PH wrote—original draft preparation; Ding DC and Lai PH wrote—review and editing.

Informed consent statement: Written informed consent was obtained from the patient (s) to publish this paper.

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

CARE Checklist (2016) statement: The authors have read CARE Checklist (2016), and the manuscript was prepared and revised according to CARE Checklist (2016).

Country/Territory of origin: Taiwan

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S-Editor: Li L
L-Editor: A
P-Editor: Li L

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3858-3863

DOI: 10.12998/wjcc.v11.i16.3858

ISSN 2307-8960 (online)

CASE REPORT

Purpura annularis telangiectodes of Majocchi: 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 scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Exbrayat JM, France; Nazzaro G, Italy

Received: February 20, 2023
Peer-review started: February 20, 2023
First decision: March 24, 2023
Revised: April 3, 2023
Accepted: May 6, 2023
Article in press: May 6, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Purpura annularis telangiectodes of Majocchi (PATM), also known as Majocchi, is a rare subclass of pigmented purpuric dermatoses. The etiology of PATM is unknown, but it seems more common in children and young women. The skin lesions are mostly symmetrical ring-shaped reddish-brown macules on the lower limbs.

CASE SUMMARY

A 9-year-old girl, who has received treated in our department, presented with reddish-brown ring-shaped rash on both lower limbs that had been present for 6 mo. These lesions, red brownish annular or petaloid patches, were mostly found on ankles and lower limber, which do not fade when adding pressure and no feel of infiltration and no atrophy when touching those lesions. Pathological examination showed deposition of hemosiderin in papillary dermis. However, dermoscopy showed the pigmentation in the center as well as the lavender patches on the edge of lesion. The child was thus diagnosed with PATM. After diagnosis, we suggested the patient avoid strenuous exercise. she was given vitamin C tablets for oral and mometasone furoate cream for external use. Follow-up examinations and treatment continue to support the clinical diagnosis to date.

CONCLUSION

This is the first report of investigating PATM using dermoscopy, which can differentiate PATM from other diseases due to its unique microscopic feature under dermoscopy. Although PATM is harmless, it still requires long-term follow-up. Moreover, dermoscopy technique can be applied for observation of multi-site lesions and correlated with histopathology. Thus, we believe this approach could be generalized for future diagnosis of PATM.

Key Words: Pigmented purpuric dermatoses; Majocchi's disease; Dermatoscope; Histology; Case report

Core Tip: Purpura annularis telangiectodes of Majocchi (PATM) also known as Majocchi's disease, is a rare subclass of pigmented purpuric dermatoses. The skin lesions are mostly symmetrical ring-shaped reddish-brown macules on the lower limbs. This disease is more commonly found among children and young women and the etiology is unknown. Currently, the diagnosis of PATM mainly depends on clinical and histopathological features. Dermoscopy, a non-invasive detection technique, could be a promising technique for future PATM diagnosis owing to its good correlation with histopathology, and multi-site observation.

Citation: Pu YJ, Jiang HJ, Zhang L. Purpura annularis telangiectodes of Majocchi: A case report. *World J Clin Cases* 2023; 11(16): 3858-3863
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3858.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3858

INTRODUCTION

Purpura annularis telangiectodes of Majocchi (PATM), also known as Majocchi disease, is a rare subclass of pigmented purpuric dermatoses (PPD). The etiology of PATM is unknown, but it seems more common among children and young women[1]. The skin lesions are mostly symmetrical ring-shaped reddish-brown macules on the lower limbs[2,3]. Thus, some researchers believe that gravity and venous hypertension may be the inducing factors of this disease[4]. The diagnosis of PATM usually depends mainly on the clinical findings and histopathological features. However, different sampling sites or time may affect the pathological diagnosis. Moreover, histopathological examination is an invasive method, which is not conducive to long-term follow-up. Dermoscopy, a non-invasive detection method, has a good corresponding relationship with histopathology and multi-site observation is more beneficial to diagnose the disease. Herein, we applied the dermoscopy to observe a girl who suffered from PATM.

CASE PRESENTATION

Chief complaints

A 9-year-old girl admitted to Kunming Children's Hospital, Kunming City, Yunnan Province, China in November 2021 due to the "repeated reddish-brown ring-shaped rash on both lower limbs for 6 mo".

History of present illness

In the beginning, the lesions were erythematous, where most of them are annular patches, appear on both insteps and ankles. Subsequently, the lesions evolved to both ankles, with sporadic itches. It recurs after topical glucocorticoids. They spread to both legs, with occasional itching. No clinic symptoms of hematuresis, hematocheiza, joint pain or hypodynamia observed during this period of time.

History of past illness

The patient had no history of systemic symptoms, allergies and no specific history of past illness.

Personal and family history

Normal.

Physical examination

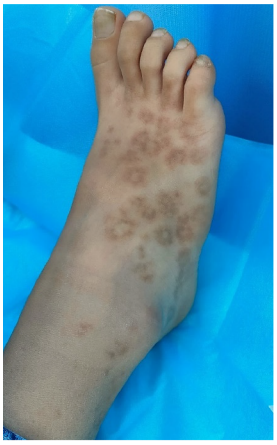
Physical examination revealed good general condition. Dermatological examination results showed that these lesions are red brownish annular or petaloid patches with various size, 1-3 cm in diameters can be observed on both insteps, ankles and lower limber. And they do not fade when adding pressure. During this process, light brownish pigmentation can be observed central of these macules. No feel of infiltration and no atrophy when touching those lesions. Such lesions on instep are shown in Figure 1.

Laboratory examinations

Blood routine, urine routine, liver function, kidney function, antinuclear antibody, coagulation function and erythrocyte sedimentation rate tests were normal.

Dermoscopy examinations

Dermoscopy showed a large number of reticular or honeycomb pigmentation in the center of the lesion,



DOI: 10.12998/wjcc.v11.i16.3858

Figure 1 Macroscopic features of the lesion. The child presented red brownish annular or petaloid patches with various size, 1-3 cm in diameters can be observed on instep.

and lavender patches and a few focally distributed punctate blood vessels were seen on the edge of lesion (Figure 2).

Pathological examinations

Pathological examination showed scattered vacuolar endothelial cells, infiltration of lymphocytes and histocytes around blood vessels, and deposition of hemosiderin in papillary dermis (Figure 3).

FINAL DIAGNOSIS

Combining with relevant examinations, the patient was diagnosed as PATM.

TREATMENT

The patient was given orally dipyridamole tablets 25 mg/bid, vitamin C tablets 0.1 g/bid, and topical mometasone furoate cream and mucopolysaccharide polysulfonate cream bid for external use.

OUTCOME AND FOLLOW-UP

The patient was given orally vitamin C tablets 0.1 g/bid, and topical mometasone furoate cream for external use. We suggested that the girl avoid prolonged stand, as well as strenuous exercises. The skin lesions subsided after 2 wk of treatment. In December 2022, the patient's disease recurred again after intense exercise, and the lesions gradually subsided one month after external medication. Follow-up is ongoing.

DISCUSSION

In this case, dermoscopy data showed a large number of reticular or honeycomb-shaped pigmentations in the center of the lesion, some lavender patches, and a few focally distributed punctate blood vessels at the edge of the lesion. These structures are often observed in lichen sclerosus and pigmented purpuric dermatosis[5]. The purplish red patches under dermoscopy correspond to red blood cell overflow in the histopathological picture, while the pigmentation corresponds to hemosiderin deposition. It is well known that overflowing red blood cells are engulfed to form hemosiderin[1], and pigmentation is the final form of purplish-red patches. The histopathology results for the early rash of PATM shows swollen vascular endothelial cells in the upper dermis and dermal papilla, with a large number of lymphocytes and histiocytes around the lumen, extravasation of red blood cells, and occasional neutrophil infiltration. However, the inflammatory infiltration of old lesions is not as obvious as in the early stages, with reduction in extravasation of red blood cells, and deposition of hemosiderin. Although the pathological manifestations of this patient were consistent with those of old lesions, the active margin could be

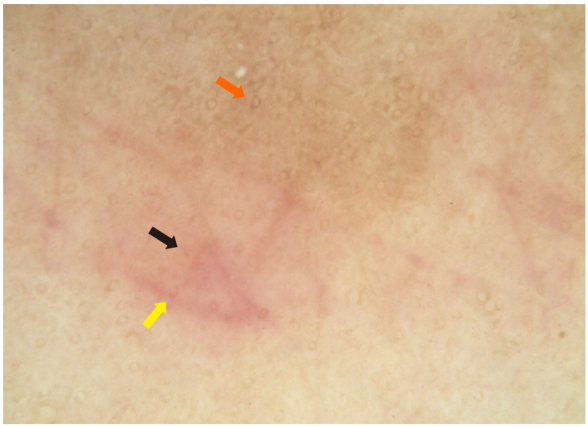


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Figure 2 Dermatoscopic appearance of the lesion. The infiltration method was used (× 50). Dermascopy showed a large number of reticular or honeycomb pigmentation (orange arrow) in the center of the lesion, and lavender patches (black arrow) and a few focally distributed punctate blood vessels (yellow arrow) were seen on the edge of lesion.

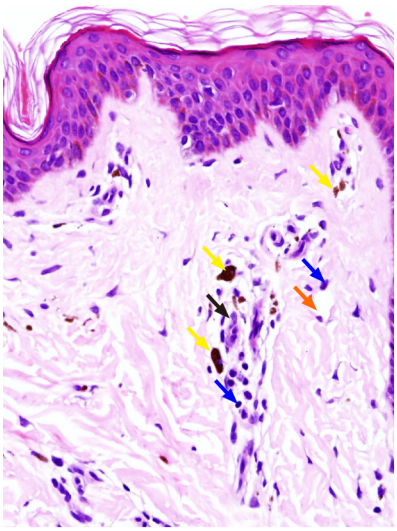

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Figure 3 Histopathological findings. Histopathology showed hyperkeratosis, scattered vacuolar endothelial cells, infiltration of lymphocytes (blue arrows) and histocytes (black arrow) around blood vessels (orange arrow), and deposition of hemosiderin (yellow arrows) in papillary dermis (Hematoxylin eosin staining: Magnification × 400).

clearly observed under dermoscopy.

Differentiating PATM from lichen aureus (LA) and purpuric mycosis fungoides (PMF) could be challenging. LA is another subtype of PPD while PMF is a cutaneous lymphoma with purpuric eruptions as the clinical manifestation[6,7]. PATM and LA can be differentiated by the distribution pattern of pigments and purplish red patches using dermoscopy. PATM shows a ring-like distribution, while LA shows a diffuse distribution[8]. Neither of them has a special vessel structure under dermoscopy, but PMF has its unique vessels such as spermatozoa-like vessels[9]. Therefore, the differences between PATM, LA and PMF on dermoscopy are clear. In addition, we could distinguish the three diseases.

Due to the detection of epidermotropism or monoclonality in inflammatory infiltrates, other hypotheses believed that PPDs represent a type of T lymphocyte, occult and metaepithelial change[10]. There are even some described cases of progression to mycosis fungoides[11,12]. To sum up, although PATM is harmless, cutaneous T-cell lymphoma needs to be ruled out in some cases[2,11,12]. Thus, long-term follow-up of PATM is necessary.

CONCLUSION

PATM, a rare subclass of PPD, also known as Majocchi's disease. The skin lesions are mostly symmetrical ring-shaped reddish-brown macules on the lower limbs and more commonly found among children and young women. The purplish red patches under dermoscopy correspond to red blood cell overflow in the histopathological picture, while the pigmentation corresponds to hemosiderin deposition. Overflowing red blood cells are engulfed to form hemosiderin. Pigmentation is the final form of purplish-red patches. According to the histopathology results, the early rash of PATM shows swollen vascular endothelial cells in the upper dermis and dermal papilla, with a large number of lymphocytes and histiocytes around the lumen, extravasation of red blood cells, and occasional neutrophil infiltration. However, the inflammatory infiltration of old lesions is not as obvious as in the early stages, with reduction in extravasation of red blood cells, and deposition of hemosiderin. Although the pathological manifestations of this patient were consistent with those of old lesions, the active margin could be clearly observed under dermoscopy. It is challenging to differentiate PATM from LA and PMF but dermoscopy enables us to visualize the special vascular structure and pigment distribution pattern and distinguish these three diseases. Although PATM is harmless, the disease is prone to relapse and may resemble the early clinical feature of T-cell lymphoma. Thus, long-term follow-up of PATM is crucial. As a non-invasive detection method, Dermoscopy enables us multi-site observation and to correlates the obtained images with histopathology, which could be a promising approach for future PATM.

FOOTNOTES

Author contributions: Pu YJ and Jiang HJ contributed to the work equally; Pu YJ carried out the studies and drafted the manuscript; Jiang HJ and Zhang L participated in its design and helped to draft the manuscript; All authors read and approved the final manuscript.

Supported by the Scientific Research Foundation of the Education Department of Yunnan Province, No. 2023J0293.

Informed consent statement: Consent was obtained from relatives of 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 CARE Checklist (2016), and the manuscript was prepared and revised according to CARE Checklist (2016).

Country/Territory of origin: China

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S-Editor: Li L
L-Editor: A
P-Editor: Li L

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3864-3869

DOI: 10.12998/wjcc.v11.i16.3864

ISSN 2307-8960 (online)

CASE REPORT

Giant cyst in heterotopic pregnancy: 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 scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Naem AA, Germany; Tolunay HE, Turkey

Received: February 21, 2023
Peer-review started: February 21, 2023
First decision: March 28, 2023
Revised: April 4, 2023
Accepted: May 6, 2023
Article in press: May 6, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

The coexistence of a heterotopic pregnancy with a giant ovarian cyst is an incredibly rare abnormal pregnancy in cases of natural conception. The incidence of this condition has increased significantly as a result of the continuous development of assisted reproductive technologies. When this type of pregnancy occurs, both the continuation of intrauterine pregnancy and the life of the pregnant woman are severely threatened. Early diagnosis and treatment using safe and effective methods are paramount in this situation.

CASE SUMMARY

A 30-year-old primigravida at a gestation age determined as 8 wk 4 d by scan was admitted to the hospital with heterotopic pregnancy and a right ovarian cyst. Laparoscopic resection of the ectopic pregnancy was performed, but the intrauterine pregnancy and ovarian cyst were preserved.

CONCLUSION

The approach to a patient with heterotopic pregnancy and a giant ovarian cyst is individualized base on the fertility requirements. We recommend the following: (1) If the patient satisfies parity and has no fertility requirement, a laparoscopic salpingectomy should be performed and the giant ovarian cyst and intrauterine pregnancy removed; (2) If the patient has fertility requirements wishes to have more children in the future, laparoscopic salpingectomy or salpingostomy should be performed and the intrauterine pregnancy preserved. Serial ovarian cyst aspiration can be performed under ultrasound and resection can be done after delivery; and (3) Heterotopic pregnancy should be diagnosed early by active surveillance during antenatal visits using ultra sound as this is important for the avoidance of catastrophic complications.

Key Words: Heterotopic pregnancy; Ectopic pregnancy; Giant ovarian cyst; Case report

Core Tip: Heterotopic pregnancy with a giant ovarian cyst is an unusual and abnormal pregnancy after natural conception, which can threaten the continuation of intrauterine pregnancy and life of the pregnant woman. Thus, early diagnosis and treatment are essential. This paper reports a rare case of heterotopic pregnancy complicated by a giant ovarian cyst. We recommend that if the patient has satisfied parity, a laparoscopic salpingectomy should be performed and the giant ovarian cyst and intrauterine pregnancy be removed; and if the patient wishes to have more children, laparoscopic salpingectomy or salpingostomy should be performed and the intrauterine pregnancy preserved.

Citation: Kong YY, Chanda K, Ying XY. Giant cyst in heterotopic pregnancy: A case report. *World J Clin Cases* 2023; 11(16): 3864-3869
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3864.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3864

INTRODUCTION

The coexistence of intrauterine and ectopic pregnancy is known as heterotopic pregnancy and has an incidence of 1/100000[1]. The rapid development of artificial reproduction technologies has resulted in increased incidence of heterotopic pregnancies and theca lutein ovarian cysts[2]. A theca lutein ovarian cyst, also called hyperreactive xanthinization, was previously believed to occur in multiple pregnancies, hypertensive disorders of pregnancy, blood group incompatibility, trophoblastic disorders, oral administration of large amounts of estrogen, and in ovulation induced by gonadotropins. This paper retrospectively analyzed a recent case of heterotopic pregnancy with a large theca lutein ovarian cyst. Early diagnosis and treatment is essential in such a situation for increasing the chance of a favorable pregnancy outcome.

CASE PRESENTATION

Chief complaints

No menstruation for more than 3 mo, vaginal bleeding for 1 d.

History of present illness

A 30-year-old female, primigravida, post-assisted reproductive technology (ART), 8 wk 4 d gestational age by scan, Chinese, Han tribe women presented with vaginal bleeding for 1 d. She had no previous history of headache, dizziness, abdominal pain, vaginal discharge, dysuria, diarrhea, coughing, or fever.

History of past illness

The patient's history of past illness was found to be non-revealing.

Personal and family history

The patient had no reproductive history and denied a family history of hereditary diseases or malignancies.

Physical examination

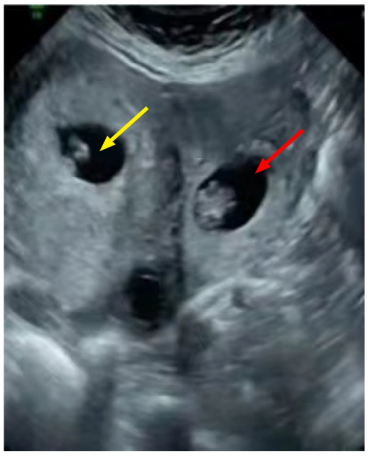
The patient was conscious, mobile, cooperative during the physical examination, and all vital signs were normal. The physical examination of the vagina resulted in blood on a gloved finger. The uterus was approximately the size of that of a woman during the 2nd month of pregnancy. The bilateral adnexal area was thickened and no tenderness was observed.

Laboratory examinations

The carbohydrate antigen 125 was 187 U/mL. Other routine blood and urine tests and tumor markers indicated no abnormalities.

Imaging examinations

A B-scan performed on admission revealed an intrauterine pregnancy at gestation age of 8 wk and 4 d with a heartbeat, enlarged left fallopian tube with a mixed mass of 3.6 cm × 3.4 cm with active blood flow (Figure 1), and a right ovarian mass of 4.9 cm × 4.3 cm.



DOI: 10.12998/wjcc.v11.i16.3864

Figure 1 Longitudinal transvaginal ultrasound demonstrates a left fallopian tube pregnancy (yellow arrow) with intrauterine pregnancy (red arrow).

Further diagnostic work-up

The patient was treated with magnesium sulfate and progesterone for fetal preservation. A reexamination after 4 d revealed the left fallopian tube had an uneven echo mass of 9.2 cm × 5.7 cm and a right ovarian mass of 11.6 cm × 7.1 cm. Close monitoring of the patient was essential considering the abnormal tumor markers, rapidly growing ectopic pregnancy in case of spontaneous rupture, and the possibility of the ovarian mass being malignant, all of which may affect the prognosis of a pregnant woman. After counseling the patient and her relatives, the decision to perform a laparoscopic exploration was taken. Intraoperatively, the uterus was enlarged, the left fallopian tube was enlarged by approximately 5 cm × 8 cm (Figure 2), and a right ovarian cystic mass of approximately 12 cm × 7 cm was recorded (Figure 3). The left ovary and right oviduct were both normal. The patient underwent left salpingectomy for the removal of ectopic pregnancy and the intrauterine pregnancy was preserved. A large theca lutein cyst was found on the right ovary during the procedure and resection was not performed as a means of avoiding a decrease in progesterone, which could have potentially led to intra-abdominal pregnancy abortion. Pathology following the left salpingectomy confirmed tubal pregnancy. The patient developed severe pain in the right lower quadrant 1 wk after surgery, and torsion of the right ovarian cyst pedicle was not excluded. Rather than opting for a second laparotomy for ovarian cystectomy, the patient underwent right ovarian cyst fluid aspiration *via* the abdomen under ultrasound guidance, and 300 mL yellow liquid was aspirated. The pain of the patient was relieved as a result.

FINAL DIAGNOSIS

From a combination of the medical history of the patient, the physical examination, and related examinations, the final medical diagnosis was determined as left tubal pregnancy complicated by a giant theca lutein right ovarian cyst and intrauterine pregnancy.

TREATMENT

Three weeks after the operation, the patient was generally in good condition and was recovering well. There was no complaint of discomfort and she was discharged. The gestation age upon discharge was 12 wk 3 d, the fetus was visible, and the size of the right ovarian cyst had been reduced.

OUTCOME AND FOLLOW-UP

The patient has since successfully delivered a baby.

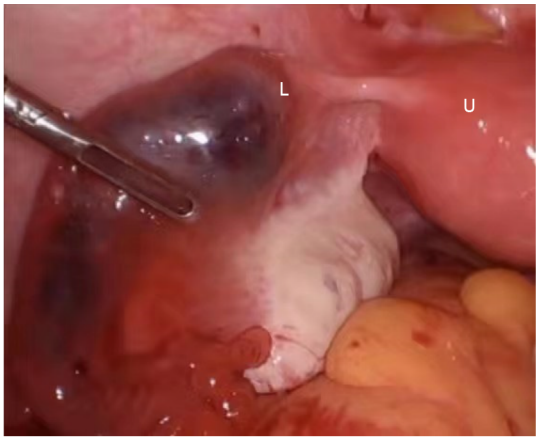


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Figure 2 Intraoperative view of an enlarged uterus (U) and enlarged left fallopian tube with ectopic gestation (L).

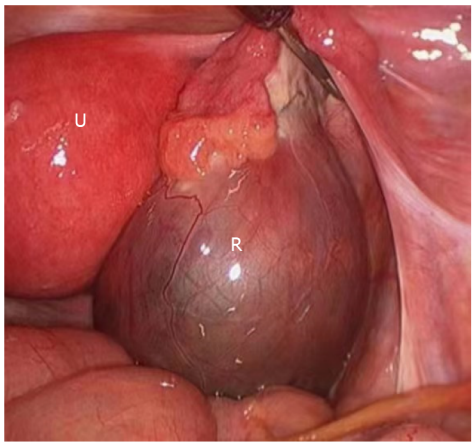

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Figure 3 Intraoperative view of an enlarged uterus (U) and a large theca lutein right ovarian cyst (R).

DISCUSSION

The clinical symptoms of an ectopic pregnancy are identical to those of an intrauterine pregnancy before rupture, but if the ectopic pregnancy ruptures, the presentation is similar to that of a simple ectopic pregnancy. However, without typical acute abdominal symptoms, the presentation may potentially be limited to vaginal bleeding and mild abdominal pain, and this is often misdiagnosed as preterm abortion, which results in treatment delay. Serum β-human chorionic gonadotropin (HCG) is one of the main tools for ectopic pregnancy diagnosis, but the time of multiplication of HCG in intrauterine pregnancy together with ectopic pregnancy is not significantly different to that of intrauterine pregnancy alone, particularly after the second trimester, which lacks diagnostic significance. Ultrasound has a certain amount of value for diagnosing this disease[3]. In this case, a mixed echogenic mass was observed outside the uterus, so ultrasound should not neglect the examination of the fetus during intrauterine pregnancy, particularly in the bilateral adnexal area, so the potential to miss the combined ectopic pregnancy can be avoided. The most common ovarian tumor type that is found during pregnancy is benign teratoma, which is generally detected before pregnancy and shows as a high-density signal on ultrasound. They are generally cystic or solid with indistinct borders, and often combined with a large amount of ascites and elevated carbohydrate antigen 125 and human epididymis protein 4, so a full evaluation of the clinical situation is required to facilitate the diagnosis and differentiation of theca lutein ovarian cysts during pregnancy[4]. Theca lutein ovarian cysts are physiological ovarian cysts and hormone-related cysts and they, can spontaneously disappear if the hormonal stimulation disappears. They also have the characteristic of self-generation[5]. Therefore, surgery is not recommended for theca lutein ovarian cyst during pregnancy, but if the ovarian cysts are twisted or have severe bleeding which leads to ovarian rupture or shock, or if ovarian enlargement results in obstructed labor, surgery is recommended, particularly if malignant tumors are highly suspected[6,7]. However, it is recommended that patients with ovarian cysts in combination with pregnancy be treated

conservatively, but if a tumor is suspected, early detection and elective surgery should be performed as a means of excluding potential malignant tumors or benign tumors with complications such as torsion of the ovarian cyst that could have a negative impact on pregnancy outcome.

Following the diagnosis of heterotopic pregnancy, treatment plan choice should be based on a combination of factors, including the number of weeks of pregnancy or whether the patient wishes to keep the intrauterine pregnancy. For patients who wish to continue intrauterine pregnancy, laparoscopic technique is considered a safe and effective treatment method that, serves as a replacement for traditional open surgery due to its advantages of early diagnosis and treatment, less injury, faster recovery time, fewer postoperative complications, and less interference with intrauterine pregnancy[8]. However, during laparoscopic salpingectomy or salpingostomy, uterine irritation is inevitable, and this can lead to intrauterine miscarriage. At the same time, there is the possibility of some products of conception remaining with salpingotomy, which can lead to persistent ectopic pregnancy. In addition, patients who are treated with salpingectomy have a lower clinical pregnancy rate than those who are treated with salpingostomy or managed expectantly[9]. Patients and their families must be made fully aware of these risks. In this case, the patient firmly requested fetal preservation. As a means of ensuring intrauterine pregnancy continuation and the complete removal of the extra uterine pregnancy, operation time was minimized and uterus stimulation was minimal. A low transverse incision close to the base of the uterus was chosen for opening the abdomen to ensure mechanical stimulation of the uterus was reduced while exposing the adnexa[10]. Intraoperative mechanical stimulation of the uterus and destruction of the corpus luteum of pregnancy should be minimized to the greatest possible extent. Postoperative pain is also known cause of miscarriage, so postoperative analgesics can be given to pregnant women, in addition to magnesium sulfate, as a means of inhibiting contractions and progesterone, which can help prevent miscarriage. Therefore, for heterotopic pregnancy that is complicated by a giant ovarian cyst, individualized treatment based on the fertility requirements of the patient is recommended. If the intrauterine embryo is well developed, laparoscopic surgery is feasible for the removal of the affected fallopian tube and preservation of the intrauterine embryo, enabling the intrauterine pregnancy to continue. Normal pregnancy with ovarian flavin cysts can be diagnosed based on clinical manifestations in combination with ultrasound examination. If complications such as ovarian torsion do not occur, they can be observed until 6 mo after the end of pregnancy, when most will spontaneously disappear. If ovarian torsion occurs and surgery is necessary, conservative surgery can be performed in order to minimize ovarian damage and to ensure the pregnancy continues before full term[11]. In this reported case, theca lutein ovarian cyst with pedicle torsion could not be ruled out by ultrasound, but guided needle ovarian cyst aspiration could be performed on the patient to relieve symptoms. The key factors for treating this disease are early diagnosis, early treatment and correct differential diagnosis of various ovarian tumors. This can help prevent ectopic pregnancy mass rupture, hemorrhage, or ovarian tumor torsion, which can lead to tissue ischemia and necrosis, resulting in serious risk to the life of the pregnant woman and intrauterine embryo. Attention should be paid, to damage during surgery, avoiding affecting uterine and ovarian blood circulation, avoiding unnecessary surgical interventions following surgery, and cooperating with drug therapy, which can improve the success rate of a continued pregnancy.

CONCLUSION

The approach patients with heterotopic pregnancy and a giant ovarian cyst should be individualized based on their fertility requirements. We recommend the following: (1) If the patient has satisfied parity and has no fertility requirements, laparoscopic salpingectomy should be performed and the giant ovarian cyst and intrauterine pregnancy removed; (2) If the patient has the fertility requirement of wanting to have more children in the future, laparoscopic salpingectomy or salpingostomy can be performed to preserve the intrauterine pregnancy. Serial ovarian cyst aspiration can be performed under ultrasound and resection can be performed after delivery; and (3) Heterotopic pregnancy should be diagnosed early by active surveillance during antenatal visits using ultrasound to avoid any catastrophic complications.

FOOTNOTES

Author contributions: Kong YY drafted the manuscript and contributed substantially to revising the manuscript; Chanda K edited the manuscript and contributed substantially to revising the manuscript; Ying XY contributed substantially to revising the manuscript.

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 CARE Checklist (2016), and the manuscript was prepared and revised according to CARE Checklist (2016).

Country/Territory of origin: China

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S-Editor: Li L
L-Editor: Filipodia
P-Editor: Li L

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3870-3876

DOI: 10.12998/wjcc.v11.i16.3870

ISSN 2307-8960 (online)

CASE REPORT

High doses of dextromethorphan induced shock and convulsions in a 19-year-old female: A case report

Shintaro Shimozawa, Daisuke Usuda, Toru Sasaki, Shiho Tsuge, Riki Sakurai, Kenji Kawai, Shun Matsubara, Risa Tanaka, Makoto Suzuki, Yuta Hotchi, Shungo Tokunaga, Ippei Osugi, Risa Katou, Sakurako Ito, Suguru Asako, Kentaro Mishima, Akihiko Kondo, Keiko Mizuno, Hiroki Takami, Takayuki Komatsu, Jiro Oba, Tomohisa Nomura, Manabu Sugita

Specialty type: Substance abuse

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Agrawal A, India; Moldovan CA, Romania

Received: February 24, 2023
Peer-review started: February 24, 2023
First decision: March 24, 2023
Revised: April 14, 2023
Accepted: May 4, 2023
Article in press: May 4, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Dextromethorphan is a prevalent antitussive agent that can be easily obtained as an over-the-counter medication. There has been a growing number of reported cases of toxicity in recent years. Generally, there are numerous instances of mild symptoms, with only a limited number of reports of severe cases necessitating intensive care. We presented the case of a female who ingested 111 tablets of dextromethorphan, leading to shock and convulsions and requiring intensive care that ultimately saved her life.

CASE SUMMARY

A 19-year-old female was admitted to our hospital *via* ambulance, having overdosed on 111 tablets of dextromethorphan (15 mg) obtained through an online importer in a suicide attempt. The patient had a history of drug abuse and multiple self-inflicted injuries. At the time of admission, she exhibited symptoms of shock and altered consciousness. However, upon arrival at the hospital, the patient experienced recurrent generalized clonic convulsions and status epilepticus, necessitating tracheal intubation. The convulsions were determined to have been caused by decreased cerebral perfusion pressure secondary to shock,

and noradrenaline was administered as a vasopressor. Gastric lavage and activated charcoal were also administered after intubation. Through systemic management in the intensive care unit, the patient's condition stabilized, and the need for vasopressors ceased. The patient regained consciousness and was extubated. The patient was subsequently transferred to a psychiatric facility, as suicidal ideation persisted.

CONCLUSION
We report the first case of shock caused by an overdose of dextromethorphan.

Key Words: Dextromethorphan; Drug overdose; Shock; Symptom; Treatment; Case report

Core Tip: Prior studies have posited that dextromethorphan acts as a voltage-gated calcium channel inhibitor, one of its mechanisms of action. It is possible that the high dose in the present case amplified this effect. Previous reports attributed fatalities to central nervous system and respiratory depression, yet shock may also be a contributing factor, as evidenced by this case. This may be a rare occurrence, as it was only observed in the emergency room. We reported the first case of shock caused by an overdose of dextromethorphan. We were able to save the patient's life in intensive care.

Citation: Shimozawa S, Usuda D, Sasaki T, Tsuge S, Sakurai R, Kawai K, Matsubara S, Tanaka R, Suzuki M, Hotchi Y, Tokunaga S, Osugi I, Katou R, Ito S, Asako S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Oba J, Nomura T, Sugita M. High doses of dextromethorphan induced shock and convulsions in a 19-year-old female: A case report. *World J Clin Cases* 2023; 11(16): 3870-3876
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3870.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3870

INTRODUCTION

Dextromethorphan is a readily obtainable and broadly used over-the-counter antitussive drug, and recent years have seen more and more poisoning cases related to dextromethorphan consumption[1-5]. Recreational dextromethorphan consumption in the United States is prevalent among younger generations. Each year, roughly a million individuals aged 12-25 years abuse it non-medicinally[6]. As a result, there are over 6000 emergency department visits in the United States each year caused by dextromethorphan abuse, and half of all dextromethorphan-toxicity-caused emergency department visits occurred in patients aged 12-20 years[7]. Other countries, including Canada, Germany, Thailand, South Korea, and Japan, have also documented similar increases in dextromethorphan abuse cases[8-12].

More broadly, there have been many instances involving mild symptoms; only a small fraction of these reports are for severe cases that necessitated intensive care[13]. We presented the case of a female who ingested 111 tablets of dextromethorphan of Chinese origin, leading to shock and convulsions. She was transported to the emergency room (ER) and requiring intensive care, which ultimately saved her life. We also reported the first case of shock caused by an overdose of dextromethorphan (Figure 1).

CASE PRESENTATION

Chief complaints

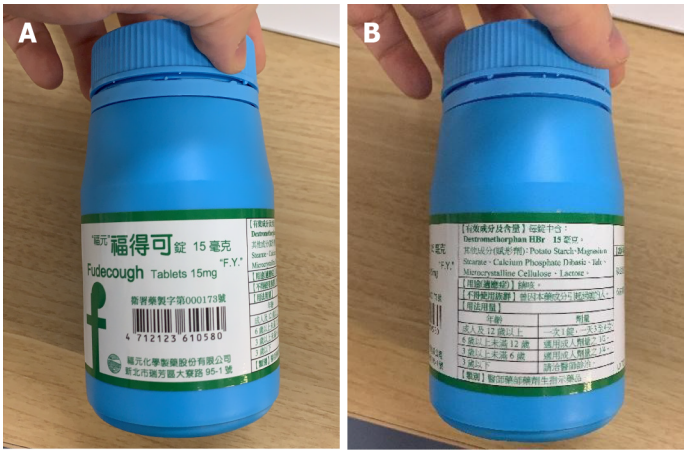
A 19-year-old Japanese female presented to the ER with a complaint of disturbance of consciousness.

History of present illness

The symptoms started 2 h before presentation.

History of past illness

The patient ingested 111 tablets of dextromethorphan (15 mg) of Chinese origin, obtained through an online importer, in a suicide attempt approximately 2 h prior to presentation. The patient's boyfriend discovered that she was lethargic. Once he saw an empty medication bottle, the patient was promptly transported to our hospital *via* ambulance.



DOI: 10.12998/wjcc.v11.i16.3870

Figure 1 The bottle of dextromethorphan pills consumed by the patient. A: Front label; B: Back label. The additives listed are potato starch, magnesium stearate, calcium phosphate dibasic, talc, microcrystalline cellulose, and lactose.

Personal and family history

The patient had a history of previous drug overdose and multiple self-inflicted injuries resulting from jumping.

Physical examination

Upon physical examination, vital signs were as follows: body temperature of 37.7 °C; blood pressure of 82/44 mmHg; heart rate of 120 beats per minute; respiratory rate of 16 breaths per minute; E4V2M4/GCS10; and oxygen saturation of 96% on room air. The radial artery was barely perceptible upon palpation; nonetheless, the extremities were warm.

Her skin was dry, and her pupils were 6 mm/6 mm and reactive. She was drowsy and had difficulty conversing. The muscle tone in her limbs was normal, with no stiffness.

Laboratory examinations

Serum creatine phosphokinase was 106 U/L, and white blood count was 10100/mm^3. The remainder of the complete blood count, prothrombin time, liver function tests, electrolytes, blood urea nitrogen and creatinine were all within normal limits.

Findings from venous blood gas analysis indicated lactic acidosis, likely correlated with shock or seizures (pH 7.114, pCO_2 46.1 mmHg, HCO_3^- 14.8 mmol/L, Glu 65 mg/dL, Lac 12.4 mmol/L). A basic drug screen (SIGNIFY ER) was negative for all drugs. No increase in anion gap or osmotic pressure gap was observed.

Imaging examinations

Echocardiography in the ER demonstrated adequate cardiac contractility (ejection fraction) of 50% or above and an inferior vena cava diameter of 10/6 mm. On a body computed tomography (CT) scan about 2 h after taking the pills, a hyper-dense area in her stomach that was thought to be a drug clot was found. On a brain CT scan, there were no significant findings. An electrocardiogram showed sinus tachycardia, with a QRS of 119 ms and a QTc of 426 ms, without ischemic changes.

FINAL DIAGNOSIS

Acute drug intoxication with dextromethorphan.

TREATMENT

Upon arrival, the patient presented with symptoms of shock and altered consciousness; a significant infusion of extracellular fluid was swiftly initiated. The patient later developed recurrent generalized convulsions and status epilepticus, necessitating endotracheal intubation. We initiated the administration of noradrenaline as a vasopressor. Continuous administration of noradrenaline (maximum 0.2 μg/kg/min) increased blood pressure and halted the convulsions. A plain CT scan revealed a hyperdense area in the patient's stomach, thought to be a drug clot, approximately 2 h post-ingestion.

Subsequently, gastric lavage was performed, and activated charcoal was administered.

OUTCOME AND FOLLOW-UP

After admission to the intensive care unit and comprehensive management, we reduced the dose of vasopressors while confirming that mean arterial pressure was maintained at 65 mmHg or higher. On the 2nd hospital day, vasopressors were discontinued, and the patient was extubated because she was alert. Despite her overall stable condition, the patient was transferred to a psychiatric facility on the 3rd hospital day due to persistent suicidal ideation.

DISCUSSION

Dextromethorphan has long been utilized as an over-the-counter cough suppressant, available in various forms, including oral strips, lozenges, liquids and liquid-filled capsules, and in various formulations. The precise mechanism by which it suppresses coughing remains unclear. Despite structural similarities to opioid agonists, dextromethorphan does not exhibit significant activity at opioid receptors. Dextromethorphan acts on agonism at Sigma-1 receptors and is efficacious as an antitussive to an extent comparable to codeine but without the analgesic or habit-forming characteristics of codeine[14]. Dextromethorphan is a medication with a well-established safety profile when used in therapeutic doses[15].

In humans, dextromethorphan distribution volume is believed to be 5.0-6.7 L/kg[7]. Its protein binding rate is 65%[16]. The serum concentration of dextromethorphan peaks 2.5 h post-ingestion. The primary metabolite of dextromethorphan, dextrorphan, reaches peak plasma concentrations between 1.6-1.7 h after oral administration. The elimination half-life of the parent compound is approximately 2-4 h in individuals with typical metabolic function. Dextromethorphan and its metabolites are primarily excreted through renal elimination, with only very small amounts of fecal excretion[15].

Approximately 90% of individuals, classified as extensive metabolizers, experience rapid and extensive first-pass metabolism of dextromethorphan, resulting in the formation of the major O-demethylated metabolite dextrorphan, mediated by the enzyme CYP2D6. It is vital to note that the enzyme CYP2D6 is polymorphically expressed; some individuals lack activity (known as poor metabolizers), and others express enzyme activity at varying levels[15,17].

The dissociative properties of dextromethorphan are similar to those of ketamine and phencyclidine, owing to the cyclohexane ring and alkylated amine (features common in dissociative agents) found in its structure[18,19]. Dextromethorphan, in higher doses, has a mechanism of action similar to those of phencyclidine and ketamine, in that it antagonizes N-methyl-D-aspartic acid receptors by binding to the calcium ion channel. Blocking the N-methyl-D-aspartic acid receptors modulates excitatory neurotransmission, which brings about hallucinations, euphoria, dissociation, agitation, coma, "out-of-body" experiences and other neurobehavioral effects[1,7,20-22]. Additionally, dextromethorphan inhibits peripheral and central uptake of catecholamine, leading to adrenergic effects such as hypertension, tachycardia and diaphoresis[23]. The life-threatening toxicity associated with dextromethorphan abuse is caused by serotonin syndrome. Because of its serotonin reuptake inhibition properties, dextromethorphan can potentiate excessive body serotonin levels when used along with common prescription selective serotonin reuptake inhibitors or monoamine oxidase inhibitors, which can cause serotonin syndrome to develop[24-26].

Additionally, studies have identified various sites of action at which dextromethorphan and its metabolite dextrorphan interact, including antagonism at nicotinic receptors (a3b4, a4b2, a7), inhibiting serotonin and norepinephrine transporters and inhibiting voltage-gated calcium channels[24]. Other research has found that distinct symptoms occur within specific dosage ranges, which are known as plateaus[18]. Plateau 1 (100–250 mg) elicits a mild stimulant effect similar to that of methylenedioxyamphetamine. Plateau 2 (250–400 mg) is characterized by effects similar to concurrent ethanol and marijuana use, with some individuals experiencing hallucinations. Plateau 3 (450–800 mg) is associated with a dissociative "out-of-body" state akin to that produced by low recreational doses of ketamine. Plateau 4 (> 800 mg) produces a fully dissociative condition similar to ketamine intoxication. Dosages above 1800 mg have been associated with death. A unique study, based on comments left on YouTube videos, also lends credence to these findings[6].

The altered cognitive state brought about by dextromethorphan can lead to injuries. Therefore, a comprehensive assessment for indications of trauma should be a part of examinations[27]. Furthermore, the dissociative and hallucinogenic effects have been reported to potentially lead to suicide, assault and homicide among individuals who are addicted to the drug[28,29]. There are no definitive diagnostic tests for dextromethorphan poisoning, despite its widespread use and potential for abuse. As such, determining diagnoses may be difficult for patients with uncertain medical histories[30,31].

For most patients, dextromethorphan toxicity can be effectively managed through supportive care, including monitoring of the airway, breathing and circulation, and hemodynamic monitoring. In some cases, airway protection may necessitate intubation with ventilator support, and sedation using medication and physical restraints may prove necessary in order to control agitation, violent behavior, and psychosis[32]. When administered within an hour of ingestion, gastrointestinal decontamination with activated charcoal is the most effective treatment for dextromethorphan overdose. Naloxone may serve as a treatment for respiratory depression and central nervous system depression, but reports on its efficacy remain controversial[33]. Due to the large volume of distribution and high protein binding rate of dextromethorphan, blood purification therapy is considered to be less effective for dextromethorphan toxicity.

In this instance, the convulsions were believed to have transpired as a result of a decline in cerebral perfusion pressure owing to shock. The possibility of distributive shock was considered, based on physical and echocardiographic findings. No elevation in blood pressure was detected, despite the administration of a significant volume of extracellular fluid. However, the infusion of noradrenaline raised the patient's blood pressure and terminated the convulsive activity. Without appropriate treatment, the patient would have likely suffered cardiac arrest.

Although the possibility of symptoms arising from other drugs or additives cannot be ruled out, there have been no documented cases thus far (to the best of our knowledge) of shock resulting from dextromethorphan poisoning. Previous research has proposed that dextromethorphan functions as a voltage-gated calcium channel inhibitor among its potential sites of action. To date, no studies have shown sufficient evidence that these receptors are meaningfully activated by therapeutic doses[34]. However, in this particular case, it is feasible that the high dose of 1665 mg, administered orally, augmented the calcium channel inhibitory effect. Blood purification was not deemed necessary, as the convulsions were swiftly mitigated through hemodynamic stabilization. However, it may prove efficacious in the event of severe symptoms.

Given that the patient in question was a petite woman, it is plausible that the dose of dextromethorphan in this scenario could have been lethal. Previous reports have attributed deaths to central nervous system depression and respiratory depression; however, shock may have been the causative factor in this particular instance. It is possible that we were merely fortuitous witnesses in the ER.

CONCLUSION

We reported the first case of shock caused by an overdose of dextromethorphan. Proper monitoring must be instituted when administrating high doses of dextromethorphan, regardless of stable blood pressure, in anticipation of potential hemodynamic disturbances.

FOOTNOTES

Author contributions: Shimozawa S wrote the manuscript; Sasaki T, Tsuge S, Sakurai R, Kawai K, Matsubara S, Tanaka R, Suzuki M, Hochi Y, Tokunaga S, Osugi I, Kato R, Ito S, Asako S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Ohba J and Nomura T assisted in writing the paper; Usuda D and Sugita M oversaw the entire process; all authors read and approved the final manuscript.

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

Conflict-of-interest statement: 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).

Country/Territory of origin: Japan

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8148; Akihiko Kondo 0000-0002-3709-8000; Keiko Mizuno 0000-0002-6326-6872; Hiroki Takami 0000-0003-2955-3752; Takayuki Komatsu 0000-0002-8730-2081; Jiro Oba 0000-0001-8473-8771; Tomohisa Nomura 0000-0001-5632-2584; Manabu Sugita 0000-0002-1956-9286.

S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Ma YJ

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3877-3884

DOI: 10.12998/wjcc.v11.i16.3877

ISSN 2307-8960 (online)

CASE REPORT

Postpartum ovarian vein thrombosis after cesarean section and vaginal delivery: Two case reports

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Specialty type: Obstetrics and gynecology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mohey NM, Egypt; Shariati MBH, Iran

Received: March 10, 2023
Peer-review started: March 10, 2023
First decision: April 10, 2023
Revised: April 18, 2023
Accepted: May 6, 2023
Article in press: May 6, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Postpartum ovarian vein thrombosis (POVT) is a rare puerperal complication. It is easily missed or misdiagnosed due to its insidious onset and lack of specific clinical symptoms and signs. This paper reports two patients who developed right ovarian vein thrombosis after cesarean section and vaginal delivery, respectively.

CASE SUMMARY

Case 1 was a 32-year-old female who underwent a cesarean section in labor at 40 wk of gestation due to fetal distress. The patient was persistently febrile after the operation and escalated antibiotic treatment was ineffective. POVT was diagnosed by abdominal computed tomography (CT) and was treated by increasing the dose of low molecular weight heparin (LMWH). Case 2 was a 21-year-old female with a spontaneous vaginal delivery at 39 wk of gestation. The patient developed fever and abdominal pain 3 days after delivery. POVT was promptly identified by abdominal CT, and the condition was quickly controlled after treatment with LMWH and antibiotics.

CONCLUSION

These two cases occurred after cesarean section and vaginal delivery, respectively. The diagnosis was mainly based on imaging examination due to the unspecific clinical symptoms and signs, the CT scan provided an especially high diagnostic value. Comparing these two cases, escalating antibiotics alone did not provide significant therapeutic benefit, but the early escalation of anticoagulant dosage seemed to shorten the disease course. Therefore, early diagnosis by CT followed by aggressive anticoagulation might have a positive effect on improving the prognosis of the disease.

Key Words: Postpartum ovarian vein thrombosis; Computed tomography; Anticoagulation;

Anti-infection; Case report

Core Tip: Postpartum ovarian vein thrombosis (POVT) is a rare puerperal complication. It is easily missed or misdiagnosed due to its insidious onset and lack of specific clinical symptoms and signs. Retrospective literature showed that anticoagulation and anti-infection agents constituted the main treatment modalities for this disease, and the definite diagnosis before treatment mainly depended on imaging diagnosis, especially computed tomography (CT) scans. This paper reports two cases in which early diagnosis and timely treatment likely led to a shorter disease course. Therefore, for patients in whom POVT is suspected, an early CT scan can assist in the early diagnosis. Of course, in view of radiation and other side effects, the clinical overuse of CT scans should still be avoided.

Citation: Zhu HD, Shen W, Wu HL, Sang X, Chen Y, Geng LS, Zhou T. Postpartum ovarian vein thrombosis after cesarean section and vaginal delivery: Two case reports. *World J Clin Cases* 2023; 11(16): 3877-3884
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3877.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3877

INTRODUCTION

Postpartum ovarian vein thrombosis (POVT) is a relatively rare puerperal complication with an incidence of 0.01%-0.18%[1-3], and is more common after cesarean delivery than vaginal delivery[4]. However, the condition is easily missed or misdiagnosed due to its unspecific clinical symptoms and signs. Delayed diagnosis and treatment may lead to serious complications such as inferior vena cava thrombosis and pulmonary embolism and even endanger maternal life. Therefore, prompt diagnosis and treatment are particularly important. This paper reports two cases of postpartum ovarian vein thrombosis and reviews the relevant literature to provide a reference for the clinical diagnosis and treatment of this condition.

CASE PRESENTATION

Chief complaints

Case 1: A 32-year-old G2P0 female who underwent a cesarean section in labor at 40 wk of gestation due to fetal distress. However, she developed persistent abdominal pain and fever after the operation.

Case 2: A 21-year-old G1P0 female with a spontaneous vaginal delivery at 39 wk of gestation. She also had symptoms such as abdominal pain and fever after delivery.

History of present illness

Case 1: The patient was hospitalized at 40 wk of gestation with possible fetal macrosomia. She had a height of 156 cm, a weight of 72 kg, and a body mass index (BMI) of 29.5 kg/m^2. The patient was administered 0.5% oxytocin (2.5 IU oxytocin added to 500 mL 0.9% sodium chloride injection) by intravenous drip to induce labor. On the same day, frequent late fetal heart deceleration was observed. As the uterine orifice was dilated to only 7 cm, an emergency cesarean section (C-section) of the lower uterine section was performed due to fetal distress. A male newborn with a birthweight of 4130 g and an APGAR score of 10-10/1-5 min was delivered. The operation lasted 32 min and went smoothly, with 300 mL of intraoperative bleeding.

The patient was administered cefuroxime at 1.5 g q8h after the C-section. Referring to the Queensland Clinical Guidelines for Venous thromboembolism (VTE) in pregnancy and the puerperium[5], her risk score was 3 (cesarean section in labor). The patient was administered low molecular weight heparin (LMWH) at 4100 IU qd for standard prophylaxis 12 h after C-section and was informed to mobilize early and move frequently to reduce the risk of thrombosis.

On postoperative day 1, the patient had a fever with a body temperature of 38.2℃ and no abdominal pain. The white blood cell (WBC) count was 16.40 × 10^9/L with a neutrophil percentage (NEUT%) of 88.7%, and the high sensitive C-reactive protein (hs-CRP) level was 67.49 mg/L. On postoperative day 2, she developed right-sided abdominal pain, and the physical examination showed tenderness on the right edge of the uterus. The body temperature was 38.3℃, and the laboratory examinations were repeated, revealing a WBC count of 16.19 × 10^9/L, NEUT% of 91.5%, and hs-CRP of 174.52 mg/L.

Therefore, she was diagnosed with a pelvic infection, and the antibiotic was changed to cefoperazone sulbactam at 2.0 g q8h. On postoperative day 4, the patient showed no improvement in abdominal pain, and the temperature was still 38.2°C, with a WBC count of 12.15 × 10^9/L, NEUT% of 83.4 %, and hs-CRP of 129.11 mg/L. However, the ultrasound of the lower abdomen and vascular ultrasound of both lower extremities showed no significant abnormalities. On postoperative day 6, the body temperature was 37.9 °C, and the right-sided abdominal pain was still present. The WBC count was 12.90 × 10^9/L, with a NEUT% of 82.7%, and an hs-CRP level of 199.22 mg/L. Considering that the abdominal pain and fever had not subsided and the significant increase in hs-CRP, the antibiotic regimen was switched to linezolid at 0.6 g q12h and piperacillin-tazobactam at 4.5 g q8h.

Case 2: The patient was hospitalized for labor at 39 wk of gestation. Her height was 156 cm, her weight was 65 kg, and her BMI was 26.7 kg/m^2. On the night of admission, a male newborn was delivered vaginally with a birth weight of 3450 g and an APGAR score of 10-10/1-5 min. The birth process went smoothly, with a total labor time of 16 h and 200 mL of hemorrhage.

Referring to the Queensland Clinical Guidelines for VTE in pregnancy and the puerperium[5], her risk score was 0. Therefore, the patient was not administered LMWH but was also informed to mobilize early and frequently move to reduce the risk of thrombosis. Two days after delivery, her body temperature was normal, and the recovery was smooth. The WBC count was 12.57 × 10^9/L, the NEUT% was 84.4%, and the hs-CRP level was 57.0 mg/L.

On postpartum day 3, the patient developed a fever of 38.3°C, accompanied by right-sided lower abdominal pain. The physical examination showed tenderness in the right lower abdomen. The WBC count was 12.04 × 10^9/L, the NEUT% was 84.5%, and the hs-CRP level was 167.91 mg/L. Her signs and symptoms were similar to those in case 1.

History of past illness

Case 1: In January 2019, the patient underwent curettage for hydatidiform mole, and the postoperative follow-up was uneventful. She had regular menstrual cycles.

Case 2: The patient had no previous medical history or any surgical interventions in the past.

Personal and family history

Case 1 and Case 2: The personal and family history was unremarkable.

Physical examination

Not applicable.

Laboratory examinations

Not applicable.

Imaging examinations

Case 1: On postoperative day 7, the body temperature was 37.8°C, and an abdominal computed tomography (CT) scan was performed, revealing a strip of high-density shadow in the meridian area of the right ovarian vein (Figure 1A and B), which was highly indicative of venous thrombosis.

Case 2: On postpartum day 3, an abdominal CT scan showed a twisted strip of shadow from the lower pole of the right kidney to the right side of the uterus, which raised suspicions of venous thrombosis. On the next day, a CT enhancement scan revealed a tortuous vascular shadow in the right adnexal area and confirmed the diagnosis of right ovarian vein thrombosis (OVT) (Figure 1C and D).

FINAL DIAGNOSIS

Based on CT scans, both patients were diagnosed with right OVT.

TREATMENT

Case 1: After POVT was diagnosed, the anticoagulation treatment was immediately changed to LMWH 4100 IU q12h. On postoperative day 9, the abdominal pain was significantly relieved, and piperacillin-tazobactam was stopped. On postoperative day 11, the body temperature returned to normal, abdominal pain had disappeared, and linezolid was stopped. On postoperative day 12, she was discharged from the hospital and treated with LMWH at 4100 IU q12h for 3 mo.

Case 2: After right OVT was diagnosed, LMWH was administered at 4100 IU q12h for anticoagulation and cefoperazone sulbactam at 2.0 g q8h for anti-infection. With the above treatment, her abdominal

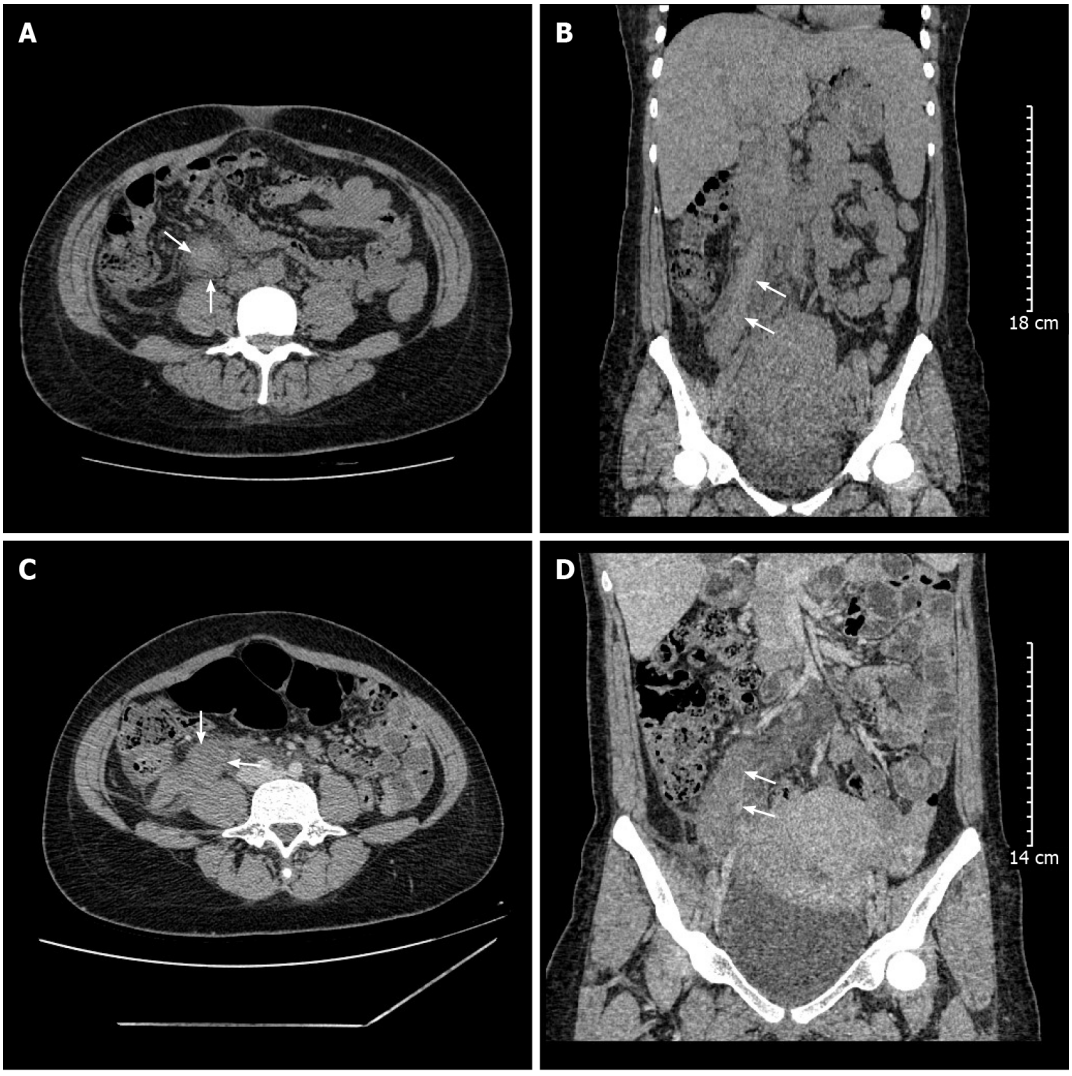

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Figure 1 Computed tomography image showing right ovarian vein thrombosis in case 1 and case 2. A: Axial view (arrows); B: Coronal view (arrows); C: Axial view (arrows); D: Coronal view (arrows).

pain was gradually relieved. On postpartum day 7, the body temperature returned to normal, with minimal abdominal pain. On postpartum day 9, the antibiotics were discontinued, and the patient was discharged. LMWH at 4100 IU q12h was administered for 3 mo.

OUTCOME AND FOLLOW-UP

Case 1: The repeat CT scan 42 days after the C-section revealed that the right OVT had disappeared (Figure 2A).

Case 2: The CT scan 42 days after delivery also revealed that the right OVT had disappeared (Figure 2B).

DISCUSSION

This paper reports two patients with POVT (the timeline from diagnosis to treatment is displayed in Figure 3), one after C-section and the other after vaginal delivery. In case 1, the disease was initially misdiagnosed, which resulted in delayed treatment and slow recovery. Having learned from case 1, our team promptly diagnosed and treated case 2, leading to a quick recovery. Therefore, the literature related to this disease was reviewed and summarized.

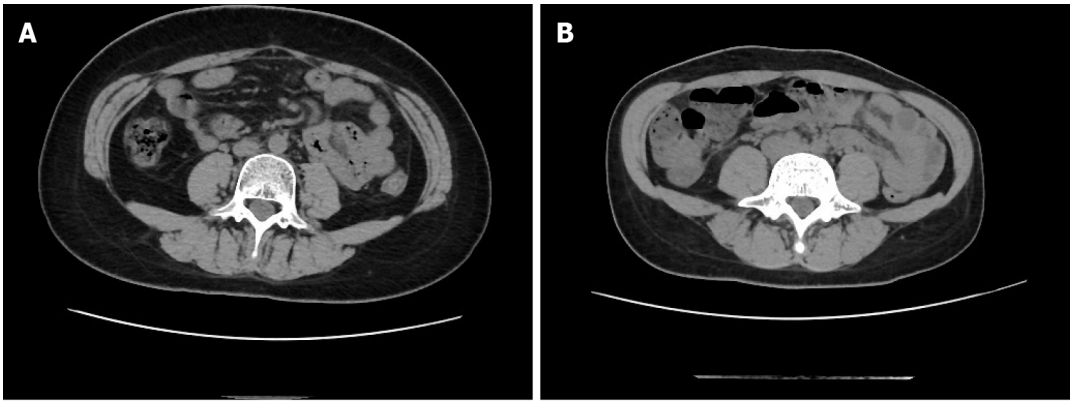

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Figure 2 Computed tomography image. A: The image of follow up computed tomography (CT) in case 1; B: The image of follow up CT in case 2.

A higher incidence has been reported after C-section than after vaginal delivery[2,6], and the right ovarian vein is also significantly more commonly affected than the left, with 80% to 90% of cases involving the right ovarian vein[7]. This finding may be attributed to the right ovarian vein being longer than the left, and the right ovarian vein is compressed by the right rotation of the enlarged uterus in late pregnancy. The two cases reported also developed thrombosis in the right ovarian vein.

POVT has an insidious onset and atypical clinical symptoms. Its most common symptom is lower quadrant abdominal pain, usually on the side of the thrombosed vein[3,8]. Other signs include fever and palpable abdominal mass[9,10]. As the ovarian veins have a deep anatomical location, positive signs on physical examination are also difficult to detect. Hence, the disease is easily missed and misdiagnosed and can lead to serious and fatal complications such as pulmonary embolism[11,12]. According to the literature[13], the peak onset of POVT is 2 d after delivery, and about 90% of cases occurred within 10 d of delivery. In the current study, the 2 cases both developed within 3 d of delivery, which is also consistent with relevant reports. The differential diagnoses include puerperal pelvic infections, ovarian tumor torsion, acute appendicitis, pyelonephritis, and renal calculi. Furthermore, both cases presented with fever and abdominal pain as the main symptoms, with no other specific manifestations. Due to the rarity of the disease and our lack of clinical experience, case 1 was misdiagnosed as a puerperal pelvic infection. However, we learned from the experience, and case 2 was diagnosed early.

The changes observed in the laboratory examination of POVT are also not specific, mostly characterized by an increase in infectious indicators such as WBC count, NEUT%, hs-CRP, and procalcitonin, while urine culture and blood culture are usually negative[14]. These are consistent with the cases reported in this paper.

Imaging examination is of great value in the diagnosis of POVT. Ultrasound has a sensitivity of 63% and a specificity of 78%, while CT has a sensitivity of 100% and a specificity of 90%, and magnetic resonance imaging (MRI) has a sensitivity of 92% and a specificity of 100%[11]. Although ultrasound is more economical and radiation-free, its application is limited by factors such as abdominal distention, resulting in low diagnostic sensitivity and specificity. MRI is radiation-free but costs much more than CT. Although CT involves radiation, it is still used as the preferred choice in diagnosing POVT due to its high sensitivity, specificity, and lower cost compared to MRI. The cases we reported confirmed that CT has higher sensitivity than ultrasound and also has high specificity.

Currently, there are no guidelines or treatment standards for POVT, and the main treatments include anticoagulation and anti-infection agents. However, the optimal treatment remains controversial.

Khishfe *et al*[15] suggested that POVT patients with fever and elevated WBC count be treated with broad-spectrum antibiotics for 7-10 d. Bannow *et al*[11] also recommended antibiotics for POVT patients with suspected infection but did not recommend a specific duration of treatment. Both cases showed signs of infection, such as fever, elevated WBC count, and hs-CRP levels, and both were treated with antibiotics.

POVT should be considered when antibiotics alone are ineffective, and the symptoms persist or even worsen[16]. In case 1, escalating antibiotics yielded unsatisfactory results, and the condition improved significantly after switching to LMWH q12h. In case 2, broad-spectrum antibiotics were administered after prompt diagnosis, with LMWH q12h, resulting in a significantly shorter disease duration than in case 1. Therefore, our cases support the majority of literature, demonstrating that anticoagulation is necessary for POVT patients, even though there are still no guidelines recommending specific anticoagulant drugs, dosage, and course[17]. In the two cases we reported, the anticoagulant treatment with LMWH at 4100 IU q12h was effective, but case 1 also reflected that the treatment with LMWH at 4100 IU qd was not effective. The duration of anticoagulation is inconclusive, and some literature suggested a mean duration of treatment of 3 mo[3,8,11]. Other authors suggested referring to the clinical management of thromboembolism in pregnancy in the absence of clear evidence[18]. Both cases

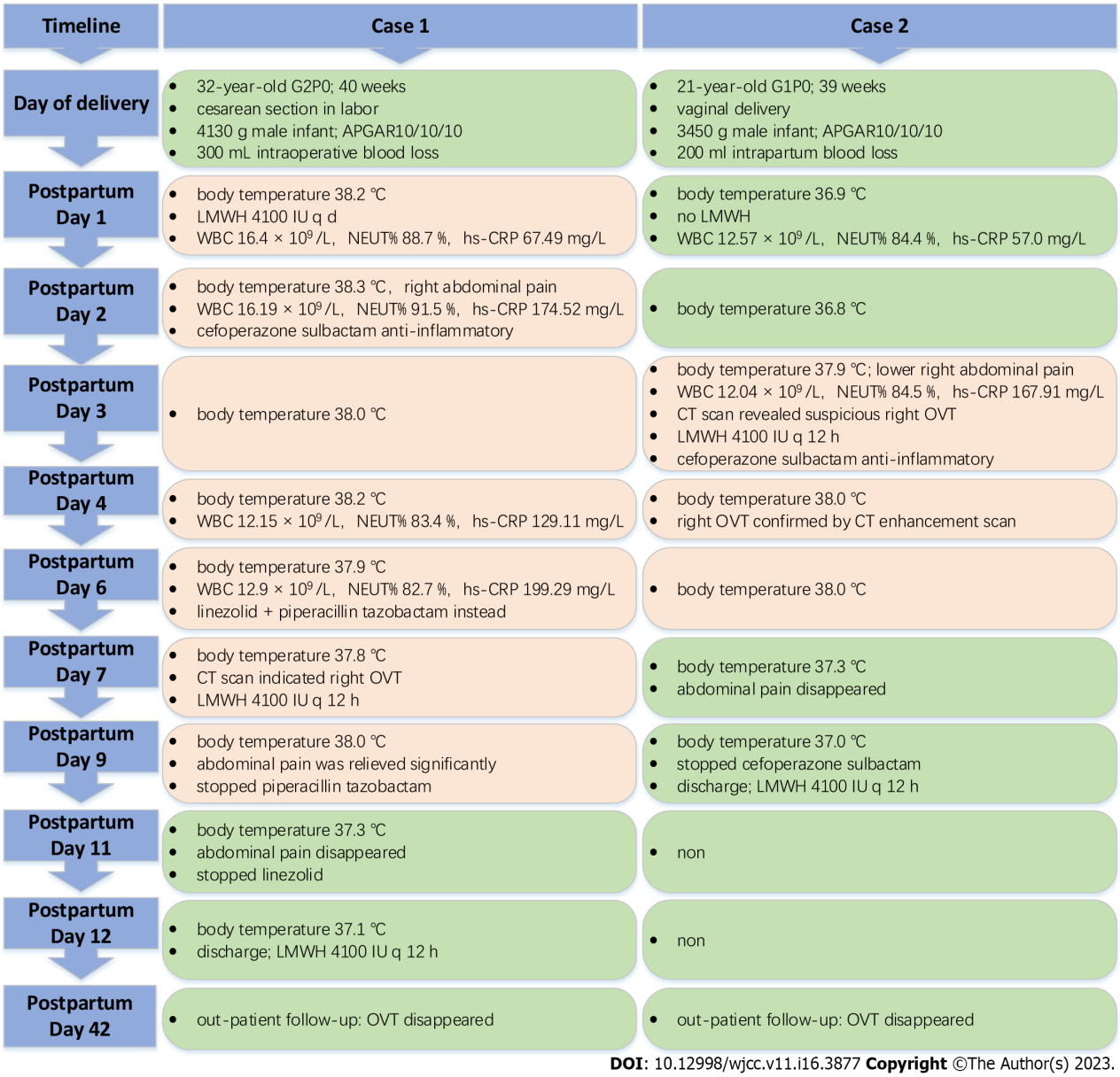

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Figure 3 Time of events and findings. LMWH: Low molecular weight heparin; WBC: White blood cell; NEUT%: Neutrophil percentage; hs-CRP: High sensitive C-reactive protein; CT: Computed tomography; OVT: Ovarian vein thrombosis.

reported in this study were anticoagulated for 3 mo, and the CT scan on postpartum day 42 revealed that the thrombus had disappeared.

CONCLUSION

In conclusion, POVT is a rare and insidious postpartum disease with non-specific symptoms and signs. However, early and definitive diagnosis and treatment are particularly important to shorten the course of the disease and reduce the occurrence of potentially serious complications, such as pulmonary embolism. POVT should be considered in postpartum women with unexplained fever and abdominal pain, especially when antibiotics alone are not effective. CT scan has a high diagnostic value and allows the early diagnosis of suspected POVT patients. Early aggressive anticoagulation and anti-infection agents should have a definite effect. However, in view of radiation and other side effects, the clinical overuse of CT scans should still be avoided.

ACKNOWLEDGEMENTS

We would like to thank these two patients for allowing us to share their cases and using their picture and we are also grateful to all of our team members who were involved in the management of the cases.

FOOTNOTES

Author contributions: Zhu HD and Shen W collected data and drafted the manuscript. Wu HL and Sang X analyzed and interpreted the data; Geng LS and Chen Y contributed to the design of the study and the revision of the manuscript; Zhou T reviewed and approved the final manuscript; All authors have read and approved the final manuscript.

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

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3885-3890

DOI: 10.12998/wjcc.v11.i16.3885

ISSN 2307-8960 (online)

CASE REPORT

Traumatic pancreatic ductal injury treated by endoscopic stenting in a 9-year-old boy: A case report

Hyung Jun Kwon, Min Kyu Jung, Jinyoung Park

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Giacomelli L, Italy; Rocha R, Brazil

Received: March 7, 2023
Peer-review started: March 7, 2023
First decision: March 24, 2023
Revised: March 27, 2023
Accepted: April 24, 2023
Article in press: April 24, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Traumatic pancreatic injury is relatively rare in children, accounting for approximately 3%-12% of blunt abdominal trauma cases. Most traumatic pancreatic injuries in boys are related to bicycle handlebars. Traumatic pancreatic injuries often result in delayed presentation and treatment, leading to high morbidity and mortality. The management of children with traumatic main pancreatic duct injuries is still under debate.

CASE SUMMARY

We report the case of a 9-year-old boy who was presented at our institution with epigastric pain after being stuck with his bicycle handlebar at the upper abdomen and then treated with endoscopic stenting because of a pancreatic ductal injury.

CONCLUSION

We believe that endoscopic stenting of pancreatic ductal injuries may be a feasible technique in certain cases of children with traumatic pancreatic duct injuries to avoid unnecessary operations.

Key Words: Pancreatic injury; Trauma; Endoscopic pancreatic stent; Pediatrics; Case report

Core Tip: Traumatic pancreatic injuries often result in delayed presentation and treatment, leading to high morbidity and mortality. The management of children with traumatic main pancreatic duct injuries is still under debate. We report the case of a 9-year-old boy who was presented at our institution with epigastric pain after being stuck with his bicycle handlebar at the upper abdomen and then treated with endoscopic stenting because of a pancreatic ductal injury. We believe that endoscopic stenting of pancreatic ductal injuries may be a feasible technique in certain cases of children with traumatic pancreatic duct injuries to avoid unnecessary operations.

Citation: Kwon HJ, Jung MK, Park J. Traumatic pancreatic ductal injury treated by endoscopic stenting in a 9-year-old boy: A case report. *World J Clin Cases* 2023; 11(16): 3885-3890
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3885.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3885

INTRODUCTION

Traumatic pancreatic injuries in children are relatively rare because the pancreas is anatomically fixed at the retroperitoneal location, and it accounts for approximately 0.3%-0.7% of all pediatric trauma cases[1-3] and 3%-12% of children with blunt abdominal trauma[4]. Traumatic pancreatic injuries often result in delayed presentation and treatment, leading to high morbidity and mortality. The optimal management of traumatic pancreatic injuries in children has remained a challenge. Herein, we report the case of a 9-year-old boy who was presented at our institution with epigastric pain after being stuck with his bicycle handlebar at the upper abdomen and then treated with endoscopic stenting because of a pancreatic ductal injury.

CASE PRESENTATION

Chief complaints

A 9-year-old boy was admitted to our trauma center with epigastric pain after being stuck with his bicycle handlebar in the upper abdomen.

History of present illness

He complained of mild pain in the epigastric area.

History of past illness

He had a no previous medical history.

Personal and family history

His personal and family history were unremarkable.

Physical examination

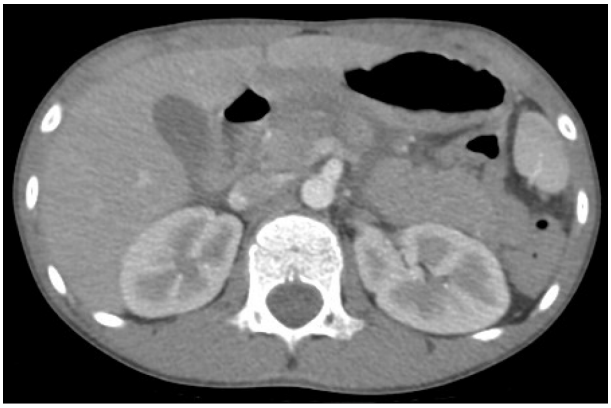
His vital signs were as follows: Blood pressure, 120/80 mmHg; heart rate, 86 beats per min; respiratory rate, 20 breaths per min; and body temperature, 36.5 °C at the time of arrival. The abdominal physical examination revealed mild tenderness in the epigastrium.

Laboratory examinations

Initial laboratory values revealed normal values for his hemoglobin, platelet, erythrocyte sedimentation rate, and C-reactive protein, however, the white blood cell count was elevated to 13.13 × 10^9/L (normal range, 4.8-10.8). Renal and hepatic function tests were also within normal limits. Serum amylase and lipase levels were elevated to 841 (normal range, 28-110) U/L and 1159 (normal range, 13-60) U/L, respectively.

Imaging examinations

The initial abdominal computed tomography (CT) showed a low attenuation line indicating the transection across the neck of the pancreas with mild fat infiltration into the transverse mesocolon (Figure 1). The pancreatic injury was classified as grade III (distal transection or parenchymal injury with duct injury) according to the American Association for the Surgery of Trauma guidelines. On day 2 after the injury, the serum amylase and lipase levels were 1251 and 1033 U/L, respectively. The follow-up abdominal CT showed progression of the pancreatic disruption and an increase in the amounts of



DOI: 10.12998/wjcc.v11.i16.3885

Figure 1 Initial abdominal computed tomography scan shows a low attenuation line indicating the transection across the neck of the pancreas.

fluid around the pancreas.

FINAL DIAGNOSIS

Endoscopic retrograde cholangiopancreatography (ERCP) was performed and revealed a major pancreatic duct disruption with contrast extravasation at the neck of the pancreas (Figure 2).

TREATMENT

Endoscopic pancreatic stenting to the distal pancreatic duct was performed. A 5-French pancreatic stent of 7 cm length was placed successfully into the distal pancreatic duct across the injury site of the pancreatic duct (Figure 3). For 2 wk after the injury, the patient was managed conservatively with fasting and total parenteral nutrition. The postprocedural course after stent placement was uneventful. Serum amylase and lipase levels were normalized. He was discharged from the hospital without complications on day 35 after the injury. The pancreatic stent was removed endoscopically without complications 2 mo after the injury.

OUTCOME AND FOLLOW-UP

Pancreatic duct stricture, pseudocyst, or pancreatic atrophy did not appear on a follow-up abdominal CT 10 mo after the injury. The patient has done well without further symptoms or complications at a follow-up of 4 years.

DISCUSSION

Traumatic pancreatic injuries are relatively rare in children because the pancreas is anatomically fixed at the retroperitoneal location, and they account for approximately 0.3%-0.7% of all pediatric trauma cases [1-3] and 3%-12% of children with blunt abdominal trauma[4]. Most traumatic pancreatic injuries in boys are related to bicycle handlebars[2]. In children, the mechanism of trauma is usually related to the direct compression of the pancreas against the underlying lumbar vertebrae, with a high rate of injury at the pancreatic neck. Traumatic pancreatic injuries often result in delayed presentation and treatment, leading to high morbidity and mortality.

Serum amylase is considered a valuable screening test for traumatic pancreatic injuries. However, the change in serum amylase level by serial estimation must be measured because the serum amylase level may be normal within 48 h after the traumatic injury[5,6].

Abdominal CT remains the most effective and widely available imaging modality to assess the traumatic pancreatic injury in children. However, several reports have mentioned the limitations of CT in detecting pancreatic ductal injuries[6-9]. It may be unreliable in the first 24 h after the traumatic injury because of early tissue edema and the relative lack of retroperitoneal fat planes in children. In addition,

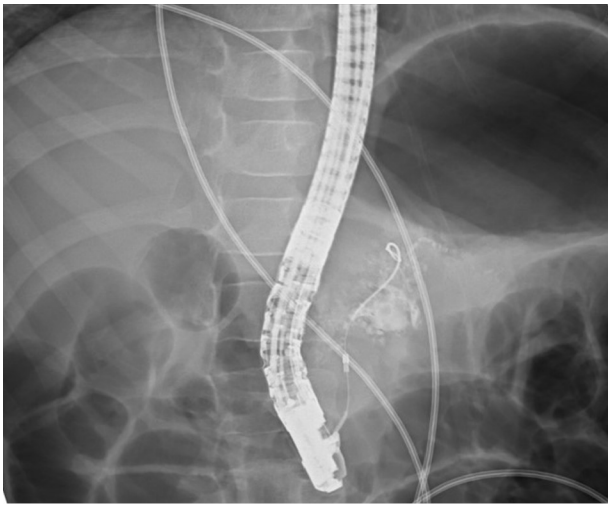


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Figure 2 Endoscopic retrograde cholangiopancreatography reveals a major disruption of the pancreatic duct with contrast extravasation at the neck of the pancreas.

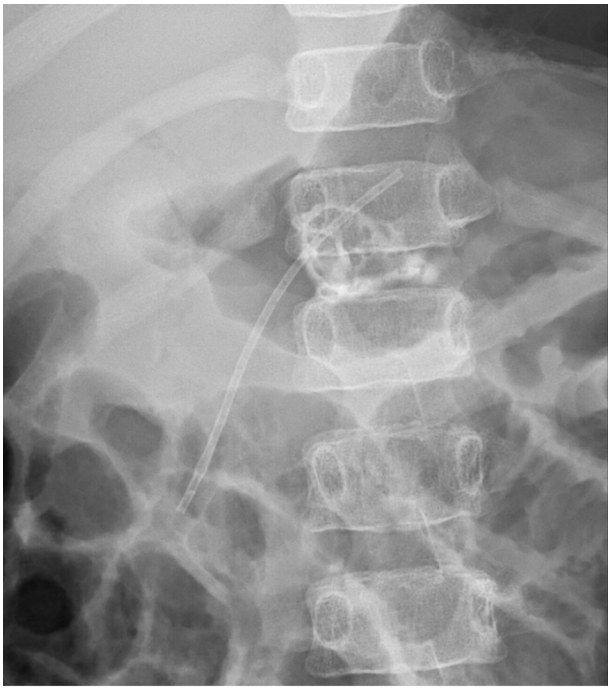

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Figure 3 A 5-Fr pancreatic stent of 7 cm in length was placed successfully into the distal pancreatic duct across the injury site of the pancreatic duct.

the transection of the pancreas may not be apparent until the tissue edema subsides to demonstrate parenchymal disruption[7].

Defining the integrity of the pancreatic duct is critical in making a treatment decision for operative *vs* nonoperative management in a patient with a traumatic pancreatic injury. Compared with CT, magnetic resonance cholangiopancreatography (MRCP) is often performed to gain supplementary information about the integrity of the pancreatic duct. MRCP can distinctly visualize the pancreatic duct injury and other signs of pancreatic injuries, such as laceration, fluid, and hematoma. However, in a multi-institutional analysis, MRCP was more useful than CT for identifying the pancreatic duct but may not be superior for confirmation of the pancreatic duct integrity in children with blunt traumatic pancreatic injuries[8]. They suggested that ERCP may be necessary to confirm pancreatic duct disruption when considering pancreatic resection[8].

The effectiveness of ERCP to delineate the pancreatic duct anatomy in traumatic pancreatic injuries has been well documented in adults. ERCP accurately demonstrates the location and degree of pancreatic duct disruption and guides treatment decisions based on the degree of the pancreatic duct injury. Furthermore, the pancreatic ductal injury may be stented with ERCP to facilitate nonoperative management. Endoscopic pancreatic stenting can also ameliorate the patient's clinical condition and resolve pancreatic fistula or pseudocyst. However, its application in children remains poorly described because of technical difficulty in cannulating the small ampulla of Vater, infection, and post-ERCP pancreatitis. Since the first description by Hall *et al*[10], several studies have suggested the safety and effectiveness of ERCP in children[11-13]. Rescorla *et al*[13] conducted ERCP in six children with major pancreatic ductal transection without serious adverse effects related to ERCP.

The optimal management of traumatic pancreatic injuries in children remains challenging. The advantages and safety of operative *vs* nonoperative management, especially in cases of traumatic pancreatic ductal injuries, are still being debated[14-18]. The nonoperative treatment of a minor pancreatic injury without a ductal injury (grade I) is generally recognized because they usually resolve spontaneously after conservative treatment[19-21]. However, there have been controversies regarding the most suitable management for children (grade II, III, or IV) with more serious pancreatic injuries or main pancreatic duct injuries. Early operative treatment might shorten the length of hospital stay and reduce the incidence of pseudocyst formation and total parenteral nutrition-associated complications. Nevertheless, there would be surgery-related complications, such as pancreatic fistula, small bowel obstruction, and incidental splenectomy[2]. Meier *et al*[17] reported that early surgical pancreatic resection restores the child's health and lessens the inconvenience and emotional stress associated with longer hospitalization than nonoperative management. Jobst *et al*[18] mentioned that distal pancreatic duct injuries were best treated by prompt spleen-sparing distal pancreatectomy. However, since most reports are retrospective studies that analyzed a small number of cases and injuries and management vary, a clear treatment guideline on how to treat pediatric patients with traumatic pancreatic injuries is not easy to establish.

CONCLUSION

In summary, we believe that endoscopic stenting of pancreatic ductal injuries may be a feasible technique in certain cases of children with traumatic pancreatic duct injuries to avoid unnecessary operations.

FOOTNOTES

Author contributions: Kwon HJ, Jung MK, and Park J contributed to manuscript writing and editing, and data collection; Kwon HJ and Park J contributed to data analysis; Jung MK contributed to conceptualization and supervision; All authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient and his parents for publication of this case 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 CARE Checklist (2016), and the manuscript was prepared and revised according to CARE Checklist (2016).

Country/Territory of origin: South Korea

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S-Editor: Li L
L-Editor: A
P-Editor: Fan JR

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3891-3898

DOI: 10.12998/wjcc.v11.i16.3891

ISSN 2307-8960 (online)

CASE REPORT

Novel mutation c.2090_2091del in neurodevelopmental-craniofacial syndrome with variable renal and cardiac abnormalities in an 18.5-mo-old boy: 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 scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Velikova TV, Bulgaria; Watanabe T, Japan

Received: March 14, 2023
Peer-review started: March 14, 2023
First decision: March 28, 2023
Revised: April 6, 2023
Accepted: April 14, 2023
Article in press: April 14, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Neurodevelopmental-craniofacial syndrome with variable renal and cardiac abnormalities (NECRC) is a rare, autosomal, dominant neurological disorder caused by mutations in the *ZMYM2* gene. To date, the clinical and functional characteristics of the novel *ZMYM2* mutation c.2090_2091del have not yet been reported.

CASE SUMMARY

The patient was an 18.5-mo-old Chinese boy with motor and language delay, microcephaly, facial dysmorphism, moderate malnutrition, single palmar crease on the left hand, synpolydactyly of the right foot, hypotonia and feeding problems. The boy who was diagnosed with NECRC was enrolled in the First Affiliated Hospital, Henan University of Chinese Medicine, and his clinical data were collected. From the whole-exon sequencing (WES) data, the pathogenic SNVs/InDels were identified, and the molecular findings were characterized. WES revealed that the heterozygous variant in the *ZMYM2* gene was c.2090_2091del, p.Ser697TrpfsTer3, a frameshift mutation, which is a NECRC-related gene mutation.

CONCLUSION

We performed a systematic literature review to identify and characterize NECRC. Substantial evidence from the literature indicated that patients with *ZMYM2* gene mutation showed different degrees of intellectual disability, motor and language retardation, facial dysmorphism, and a few had congenital heart defects, kidney and urinary tract abnormalities. Early diagnosis and prompt management with comprehensive rehabilitation training are beneficial, but may not improve long-

term outcomes.

Key Words: ZMYM2; NECRC; Frameshift mutation; Global developmental delay; Case report

Core Tip: We describe a patient with neurodevelopmental-craniofacial syndrome with variable renal and cardiac abnormalities caused by *ZMYM2* mutation. Bioinformatics analysis suggested the presence of a novel complex heterozygous variant in the *ZMYM2* gene.

Citation: Li Y, Zhou Z, Xu Y, Wang ZR. Novel mutation c.2090_2091del in neurodevelopmental-craniofacial syndrome with variable renal and cardiac abnormalities in an 18.5-mo-old boy: A case report. *World J Clin Cases* 2023; 11(16): 3891-3898
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3891.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3891

INTRODUCTION

Neurodevelopmental-craniofacial syndrome with variable renal and cardiac abnormalities (NECRC) is an autosomal dominant disorder characterized by craniofacial dysmorphology associated with mild developmental delay, mildly impaired intellectual development or learning difficulties, speech delay, and behavioral abnormalities. Approximately half of patients have congenital abnormalities of the kidney and urinary tract (CAKUT) and/or congenital cardiac defects, including septal defects. We identified a patient with a novel de novo frameshift variant exhibiting the combinational phenotype of developmental delay and facial dysmorphism. Medication combined with comprehensive rehabilitation training was not effective. A literature review including the medical history, clinical symptoms and genetic features of NECRC patients with *ZMYM2* mutations, which further specified the phenotype and genotype of these patients was also carried out. This case report was approved for publication by the Ethics Committees of the First Affiliated Hospital, Henan University of Chinese Medicine, and written informed consent was obtained from the patient's parents and family.

CASE PRESENTATION

Chief complaints

The patient, an 18.5-mo-old boy, was admitted to the First Affiliated Hospital, Henan University of Chinese Medicine on August 31, 2022, due to developmental delay for more than 1 year.

History of present illness

Developmental delay, communication disability, attention deficit hyperactivity disorder, sluggish response, clumsy in movement and behavioral concerns were identified in this patient. He also exhibited decreased appetite, sleep deterioration, and ingestion of a liquid diet. Treatment with lysine hydrochloride resulted in a poor effect and zinc gluconate granules 35 mg twice daily on June 18, 2022 were ineffective. Oxiracetam capsules 400 mg twice daily were added on July 21, 2022 which were mildly effective.

History of past illness

At the age of 6 mo, the patient presented his initial symptom of motor retardation, he had a history of poor motor and language development milestones: he could not sit steadily until 12 mo, could walk with help at 17 mo, could not walk smoothly until 18.5 mo, and only had a single tone. The patient was diagnosed with "global developmental delay" aged 6.9 mo.

Personal and family history

The patient had an abnormal birth history: His mother, a 29-year-old woman, was hospitalized for 2 wk due to small fetal heart at 35 wk of gestation. The boy was delivered by cesarean section at 37 wk of pregnancy because of oligohydramnios, his birth weight was 3000 g (-1 SD), birth length was 51.0 cm (0.80 SD) with no history of asphyxia or hypoxia. The boy is the second child of healthy non-consanguineous parents, his elder sister could only say "baba" and "mama" aged 2 years, and whose language

is currently slightly delayed aged 4 years and 7 mo. Her intelligence, height, weight and facial features are normal. There is no family history of intellectual disability, motor or language retardation.

Physical examination

At 18.5 mo old, his height is 85.5 cm (0.50 SD), weight is 9.2 kg (-2 SD), and head circumference is 45.5 cm (-0.5 SD). He has protruding ears, wide interpupillary distance, broad nasal bridge, thin lips, single palmar crease on the left hand, and synpolydactyly of the right foot (Figure 1). No obvious abnormalities were detected on heart and lung auscultation, abdominal examination, no pigmentation on the skin, no cafe-au-lait-spots, withered and yellow hair, normal hair distribution, no change in physiological curvature of the spine, hypotonia, and normal patellar tendon reflex.

Laboratory examinations

The child has performed the Gesell Developmental Schedule (GDS) four times at different ages (Table 1). At 18.5 mo, the Alberta Infant Motor Scale (AIMS) scores were as follows: Prone position: 21; supine position: 9; sitting position: 12; standing position: 9; total score: 51; AIMS percentile: < 5; equivalent age: 11.5 mo, indicating that motor development was obviously delayed. Electromyographic evoked potential: Visual evoked potentials (VEP): The latency of bilateral P100 was normal, and brainstem auditory evoked potentials (BAEP): The peak latencies of bilateral I, III and V waves and the interpeak latencies of I-III waves and III-V waves were normal.

Further examinations, including 25-hydroxyvitamin D level was 54.4 ng/mL (normal range: ≥ 20 ng/mL) at the age of 6.9 mo; thyroid function: T3: 2.590 nmol/L (normal range: 1.32-4.07 nmol/L), T4: 146.200 nmol/L (normal range: 73-206 nmol/L), TSH: 5.530 mIU/L (normal range: 0.73-8.35 mIU/L), were in the normal range for the age of 8.7 mo. At 14.5 mo, neuromuscular function showed that the activity of the surface electromyographic signal (sEMG) of the gastrocnemius and adductor muscle was normal. Sensory function tests showed sensory processing disorder, chromosome karyotype analysis showed no obvious abnormalities, and blood metabolic screening (blood amino acids and acyl carnitine) was normal. Urinary metabolic screening (urine organic acid analysis) showed that 2-hydroxyisobutyric acid-2 was 1.5 (normal range: 0.0-0.5), oxalic acid-2 was 9.3 (normal range: 0.0-1.0), phosphate-3 was 132.3 (normal range: 0.0-72.7), palmitic acid-1 was 60.8 (normal range: 0.0-23.3), illustrates that insufficient energy production in the body. Otoacoustic emission (OAE) showed that both the left and right ear passed; acoustic impedance testing: both left and right ear were As, explains the pressure in the middle ear cavity is normal, the peak value decreases < 0.33 cc. Serum vitamin A level was 0.34 mg/L (normal range: 0.30-0.70 mg/L) and serum vitamin E was 11.9 mg/L (normal range: 5.0-20.0 mg/L).

Imaging examinations

At the age of 14 mo, cardiac color ultrasound showed that there was no obvious abnormality of intracardiac structure, and a normal range of left ventricular systolic function was observed. At 18.5 mo old, color ultrasound of the urinary system showed that there were no obvious abnormalities in the kidneys, ureter and bladder. At the age of 12.1 mo, digital radiography showed synpolydactyly of the right foot. At the age of 14.5 mo, magnetic resonance imaging (MRI) of the brain showed that the bilateral frontotemporal subarachnoid space was slightly wider.

Further diagnostic work-up

A retrospective case study of the boy diagnosed with NECRC was performed in August 2022. He underwent a neurological examination, GDS, AIMS, VEP, BAEP, brain MRI, sEMG, OAE, blood and urinary metabolic screening. His intellectual disability was estimated according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-5. The clinical data of family members were obtained, investigated and independently reviewed by two neurologists.

Genomic DNA extraction

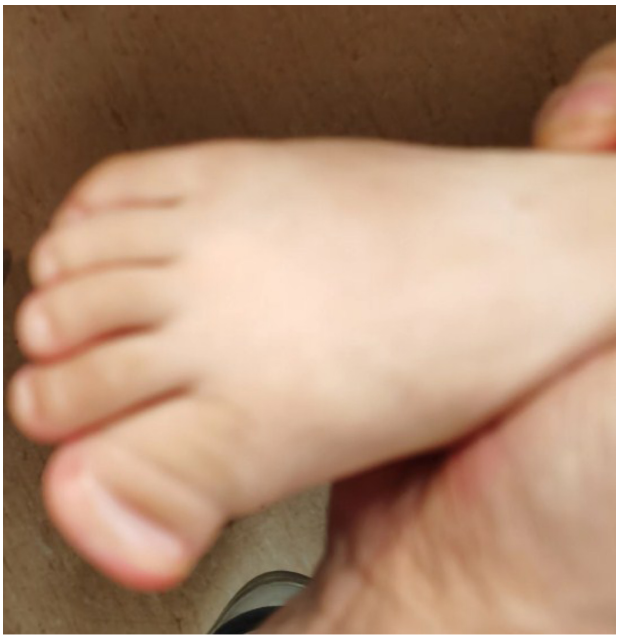
Genomic DNA was extracted from ethylene diamine tetraacetic acid-treated peripheral blood with informed consent from the patient's family using the QIAamp R Blood Mini Kit (Qiagen, Hilden, Germany).

Whole-exon sequencing

The extracted DNA sample was subjected to 0.8% agarose gel electrophoresis analysis, and it was confirmed that the genomic DNA sample was free of serious degradation and impurities, and was evaluated by NanoDrop2000 and Qubit3.0 to determine the concentration and purity of DNA. The DNA was sheared with an M220 Focused-ultrasonicator (Covaris, Woburn, MA, United States), the genomic DNA was fragmented to lengths ranging from 150 to 300 bp, with an average length of 250 bp. The purified product was screened by AMPureXP magnetic beads, and the length of the screened fragment was 400 bp. The DNA target region was captured by hybridizing the genomic DNA sample library with the XGen® Exome Research Panel kit (IDT, United States), which can specifically enrich the exon region of the genome for further processing. The amplified product was purified, the library was quantified by Qubit and inspected with the Bioanalyzer2100 to detect fragment distribution of the library for

Table 1 The developmental quotient of the Gesell developmental schedule

Age	Gross motor	Fine motor	Adaptive ability	Language	Personal social	Comprehensive developmental quotient	Result
6.9 mo	80.0	80.0	87.0	72.0	80.0	80.0	Low developmental quotient
12.1 mo	74.0	62.0	66.0	66.0	74.0	69.0	Low developmental quotient
14.5 mo	72.0	62.0	62.0	41.0	62.0	60.0	Low developmental quotient
18.5 mo	60.8	63.3	75.0	37.8	64.1	60.2	Mild defect



DOI: 10.12998/wjcc.v11.i16.3891

Figure 1 Characteristics of the right foot.

sequencing. The captured and amplified DNA sample was sequenced using Illumina NovaSeq6000 (Illumina, San Diego, CA, United States) with 150 base-paired end reads.

Detection of SNVs/Indels

Sequencing data were analyzed to identify disease-associated SNVs/Indels according to an in-house pipeline. Both public software and commercial packages were used during bioinformatics analysis. Raw data were processed with FASTP with adapters removing low-quality reads. The paired-end reads were then performed against the Ensemble GRCh37/hg19 reference genome with the Burrows-Wheeler Aligner. Base quality score recalibration and SNVs/Indels were conducted by the HaplotypeCaller tool of GATK after the necessary post-processes on primary alignment. SNVs/Indels were screened according to sequence depth and variant quality, and high quality and reliable variants were obtained. Notably, the online system was independently used to annotate database-based minor allele frequencies (MAFs), and the American College of Medical Genetics and Genomics (ACMG) practice guideline-based pathogenicity of every yielded gene variant was determined for conservative analysis and protein product structure prediction. Each variant was compared against several public databases, dbSNP, gnomAD, 1000 genomes project, Exome Aggregation Consortium (ExAC), Chigene in-house MAFs database and NHLBI Exome Sequencing Project 6500 (ESP6500) to achieve allele frequency in the general population. Mutationtaster, Provean, Sift, M-Cap, Polypen2_hdiv, Polypen2_hvar, and Revel software packages were used to predict protein product structure variation.

Genetic analysis

Whole-exon sequencing was performed to identify disease-causing variants. A novel heterozygous variant (NM_197968.3: c.2090_2091del, p.Ser697TrpfsTer3) of *ZMYM2* gene that occurs in exon 11 was identified, as evidenced by the deletion of nucleotides from 2090 to 2091 of the *ZMYM2* gene

(c.2090_2091del), resulting in the change of serine at position 697 to tryptophan and downstream amino acid at position 3 was the stop codon (p.Ser697TrpfsTer3). From the pedigree of the family, it was found that neither of the parents carried the variant, they were wild-type and had no obvious clinical phenotype (Figure 2). The clinical phenotype associated with *ZMYM2* gene mutation is NECRC, which has not been reported in the control population (gnomAD and ClinVar).

This frameshift variant was detected according to ACMG from the following evidence: (1) There was a frameshift variant in the *ZMYM2* gene where loss of function (LOF) is a known mechanism of the disease, PVS1; (2) All sequence variants in the proband and parental samples were confirmed by Sanger sequencing analysis and the variant was de novo, and the phenotype was in accordance with the *ZMYM2* gene, PS2_Moderate; and (3) The variant was absent in the control population in the Exome Sequencing Project, gnomAD, 1000 Genomes Project or ExAC, PM2_Supporting. With the evidence of PVS1 + PS2 + PM2, the class of this variant was categorized as pathogenetic.

FINAL DIAGNOSIS

The patient was diagnosed with NECRC and *ZMYM2* gene (c.2090_2091del, p.Ser697TrpfsTer3) mutation.

TREATMENT

Early comprehensive rehabilitation training was conducted on the basis that routine treatment might not improve the long-term outcome of NECRC patients.

OUTCOME AND FOLLOW-UP

Detailed history-taking and follow-up examinations 6 mo later showed that the patient was lagging behind in motor and language development.

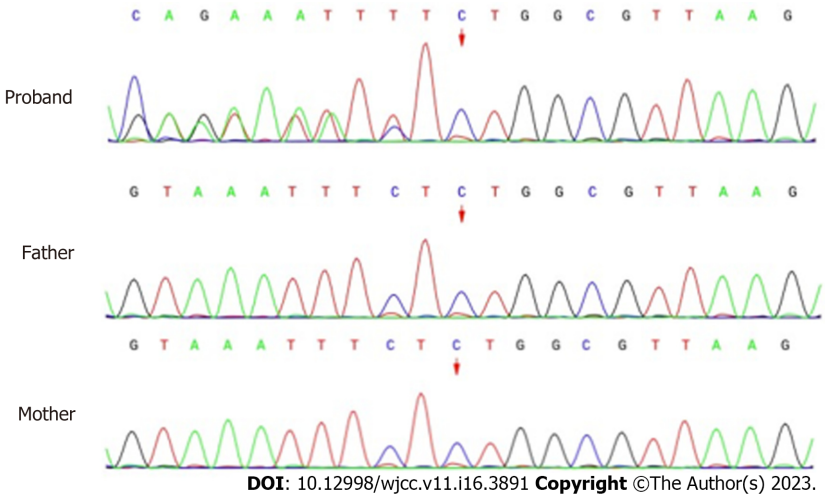
DISCUSSION

The data in our study indicated that *ZMYM2* mutation was the cause of NECRC, and the mutation site of c.2090_2091del (p.Ser697TrpfsTer3) in the *ZMYM2* gene was a novel frameshift mutation. This is the first report of the *ZMYM2* (c.2090_2091del) mutation in a pediatric patient and expands the genotype and phenotypic spectrum of NECRC.

ZMYM2, also known as ZNF198, FIM or RAMP, is a member of the family of MYM-type zinc finger proteins. ZMYM2 is a cellular transcription factor with a zinc finger structure coding gene which localizes to the nucleus, specifically the promyelocytic leukemia (PML) body, and is a novel B-MYB binding protein that contains 1377 amino acids with a molecular mass of 150 kDa. ZMYM2 is encoded by the zinc-finger protein that harbors 2 putative nuclear localization signals (NLS) and 10 MYM type zinc fingers, and the zinc finger domain acts as a transcription factor that mainly binds to the targets DNA and RNA. The zinc finger structure also mediates protein-protein interactions to regulate the efficiency of binding nucleic acids[1]. The N-terminal of ZMYM2 includes 3 action sites related to Small Ubiquitin Like Modifier, including a MYM zinc finger domain and a proline/valine-rich domain, is related to the formation and stabilization of PML nuclear bodies (PML-NBs), the C-terminal acidic domain contains a putative NLS and a region similar to Cre-likedomain[1-4], and mutant mRNA transcripts are predicted to undergo nonsense-mediated decay, which prevents its translation, leading to ZMYM2 haploinsufficiency and LOF[5].

ZMYM2 has a specialized role in pronephric development in a subset of regions, LOF variants in ZMYM2 induce CAKUT-like defects. Quantification of sites with morpholino oli-gonucleotides knockdown of ZMYM2 demonstrated a loss of posterior atp1a1 signal in 30% of embryos, and human disease features are replicated in *Xenopus tropicalis* larvae with morpholino knockdowns, in which expression of truncated ZMYM2 proteins, based on individual mutations, failed to rescue renal and craniofacial defects, and heterozygous ZMYM2-deficient mice showed features of CAKUT with high penetrance. The discovery of monogenic causes of CAKUT, indicating potential mutation and LOF in ZMYM2 in its interaction, provides a new way to identify the cause, study the pathogenesis of this type of disease and develop relevant treatment regimens.

We also reviewed the literature[5] and found 15 different heterozygous nonsense or frameshift mutations of *ZMYM2* in 16 unrelated families, and 19 affected individuals with CAKUT and/or syndromic extra-renal features, and the heterozygous truncated mutations affected reproductive



DOI: 10.12998/wjcc.v11.i16.3891 **Copyright** ©The Author(s) 2023.

Figure 2 *ZMYM2* gene sequencing of the proband and his parents.

function. The genes related to the single gene form of CAKUT accounted for 14%-20% of cases[6-8], neurological manifestations were noted in 17 affected individuals in 15 unrelated families, including 5 individuals with intellectual disability, 10 individuals with motor retardation, 5 individuals with speech delay, 8 individuals with urinary system abnormalities, 6 individuals with heart abnormalities, 4 individuals with hypodystonia and 5 individuals with microcephaly.

ZMYM2 selectively binds to the LSD1–CoREST– HDAC1 ternary complex, which is characterized as a corepressor of transcription by interacting with different nuclear receptors, and is associated with LSD1-containing corepressor complexes, such as the LSD1-CoREST-HDAC1 complex on chromatin to regulate gene expression[5,9]. There are multiple ZMYM2 interactors, including members of the LSD1- CoREST-HDAC1 pathway, suggesting that the wider range of ZMYM2 interaction groups, including DNA-binding transcription factors, transcriptional-corepressors, and proteins related to chromatin regulation and tissue, represent potential candidates for urinary tract malformations[3].

FOXP transcription factors play important roles in neurodevelopment, and FOXP cooperatively regulates gene expression by forming homo- and hetero-dimers with each other. ZMYM2 is a novel FOXP-interacting transcription factor[10], and other genes in this interaction group can also be considered candidates for participation in the disease due to FOXP1 or ZMYM2 LOF mutations. Most pathogenic pathways of ZMYM2-like proteins remain elusive, and further work is required to clarify the role of potential interactions in the pathogenesis of NECRC caused by *ZMYM2* mutations.

CONCLUSION

Relatively few genetic findings have reached the clinic, and in the wide array of inherited metabolic disorders, NECRC has attracted increasing attention due to the neurological damage it causes. The *ZMYM2* gene (c.2090_2091del, p.Ser697TrpfsTer3) mutation induces a variety of clinical phenotypes, such as neurodevelopmental disorders, intellectual disability, autism spectrum disorder, schizophrenia, congenital heart defects, hydroureter, duplex and cystic kidneys. For patients with suspected NECRC, accurate molecular diagnosis can be provided promptly in children carrying the genetic mutation, which is of great significance for early intervention, precise treatment and family genetic counseling on NECRC.

ACKNOWLEDGEMENTS

The authors are thankful to the patient and his family for making this study possible. Responsibility for interpretation of data, conclusions and opinions lies with the author.

FOOTNOTES

Author contributions: Li Y acquisition of clinical data, interpretation of data and writing-review and editing, analysis of the bioinformatics data; Zhou Z design of the work, acquisition of clinical data; Xu Y and Wang ZR evaluation and care of the patient; and all authors wrote this manuscript.

Supported by the National Natural Science Foundation of China, No. 82205190; and the Foundation for Distinguished Young Talents in Higher Education of Henan, No. [2018]16.

Informed consent statement: The patient's family provided informed written consent prior to study enrollment for publication of this case report.

Conflict-of-interest statement: All 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).

Country/Territory of origin: China

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S-Editor: Liu XF
L-Editor: Webster JR
P-Editor: Zhang YL

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3899-3906

DOI: 10.12998/wjcc.v11.i16.3899

ISSN 2307-8960 (online)

CASE REPORT

Reading impairment after neonatal hypoglycemia with parieto-temporo-occipital injury without cortical blindness: 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 scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Nambi G, Saudi Arabia; Surani S, United States

Received: March 17, 2023
Peer-review started: March 17, 2023
First decision: April 11, 2023
Revised: April 24, 2023
Accepted: April 27, 2023
Article in press: April 27, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Perinatal brain injury may lead to later neurodevelopmental disorders, whose outcomes may vary due to neuroplasticity in young children. Recent neuro-imaging studies have shown that the left parietotemporal area (which includes the left inferior parietal lobe) is associated with phonological awareness and decoding skills, which are essential skills for reading acquisition in children. However, the literature on the effect of perinatal cerebral injury on the development of phonological awareness or decoding ability in childhood is limited.

CASE SUMMARY

We report the case of an 8-year-old boy who presented with reading difficulty following a perinatal injury in the parieto-temporal-occipital lobes. The patient was born at term and was treated for hypoglycemia and seizures during the

neonatal period. Diffusion-weighted brain magnetic resonance imaging on postnatal day 4 revealed cortical and subcortical hyperintensities in the parieto-temporo-occipital lobe. At the age of 8 years, physical examination was unremarkable, aside from mild clumsiness. Despite occipital lobe injury, the patient had adequate visual acuity, normal eye movement, and no visual field defects. Full-scale intelligence quotient and verbal comprehension index on Wechsler Intelligence Scale for Children-Fourth Edition were 75 and 90, respectively. Further assessment revealed adequate recognition of Japanese Hiragana letters. However, he had significantly slower reading speed in the Hiragana reading test than control children. The phonological awareness test revealed significant errors (standard deviation +2.7) in the mora reversal task.

CONCLUSION
Patients with perinatal brain injuries in the parietotemporal area require attention and may benefit from additional reading instructions.

Key Words: Brain diseases; Hypoglycemia; Dyslexia; Long-term care; Education; Case report

Core Tip: Limited research on the effect of perinatal cerebral injury on the development of reading ability in childhood is available. Herein, we report the case of an 8-year-old boy presenting with reading difficulty (dyslexia) following perinatal injury in the parieto-temporal-occipital lobes. Despite occipital lobe injury, the patient had adequate visual acuity, normal eye movement, and no visual field defects. His verbal comprehension index on the Wechsler Intelligence Scale for Children-Fourth Edition and ability to adequately recognize Japanese Hiragana letters were adequate. However, he showed remarkably poor reading fluency and phonological awareness. Careful attention should be paid to patients with perinatal brain injury in the parietotemporal region.

Citation: Kurahashi N, Ogaya S, Maki Y, Nonobe N, Kumai S, Hosokawa Y, Ogawa C, Yamada K, Maruyama K, Miura K, Nakamura M. Reading impairment after neonatal hypoglycemia with parieto-temporo-occipital injury without cortical blindness: A case report. *World J Clin Cases* 2023; 11(16): 3899-3906
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3899.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3899

INTRODUCTION

Reading is crucial for academic and social success. For reading acquisition, developing phonological awareness and decoding skills in early childhood is vital[1]. Phonological awareness is the ability to recognize, identify, and manipulate syllables and phonemes in language[2]. Decoding is the process of using vowel and consonant combinations to determine word pronunciation[1].

Previous studies using diffusion tensor imaging have demonstrated that microstructural differences in the left parietotemporal region correlate with reading proficiency in the general population[3,4]. In addition, studies using functional magnetic resonance imaging have demonstrated that the left parieto-temporal area is essential for decoding each letter to its respective sound, even for Japanese Hiragana letters[5,6]. Currently, literature describing the effect of prenatal injury to the parietotemporal area on reading ability in later life is limited.

CASE PRESENTATION

Chief complaints

An 8-year-old boy with reading difficulties was referred to our hospital. His mother reported that he struggled with chunking letters when reading, while accurately differentiating between similar Hiragana letters.

History of present illness

The patient was born at term *via* emergency cesarean section due to pregnancy-induced hypertension, with a birth weight of 2628 g and Apgar scores of 10 (at 1 min and 5 min). His mother had finished junior college and did not have diabetes mellitus. On day 2, he was admitted to the neonatal intensive

care unit for poor feeding, apnea, and hypoglycemia (25 mg/dL), and was treated with oxygen and intravenous glucose. On day 3, he experienced neonatal seizures and was administered midazolam for 1 wk. No signs of infection or inborn metabolic errors were observed. Diffusion-weighted imaging on day 4 revealed cortical and subcortical hyperintensities in the bilateral occipital, parietal, and temporal lobes (Figures 1A-C), which diminished on day 12. The patient was discharged after 2 wk.

His developmental milestones were mildly delayed during infancy; he walked, uttered single words, and said two-word sentences at 18, 16, and 27 mo, respectively. His head circumference during youth was within the normal range and his intelligence quotient on the Tanaka-Binet Intelligence Scale at the age of 4 years was 76. He received temporary educational support for simple calculations and clock reading in the first grade, but required no educational support in the second grade, although he received private tutoring after school. His reading problems emerged in the third grade, where he struggled with longer sentences. He had no difficulties solving simple calculations for his age and could solve mathematical problems when the words were read aloud.

History of past illness

No other relevant history was noted.

Personal and family history

No dyslexia or other psychological problems were reported within the family.

Physical examination

Ophthalmological examination showed that his vision was spared (Table 1). Neurological examination showed some soft neurological signs, which were otherwise normal. He had no dysarthria.

Laboratory examinations

Laboratory test values were within normal limits, including those for thyroid function.

Imaging examinations

Magnetic resonance imaging scans obtained at 8 years of age showed mild volume loss in the parieto-temporal region compared with the frontal region, with minimal cortical changes (Figures 1D and F). Fluid-attenuated inversion images obtained at 8 years of age showed a high-intensity area in the white matter of the bilateral parieto-temporo-occipital lobes, which included the periventricular region at the trigone of the lateral ventricles and centrum semiovale (Figures 1E-G). Coronal T2-weighted imaging showed ulegyria in the bilateral parieto-temporal regions (Figure 1H).

FURTHER DIAGNOSTIC WORK-UP

To assess his comorbid neurodevelopmental disorders, his mother rated him using the attention-deficit/hyperactivity disorder (ADHD) Rating Scale-IV. His inattention and hyperactivity-impulsivity subscale scores were in the 80th and 50th percentiles, respectively. Additional interviews did not indicate comorbid ADHD or autism spectrum disorder.

The psychological test results are presented in Table 1. His full-scale IQ on the Wechsler Intelligence Scale for Children-Fourth Edition was subnormal, while his verbal comprehension index was normal. The patient showed impaired cerebral visual perception. His ability to recognize Japanese hiragana letters was adequate for his age, as shown in the Reading/Decoding subtest of the Kaufman Assessment Battery for Children-Second Edition (K-ABC II), which analyzes only the accuracy of letter recognition and is unable to detect the disability of the decoding speed (Table 1). We focused on reading speed for the screening of reading disabilities, as Japanese hiragana characters are phonograms whose letter-to-sound correspondence is extremely clear[7]. In such languages, reading speed is more sensitive than reading errors as an indicator of reading ability[8]. Using the hiragana reading test, a time trial test to evaluate both the accuracy and speed of Japanese hiragana, it was revealed that his hiragana reading speed was significantly impaired. Moreover, his phonological weakness was indicated by significant errors in the Mora reversal test[9,10].

FINAL DIAGNOSIS

The findings of this evaluation resembled those associated with dyslexia, with poor decoding skills and phonological weakness. Dyslexia is characterized by reading disabilities, which are typically caused by impaired decoding skills and phonological weakness[1].

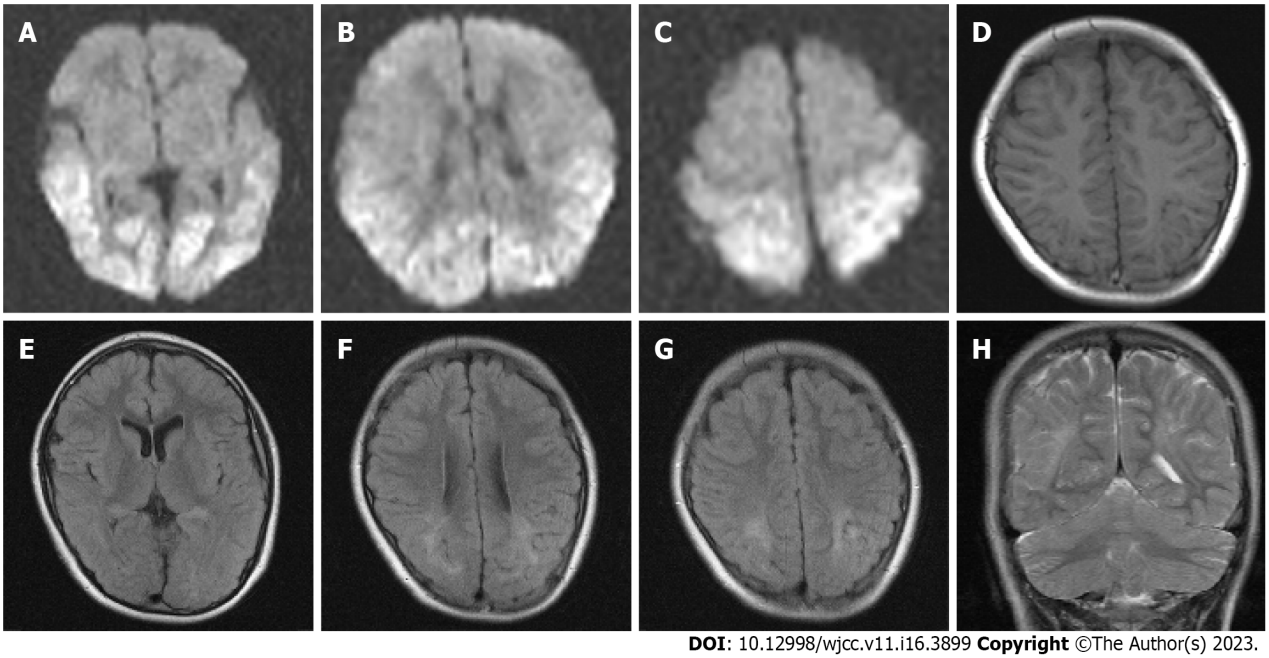
Table 1 Patient's physical examination and psychological test outcomes at age of 8 years

Physical examination parameters	
BCVA, LogMAR (OD/OS)	0.00/0.10
SER(D), (OD/OS)	-2.875/0.375
Eye movement	Normal
Strabismus	No
Fundus oculi	Normal
Confrontational visual field test	Not defected
Neurologic examination	Mildly poor performance in diadochokinesis and finger opposition test
Psychological test parameter	
Wechsler Intelligence Scale for Children-IV	
Full scale intelligence quotient	75
VCI/PRI/WMI/PSI	90/76/76/73
Subtest digit span, SD	-0.67
Developmental test for visual perception	
Perceptional quotient	64
Subtest I/II/III/IV/V, perceptual age equivalent (year:month)	5:03/5:00/4:06/5:08/6:06
Kaufman Assessment Battery for Children II	
Cognitive ability	62
Sequential processing/simultaneous processing/planning/learning	68/60/66/69
Academic achievement	84
Knowledge/reading/writing/arithmetic	88/96/66/102
Subtest reading/decoding	13
Subtest reading and comprehension	6
Subtest verbal knowledge	11
Subtest expressive vocabulary	6
Hiragana reading test	
Reading time/error, SD	
Single mora task	+5.17/+6.63
Word task (words)	+4.06/+0.86
Word task (non-words)	+2.95/+3.25
Sentence task	+5.52/+2.00
Phonological awareness task (mora reversal task)	
Error, SD	
Three-mora word	+0.66
Four-mora word	+2.70

BCVA: Best-corrected visual acuity; OD: Oculus dexter; OS: Oculus sinister; SER: Spherical equivalent refraction; D: Diopter; VCI: Verbal comprehension index; PRI: Perceptual reasoning index; WMI: Working memory index; PSI: Processing speed index; SD: Standard deviation.

TREATMENT

We recommended support using a strategy for children with dyslexia[11]. We insisted to use special textbooks or paper materials with enlarged letters and wider line spacing for dyslexic children. However, the patient refused to do so as he preferred to use the same equipment and materials as other children. Thus, instead, he was given a reduced load of homework and was also assigned an additional



DOI: 10.12998/wjcc.v11.i16.3899

Figure 1 Diffusion-weighted images on day 4, and T1- and T2-weighted images, and fluid-attenuated inversion images at 8 years of age. A-C: Diffusion-weighted images reveal cortical and subcortical hyperintensities in the bilateral occipital, parietal, and temporal lobes; D and F: T1-weighted image and fluid-attenuated inversion image show mild volume loss in the parieto-temporal region, compared with the frontal region, with minimal cortical changes; E-G: Fluid-attenuated inversion images show a high-intensity area in the white matter of the bilateral parieto-temporo-occipital lobes, which includes the periventricular region at the trigone of the lateral ventricles and centrum semiovale; H: T2-weighted image shows ulegyria in the bilateral parieto-temporal regions.

support caregiver for his class so that written materials could be read aloud for him.

OUTCOME AND FOLLOW-UP

Before his medical assessment, he was not an active participant in the class, and he had lost his confidence. After his disability was explained to the patient, his parents, and his teachers and classmates, and after his study environment was improved, his willingness to participate in class increased and he showed better adaptation to school activities and works.

DISCUSSION

A range of long-term developmental deficits may become apparent after perinatal brain injury, depending on the lesions present, and neuroplasticity may modify developmental outcomes[12-14]. Neonatal encephalopathy associated with hypoglycemia commonly affects the occipital lobes and posterior parietotemporal regions. It is reported to cause cortical visual impairment related to occipital lobe injury, intellectual disabilities, cerebral palsy, and intractable epilepsy[15-18]. These individuals are also reported to be at risk of learning and behavioral problems, hyperactivity, attention deficits, and autistic features at school age; however, little has been reported regarding their reading skills[16,18].

In the present case, the patient's reading disability was evident from his significantly impaired reading speed. Although the development of his phonological awareness was significantly delayed compared to that of control children, as shown by significant errors in the mora reversal task, his phonological working memory was spared, as demonstrated by the digit span subtest score on the Wechsler Intelligence Scale for Children-Fourth Edition[9]. In addition, his reading disability was not based on ophthalmological problems or inadequate letter recognition and was demonstrated by his adequate ability to recognize Japanese Hiragana characters shown in the K-ABC II, a test that is not time-limited. Based on these details, we suspected that his reading impairment was related to decoding skill impairment caused by perinatal brain injury that involved the bilateral parietotemporal area.

Little is known regarding the effects of perinatal brain injury on reading ability in later life. Previous studies have shown that at school age, perinatal brain injuries, such as intraventricular hemorrhage, ventriculomegaly, and periventricular leukomalacia, are significant risk factors for lower academic skills (including reading performance) in extremely low birth weight children, independent of gestational age [19,20]. However, this study did not conduct further analysis of the relationship between the affected

brain region and impaired reading ability. Recently, we reported a three-case series of Japanese preterm-born school-aged children with Hiragana-reading deficits. Their reading deficit was strongly suspected to be related to decoding impairment due to perinatal brain injury, specifically periventricular leukomalacia in the parietotemporal region[10]. In contrast, a case report of a girl with periventricular leukomalacia described the possibility of neuroplasticity in young children. The patient's reading and phonological processing skills were spared, although her arcuate fasciculi were destroyed. Based on findings of multiple analyses of diffusion tensor imaging, it was speculated that her spared skills were related to other intact white matter tracts[13]. Our case findings add that perinatal injury in the parietotemporal area is a risk factor for decoding impairment, even in children born at term, while neuroplasticity may modify their outcomes.

Other factors may have affected the patient's reading ability. First, his impaired cerebral visual perception might have affected his reading speed. Poor decoding skills and phonological awareness are recognized as typical characteristics of dyslexia, even in Japanese Hiragana readers[9,21]. However, cerebral visual impairment may affect reading ability when a visual attentional disorder or simultanagnosia are present, as well as when vision clarity, the visual field, or the ability to recognize the spelling materials are impaired[22]. We did not investigate the presence of a visual attentional skill disorder or simultanagnosia in our patient. However, it should be noted that our patient had adequate skill to recognize Hiragana letters, while his phonological awareness was poor. Second, we did not test his naming-speed skills, such as rapid automatized naming tasks. Naming-speed skill is an important factor that affects decoding fluency, reduction of which may affect reading ability even in Japanese Hiragana users[23,24]. Third, we did not exclude the possibility of spontaneous learning disorders. Finally, we did not compare his reading speed with that of full scale intelligence quotient-matched children or with those with a similar perceptual reasoning index or processing speed index. His borderline full scale intelligence quotient score may have affected his reading speed or mora reversal test results; however, this effect may be limited because a recent study has shown no difference in Hiragana non-word fluency reading scores among Japanese students with dyslexia with normal or borderline intelligence quotient[25].

CONCLUSION

School-age survivors of neonatal encephalopathy in the posterior region, involving the parietotemporal area, may be at risk of impaired reading ability even when their ophthalmologic findings are spared. Thorough assessments, including ophthalmological evaluation, psychological tests, and reading tests, are required to assess any educational support needs.

FOOTNOTES

Author contributions: Kurahashi N contributed to the conceptualization, methodology, investigation, writing-original draft of the manuscript; Kurahashi N Ogaya S, Maki Y, and Nonobe N involved in the resources; Ogaya S, Maki Y, Nonobe N, Kumai S, Hosokawa Y, Ogawa C, Yamada K, Maruyama K, Miura K, and Nakamura M participated in the writing-review and editing; and all authors have read and approved the final manuscript.

Supported by the JSPS KAKENHI, JP19K14292.

Informed consent statement: Informed written consent was obtained from the parents of the participant 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: Wang JJ
L-Editor: A

P-Editor: Zhao S

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3907-3914

DOI: 10.12998/wjcc.v11.i16.3907

ISSN 2307-8960 (online)

CASE REPORT

Unusual clinical presentation of oral pyogenic granuloma with severe alveolar bone loss: A case report and review of literature

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Specialty type: Dentistry, oral surgery and medicine

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gica N, Romania; Kukiattrakoon B, Thailand

Received: March 16, 2023
Peer-review started: March 16, 2023
First decision: April 11, 2023
Revised: April 18, 2023
Accepted: May 4, 2023
Article in press: May 4, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Pyogenic granuloma (PG) is a localized, reddish and vascularized hyperplastic lesion of the connective tissue which occurs in the oral cavity. In most cases, the presence of this lesion does not show alveolar bone resorption. The pathology is diagnosed clinically with some caution. However, the diagnosis and treatment are usually corroborated with histopathological evidence.

CASE SUMMARY

Three clinical cases of PG associated with bone loss were described in this study. The three patients presented tumor-like growth which bled on touch, and were associated with local irritant factors. Radiographs showed bone loss. All cases were treated with conservative surgical excision. The scarring was satisfactory, and there was no case of recurrence. The diagnoses were based on clinical findings, and were confirmed histopathologically.

CONCLUSION
The occurrence of oral PG with bone loss is unusual. Therefore, clinical and radiographic evaluations are important for the diagnosis.

Key Words: Hyperplastic lesion; Pyogenic granuloma; Alveolar bone loss; Case report

Core Tip: Pyogenic granuloma is a soft tissue tumor of the oral cavity which frequently does not present alveolar bone resorption. However, these three clinical cases of pyogenic granuloma were associated with bone loss, an unusual feature of this pathology. The patients were treated with conservative surgical excision. The diagnoses were based on the clinical findings which were confirmed with histopathology. These cases underline the importance of clinical and radiographic evaluation as guides for accurate diagnosis so as to enhance the development of an appropriate treatment plan in unusual cases.

Citation: Lomelí Martínez SM, Bocanegra Morando D, Mercado González AE, Gómez Sandoval JR. Unusual clinical presentation of oral pyogenic granuloma with severe alveolar bone loss: A case report and review of literature. *World J Clin Cases* 2023; 11(16): 3907-3914
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3907.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3907

INTRODUCTION

Pyogenic granuloma (PG) is a soft tissue tumor of the oral cavity[1-3]. The etiology of the tumor is unknown, although it is thought that it probably originates from exacerbated response of the connective tissue to trauma, local irritation or hormonal imbalances[1,4]. Pyogenic granuloma has also been considered an "infectious" entity, due to the presence of botryomycosis[1].

PG presents clinically as a smooth mass with a lobular architecture which is usually pedunculated, although some lesions are sessile[5,6]. Radiographic evaluation of this mass has not been considered as a diagnostic strategy. However, the characteristic bone loss associated with PG has been reported only in few clinical cases in India[7-9]. In this study, we report three cases of female patients who presented PG associated with bone loss.

CASE PRESENTATION

Chief complaints

Case 1: A 32-year-old woman presented with a lump on the palate that bled frequently and interfered with chewing.

Case 2: A 42-year-old woman presented with a bulge near the upper lip. The patient complained of pain when chewing and mobility of the central incisor.

Case 3: A 38-year-old woman had two enlargements which bled frequently and interfered with chewing.

History of present illness

Case 1: The patient stated that the lesion appeared approximately 3 mo prior to the clinical diagnosis.

Case 2: In the course of anamnesis, it was revealed that the lesion had 5 mo of evolution. It bled on touch, and it had a firmer consistency than before.

Case 3: The patient said that the lesion had 6 mo evolution period, during which it grew until chewing became an uncomfortable exercise.

History of past illness

Case 1: The patient did not have any history of systemic disease. Thus, the medical record was not relevant.

Case 2: The medical record was not relevant, since the patient denied any pathology or systemic disease.

Case 3: The patient did not mention presence of any systemic disease, and she was not undergoing any medical treatment.

Personal and family history

Case 1: None.

Case 2: Father was diagnosed with Type 2 diabetes mellitus 5 years earlier.

Case 3: Mother was diagnosed with high bold pressure in 2017.

Physical examination

Case 1: Oral examination revealed a localized exophytic lesion manifested as a 25 mm × 12 mm erythematous mass with smooth consistency which bled on provocation. The lesion was pedicled and attached to the marginal gingiva of dental organ 22, and it extended to the middle third of palatal surface of dental organs 21 and 23 (Figure 1A). In addition, dental organ 22 presented grade-three mobility and extensive caries along the palatine surface.

Case 2: During the oral examination, a semi-ovoid 16 mm × 10 mm formation of gingival mucosa was found. The surface was smooth and reddish in color. The growth was pedicled and attached to the marginal gingiva of dental organ 21 (Figure 2A). This dental organ presented grade-three mobility, supra and sub-gingival calculus, and probing depth of 8 mm.

Case 3: During the clinical examination, two reddish exophytic lesions with smooth surfaces were identified. The lesions were about 20 mm × 15 mm and 10 mm × 12 mm in size. They were pedicled and attached to the interproximal zone of dental organs 46 and 47 (Figure 3A). Supra- and sub-gingival calculus were identified in the two dental organs.

Laboratory examinations

Case 1: Hemoglobin level was slightly low (11.8 g/dL). The other results were within normal limits.

Case 2: Neutrophil count was slightly high (72%). However, the levels of the other white cells were within normal limits [platelet level (309 × 10^3/μL) was normal, and hemoglobin level (14.5 g/dL) was normal].

Case 3: Hemoglobin, neutrophil and platelet levels were within normal limits.

Imaging examinations

Case 1: Periapical radiography showed horizontal bone loss up to the middle third region of dental organ 22 (Figure 1B).

Case 2: Panoramic radiography showed generalized alveolar bone loss in both arches (Figure 2B).

Case 3: Periapical radiography showed interproximal bone loss between dental organs 47 and 48 (Figure 3B); and between dental organs 46 and 47 (Figure 3C).

MULTIDISCIPLINARY EXPERT CONSULTATION

Case 1

Based on all the information obtained from anamnesis, and from radiographic imaging, clinical features of lesion such as ulcerated surface, bleeding on provocation, as well as the adjacent local irritants, a presumptive diagnosis of pyogenic granuloma was made.

Case 2

The information obtained from the clinical, radiographic examination, and the history of evolution of the lesion led to a presumptive diagnosis of pyogenic granuloma.

Case 3

Based on all the information obtained during the clinical and radiographic examinations, as well as the clinical features of the lesion, and the adjacent local irritants, the presumptive diagnosis was pyogenic granuloma.

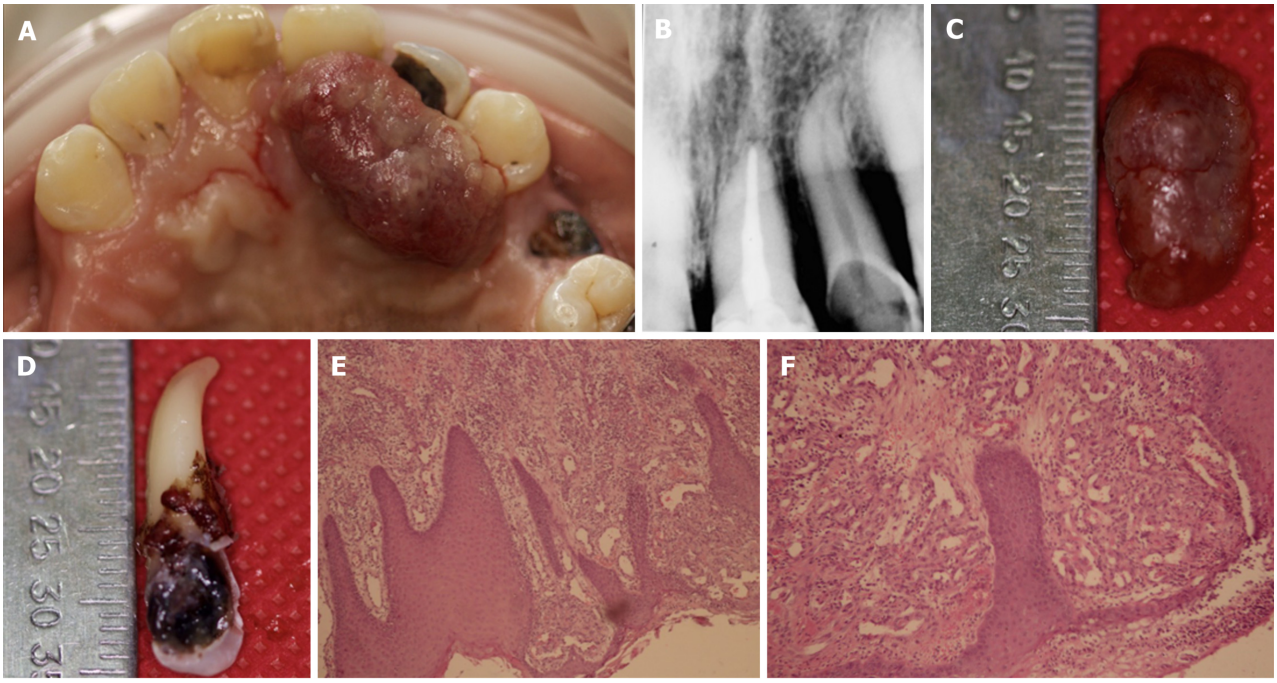

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Figure 1 Clinical, radiographic and histological view of lesion case 1. A: Exophytic and hemorrhagic lesion on the palate; B: Intraoral periapical radiograph of dental organ 22 showing alveolar crestal bone resorption; C: Excised specimen; D: Extracted dental organ 22 showing the extent of caries; E and F: Histopathological views.

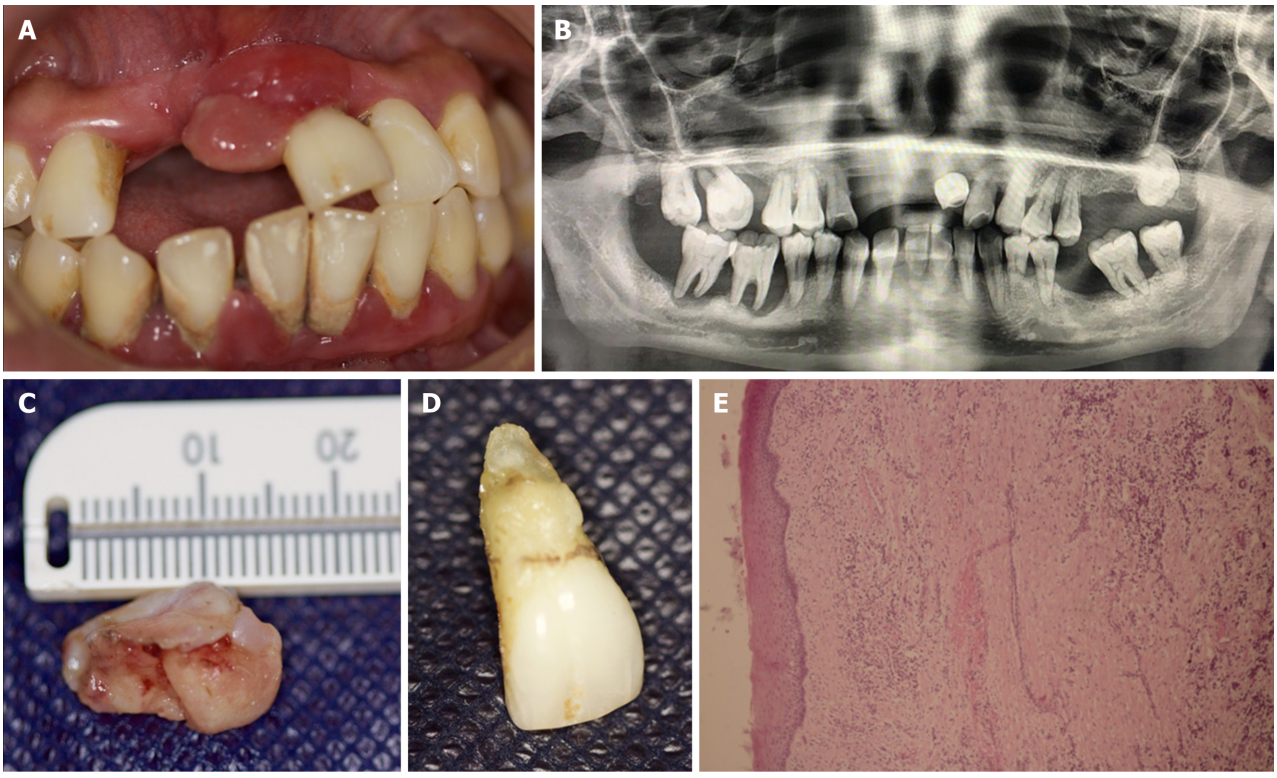

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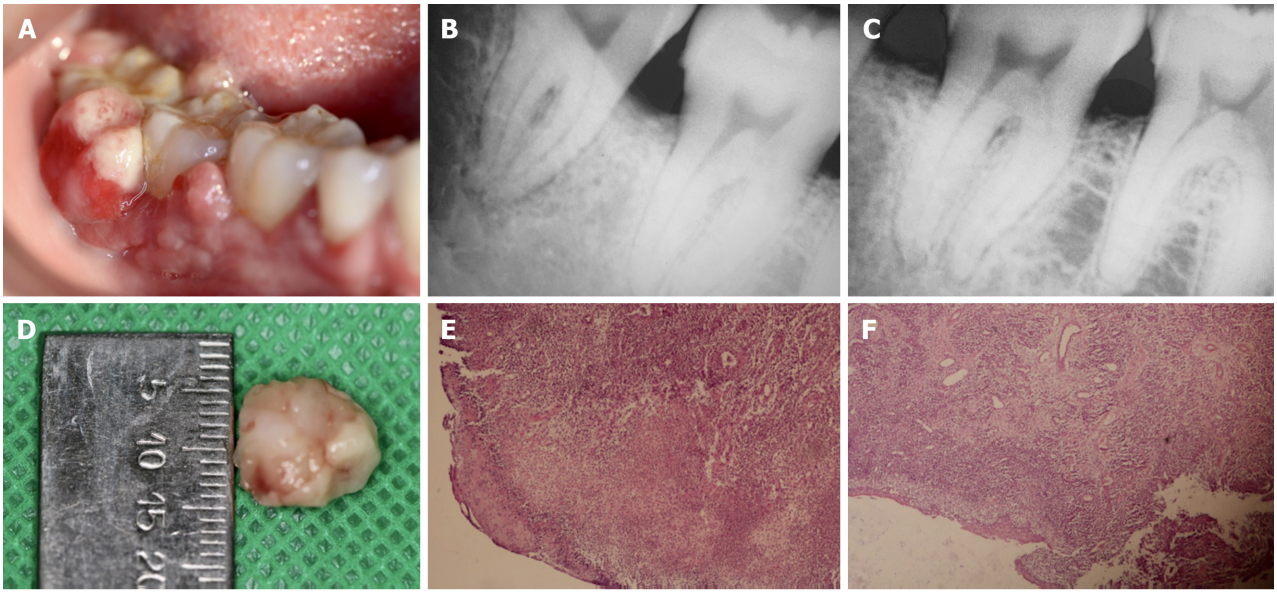
Figure 2 Clinical, radiographic and histological view of lesion case 2. A: Exophytic lesion associated with dental organ 21; B: Panoramic radiography; C: Excised specimen; D: Extracted dental organ 21; E: Histopathological view.

FINAL DIAGNOSIS



DOI: 10.12998/wjcc.v11.i16.3907

Figure 3 Clinical, radiographic and histological view of lesion case 3. A: Exophytic lesion associated with dental organs 46 and 47; B and C: Intraoral periapical radiographs showing interproximal bone loss between teeth 47 and 48; D: Excised specimen; E and F: Histopathological views.

Microscopic examination revealed a segment of buccal mucosa with fibrous stroma and a diffuse lymphoplasmacytic-type inflammatory infiltrate. There was evidence of old and recent stromal hemorrhages around newly-formed, congested blood vessels having irregular contours and varied diameters, with hyperplastic endothelial cells covered by epithelium with extensive areas of erosion. This histological examination confirmed the diagnosis of PG (Figures 1E and F).

Case 2

Histological analysis revealed a segment of mucosal stratified squamous epithelium with underlying fibrovascular stroma and a dense infiltrate of chronic inflammatory cells, stromal hemorrhage, large number of budding capillaries, fibroblasts, and areas of extravasated blood. Therefore, the diagnosis of PG with gingival hyperplasia was confirmed (Figure 2E). Along with this final diagnosis, and based on the results of intraoral clinical examination, periodontal chart, and X-ray, a stage III grade generalized periodontitis was also diagnosed.

Case 3

On microscopic examination, sections showed stratified squamous epithelium with non-neoplastic endothelial cell proliferation, formation of new blood cells, as well as acute and chronic inflammatory cell infiltration in a collagenous matrix around the newly formed, congested blood vessels with irregular contours and varied diameters. The blood vessels were covered by epithelium with extensive areas of erosion. These features corroborated the presumptive diagnosis of PG (Figures 3E and F).

TREATMENT

Case 1

The exophytic lesion was removed with excisional biopsy (Figure 1C). The procedure was performed under local infiltrated anesthesia [2% mepivacaine with epinephrine (10 μg/mL)]. The incision was made with a 15C scalpel blade on the base of the pediculated lesion. The gingival tissues were remodeled with LaGrange scissors. Due to the extent of bone loss, degree of mobility, and the extensive caries in dental organ 22, a decision was made to remove it (Figure 1D). Oral prophylaxis was performed with an ultrasonic device and Gracey 1-2 curettes in order to remove the local irritants on the adjacent teeth. After the procedures, 500-mg amoxicillin tablets were prescribed for the patient, to be taken 3 times daily for 5 d, and post-surgery indications were given.

Case 2

The exophitic mass was removed through an excisional biopsy (Figure 2C), along with the extraction of dental organ 21. The extraction was performed without complications (Figure 2D). The procedure was performed under local infiltrated anesthesia [2% mepivacaine with epinephrine (10 μg/mL)]. The

incision was made with a 15C scalpel blade on the base of the pediculated lesion. Oral prophylaxis was also performed with ultrasonic device and McCall 13-14 and 17-18 curettes. After the procedures, amoxicillin tablets (500 mg) were administered to the patient 3 times daily for 5 d, and post-surgery indications were given.

Case 3

An excisional biopsy was performed under local infiltrated anesthesia [2% mepivacaine with epinephrine (10 μg/mL)]. The incision was made with a 15C scalpel blade on the based of the lesion. The incision was extended to the periosteum, and a 2-mm margin was included from the adjacent soft tissues (Figure 3D). Oral prophylaxis was performed with an ultrasonic device and McCall 17-18 curettes in order to remove the calculus on dental organs 46, 47 and 48. Post-surgery indications were given, and the patient was placed on 500 mg tablets of amoxicillin 3 times daily for 5 d.

OUTCOME AND FOLLOW-UP

Case 1

After three months of follow-up, the scarring was satisfactory, and there was no recurrence.

Case 2

The scarring was satisfactory after three months of follow up, and there was no recurrence. Additional therapy was started for the periodontitis.

Case 3

After three months of follow-up, the scarring was satisfactory, and there was no recurrence

DISCUSSION

PG is a localized, reddish and vascularized gingival hyperplastic lesion[10-12]. It has been reported that oral PG accounts for an incidence of 52.71% among all non-neoplastic lesions[13]. It occurs more frequently in women than in men, and the major site of predilection is the gingiva[14]. Other lesion sites are the buccal mucosa, upper lip, lower lip, tongue, paladar and labial mucosa[9-12].

PG is considered a reactive self-limited pathology that presents as an exuberant proliferation of connective tissue in response to stimulation by some local irritant factor. Tripathi *et al*[8] and Verma *et al* [9] concluded, in their clinical case reports, that poor oral hygiene leading to abundant biofilm and dental calculus accumulation causes chronic irritation and contributes to the development of oral PG, similar to the cases presented. In the third case the presence of supra and sub gingival calculus was identified in the dental organs, which could be associated with the appearance of PG, and the periapical radiograph showed interproximal bone loss. However, in the first clinical case, we reported the presence and extent of dental caries in dental organ 12. Dental caries is caused by etiologic agents, such as *Staphylococci* and *Streptococcus* which produce colonies with fungal characteristics[15]. Chronic trauma provides a pathway for invasion of these microorganisms that induce proliferation of vascular connective tissue. Thus, it can be inferred that these pathogens also act as stimuli that favour the formation and growth of pyogenic granuloma[1,16].

In the oral cavity, PG appears a smooth or lobulated exophytic and red erythematous papule on a pedunculated or sessile base, and it is usually hemorrhagic and compressible[1,2,16]. The surface of PG is characteristically ulcerated[17], and its color varies from red, reddish purple to pink, depending on the degree of vascularity and the age of the lesion[16,17]. Newly -formed lesions are highly vascular, and appear more reddish in color, relative to old lesions. In contrast, mature lesions are pink in color and firm in consistency due to presence of high level of collagen fibers[3,17].

Most researchers have reported that radiographic evaluation of pyogenic granuloma does not show relevant features because the lesion arises from soft tissues[1,18-20]. However, pyogenic granuloma is a benign inflammatory lesion that expresses significantly more vascular endothelial growth factors and basic fibroblast growth factors than healthy gingiva and periodontitis[21]. In all three clinical cases described, bone tissue loss is observed and, although infrequent, PG can cause significant bone loss on rare occasions, as reported by Mastammanavar *et al*[7], Tripathi *et al*[8], and Verma *et al*[9]. Growth factors such as fibroblast growth factor-2, growth arrest-specific gene 6, and tumor necrosis factor-α stimulate mature osteoclast function and survival through extracellular signal-regulated kinase (ERK) activation, resulting in degradation or resorption of organic and inorganic bone components[22]. We may reasonably hypothesize that the severe alveolar bone loss in the three clinical cases presented was due to the activation of ERK signal pathway. Therefore, we suggest that bone loss should be considered as a possible diagnostic feature of pyogenic granuloma, notwithstanding the fact that the lesion arises from soft tissues.

In all clinical cases evaluated, the recommended management of this pathology involves surgical excision. However, different treatment modalities have been applied. These comprise Nd: YAG laser [23], CO_2 laser[24], flashlamp pulsed dye lasers[25,26], cryotherapy[27,28] and intra-lesional steroids [29]. The rate of recurrence of PG is 16%. This is due to incomplete excision of lesion and failure to remove local etiologic factors such as plaque, calculus and source of trauma[30,31]. For the latter, we recommend oral prophylaxis and elimination of local irritant factors, in addition to simultaneous resection of the lesion. It is essential to continuously implement complete dental evaluation involving preventive measures consisting of elimination of local irritant factors (dental biofilm, dental calculus, over contoured restorations, *etc*.) and meticulous oral hygiene care [brushing after eating (at least twice a day), using toothpaste on a soft-bristled toothbrush, and daily flossing]. These strategies decrease the possibility of appearance and development of pyogenic granuloma.

CONCLUSION

We presented three cases of oral PG with an unusual feature *i.e.*, alveolar bone loss. The clinical cases showed various etiological factors such calculus and periodontitis, which generate or contribute to the formation of PG. This hyperplastic lesion may occur as a single entity, or it may be associated with a non-neoplastic reactive proliferative process such as gingival hyperplasia. Surgical excision, oral prophylaxis and the elimination of local irritant factors are procedures that may be effectively implemented to minimize the recurrence of this lesion. Likewise, diagnosis, treatment plan and continuous dental evaluation are very essential. These case reports indicate that the clinical diagnosis of PG is a complex process. Therefore, it is important to know the clinical characteristics of the lesion at various locations.

FOOTNOTES

Author contributions: Bocanegra Morando D and Lomelí Martínez SM contributed to diagnosis, surgical treatment and manage of patients; Mercado González AE and Gómez Sandoval JR contributed to acquisition and analysis of data; Lomelí Martínez SM and Gómez Sandoval JR drafted manuscript and critically revised manuscript; all authors have read and approved the final manuscript.

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

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

CARE Checklist (2016) statement: The authors have read the CARE checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Mexico

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S-Editor: Liu JH
L-Editor: A
P-Editor: Zhang YL

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3915-3920

DOI: 10.12998/wjcc.v11.i16.3915

ISSN 2307-8960 (online)

CASE REPORT

Intraoperative photodynamic therapy for tracheal mass in non-small cell lung cancer: A case report

Hee Suk Jung, Hyun Jung Kim, Kwan Wook Kim

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liu ZW, China; Yu F, China

Received: March 17, 2023
Peer-review started: March 17, 2023
First decision: March 28, 2023
Revised: April 6, 2023
Accepted: May 6, 2023
Article in press: May 6, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Tracheal neoplasms represent less than 0.1% of all malignancies and have no established treatment guidelines. Surgical resection with reconstruction is the primary treatment. This study demonstrates successful treatment of concurrent lung and tracheal tumors using surgical excision and intraoperative photodynamic therapy (PDT), highlighting the effectiveness and safety of this approach.

CASE SUMMARY

A 74-year-old male with a history of smoking and chronic obstructive pulmonary disease was diagnosed with tracheal squamous cell carcinoma and right lower lobe adenocarcinoma. A multidisciplinary team created a treatment plan involving tumor resection and PDT. The tracheal tumor was removed through a tracheal incision and this was followed by intraluminal PDT. The trachea was repaired and a right lower lobectomy was performed. The patient received a second PDT treatment postoperatively and was discharged 10 d after the tracheal surgery, without complications. He then underwent platinum-based chemotherapy for lymphovascular invasion of lung cancer. Three-month postoperative bronchoscopy revealed normal tracheal mucosa with a scar at the resection site and no evidence of tumor recurrence in the trachea or lung.

CONCLUSION

Our case of concurrent tracheal and lung cancers was successfully treated with surgical excision and intraoperative PDT which proved safe and effective in this patient.

Key Words: Tracheal neoplasm; Non-small cell lung carcinoma; Pulmonary surgical procedure; Photochemotherapy; Prognosis; Case report

Core Tip: This case report presents successful treatment of a rare case of concurrent tracheal and lung cancers in a 74-year-old male patient using surgical excision and intraoperative photodynamic therapy (PDT). This approach proved to be safe and effective, resulting in complete regression of the tracheal tumor. The patient's treatment included a combination of lobectomy, tracheal tumor excision, and intraluminal PDT, demonstrating the potential of this approach in managing such complex cases.

Citation: Jung HS, Kim HJ, Kim KW. Intraoperative photodynamic therapy for tracheal mass in non-small cell lung cancer: A case report. *World J Clin Cases* 2023; 11(16): 3915-3920
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3915.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3915

INTRODUCTION

Tracheal neoplasms account for fewer than 0.1% of all cancer cases[1]. Most tracheal malignancies are secondary tumors, originating from direct infiltration from nearby structures and, less frequently, from hematogenous or lymphatic spread of remote cancers[2]. Due to the rarity of this type of cancer, no definitive treatment guidelines based on randomized clinical trials exist, leaving treatment selection and sequencing to the discretion of the surgeon.

Surgical resection with reconstruction is the primary treatment for tracheal tumors. Segmental resection and reconstruction of the central airway can be effectively and safely performed in most patients. Although complications following tracheal surgery are rare, they can be devastating. Herein, we report the successful treatment of a case of concurrent lung and tracheal tumors through surgical excision and intraoperative photodynamic therapy (PDT).

CASE PRESENTATION

Chief complaints

A 74-year-old male patient presented to the clinic with complaints of intermittent hemoptysis and wheezing.

History of present illness

The patient started observing blood-tinged sputum 1 mo prior to presentation, and his dyspnea worsened 1 wk prior to presentation.

History of past illness

The patient was a former smoker with a 140 pack-year history and a history of moderate-to-severe chronic obstructive pulmonary disease. Two years prior, he had received a percutaneous coronary intervention for stable angina; the treatment had involved implanting a drug-eluting stent in the left obtuse marginal branch of the left circumflex artery.

Personal and family history

The patient had no personal or family history of malignant tumors.

Physical examination

Initial physical exam revealed the following: temperature of 36.5 °C; blood pressure of 110/63 mmHg; heart rate at 73/min; respiratory rate at 22/min; and O_2 saturation at 93% on room air. Lung examination revealed a barrel chest and poor air entry with moderate inspiratory and expiratory wheezing. Heart and abdominal examinations were within normal limits.

Laboratory examinations

Arterial blood gas testing on admission revealed a pH of 7.5, pCO_2 of 24 mmHg, pO_2 of 62 mmHg, and HCO_3^- of 20.5 mEq/L. No other abnormality was found on routine laboratory testing.

Imaging examinations

A computed tomography scan of the chest revealed a suspicious polypoid mass in the right mid-tracheal wall and a 3-cm mass in the right lower lobe of the lung (Figure 1). The patient underwent bronchoscopy, which revealed a single tracheal polyp causing up to a 70% tracheal obstruction (Figure 2).

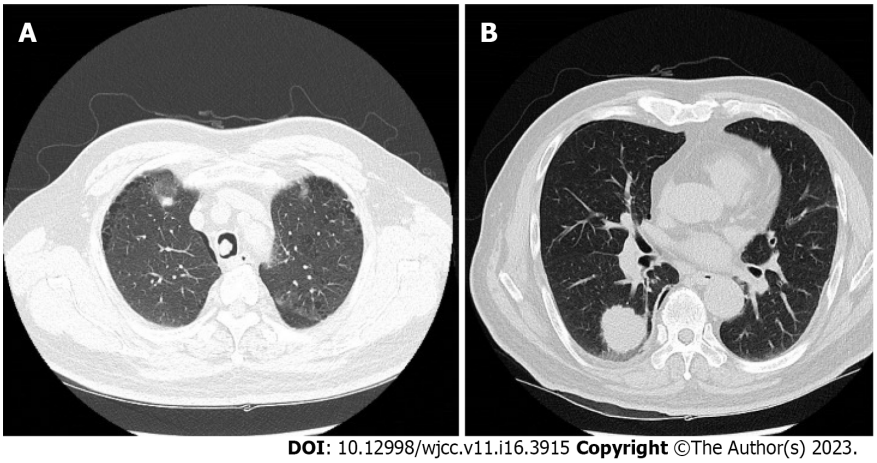

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Figure 1 Computed tomography of the patient's chest. A: A 10-mm lesion was seen on the right side of the mid-trachea; B: A 30-mm nodule was seen in the right lower lung lobe.

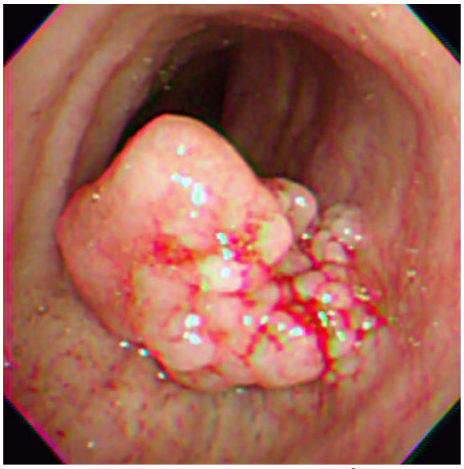

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Figure 2 Preoperative flexible bronchoscopy image. A 10-mm polypoid mass was seen obstructing 70% of the tracheal lumen.

FINAL DIAGNOSIS

Biopsy samples were taken. The pathology results showed the tracheal lesion to be squamous cell carcinoma and the lung mass to be adenocarcinoma.

TREATMENT

A multidisciplinary conference was held to discuss the case. Initially, the plan was to perform a tumor resection of the tracheal lesion through rigid bronchoscopy, but this technique was unavailable at the time of surgery due to problems with the equipment. The next option was to perform a tumor resection through a tracheal incision, followed by PDT. At 48 h before surgery, a 2 mg/kg dose of the photoactive compound Photofrin® (Pinnacle Biologics Inc., Bannockburn, IL, United States) was combined with 40 mL of isotonic saline solution and administered *via* intravenous injection. To ensure patient safety, selective veno-venous extracorporeal membrane oxygenation (ECMO) was initiated prior to general anesthesia, to guard against introducing it in the possible setting of airway compromise.

Throughout the surgery, the patient was maintained with 3–4 L/min flow of 100% fraction of inspired oxygen gas at 2–3 L/min, without the need for additional heparin infusions. The tumor was resected at its base using an electrocautery snare, followed by administration of intraluminal PDT (Figure 3). For the PDT, the laser light was irradiated through an optic fiber featuring a 30-mm cylindrical disperser. A 630-nm diode laser (Diomed, Cambridge, United Kingdom) was utilized to emit light into the tracheal lumen (120 J/cm^2 at 300 mW for a duration of 400 s). The tracheal margins were reconnected using absorbable continuous sutures. The anastomosis was checked using the underwater

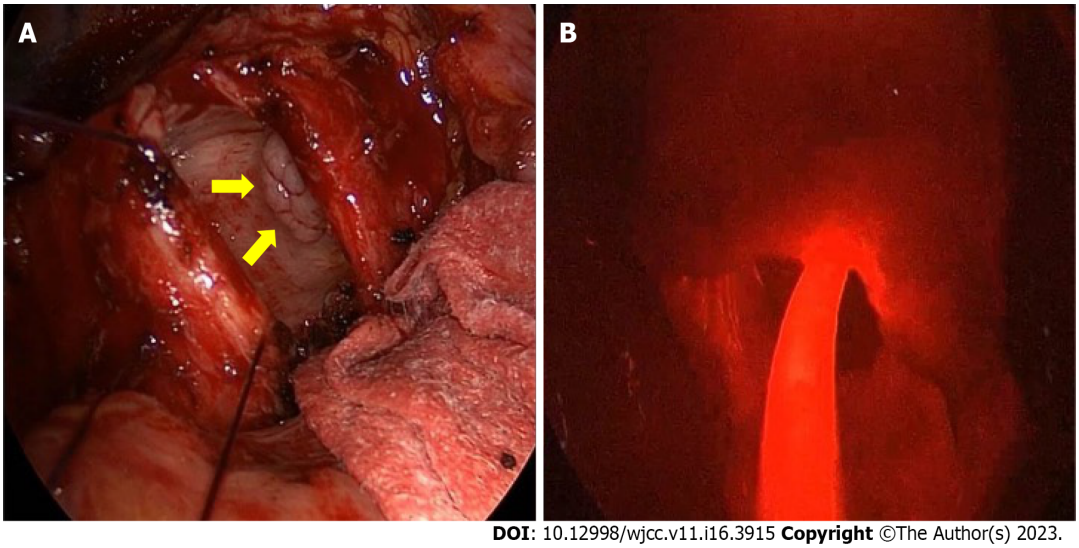

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Figure 3 Intraoperative view. A: The trachea was divided and a multi-lobulated tumor (arrows) was identified; B: An optic fiber was placed into the tracheal lumen after removal of the mass. The field appeared diffusely red, and the tip of the cylindrical diffuser was irradiated in the tumor bed.

method after placement of the endotracheal tube. After reinforcing the trachea, conventional lobectomy of the right lower lobe was performed, and no air leaks were observed at a ventilatory pressure of 25 cmH_2O. The patient was ventilated with an endotracheal tube, and a simple sweep gas test, confirmed by pulse oximetry which showed successful performance. ECMO and use of the central venous catheter were discontinued.

After transferring the patient to the intensive care unit, he was maintained on a ventilator. On day 3 after surgery, a second PDT with the same energy as before was administered using flexible bronchoscopy. The patient was discharged 10 d after tracheal surgery with no complications. As there was evidence of lymphovascular invasion in the histopathology of the lung cancer, platinum-based adjuvant chemotherapy was initiated 6 wk after the operation.

OUTCOME AND FOLLOW-UP

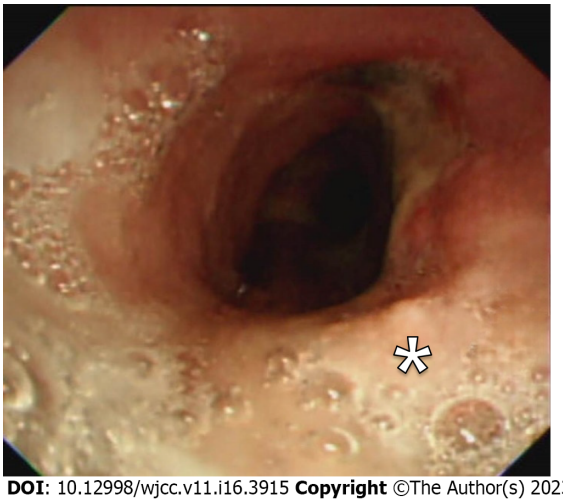
A bronchoscopy conducted 3 mo after the surgery demonstrated tracheal healing, evidenced by re-epithelialization of the healthy mucosal tissue at the site of resection (Figure 4). No recurrence of the tumor was observed during the 15 mo follow-up period.

DISCUSSION

Tracheal tumors are rare, accounting for less than 1% of all malignancies[1]. Despite their infrequency, they can cause severe airway obstruction in patients. The exact cause of these tumors remains unknown, but risk factors such as smoking, exposure to specific chemicals, and familial history may contribute to their development. The most appropriate treatment plan for a tracheal tumor is dependent on its type and stage, as well as the overall health of the patient. Treatment may include surgical excision, radiation therapy, PDT, chemotherapy, and/or stenting.

PDT has been used as a palliative treatment for malignant airway obstructions in the trachea or bronchi. Based on a recent analysis, patients with early-stage central lung cancer who underwent PDT experienced a full response in 30%-100% of instances, with the total 5-year survival rate being 61%[3]. Ji *et al*[4] discovered similar outcomes, demonstrating that employment of a second-generation photosensitizer in PDT effectively alleviated airway blockage in advanced non-small cell lung cancer. Overall, PDT has demonstrated efficacy against various types of tumor cells and can be performed on patients who have undergone previous treatments such as surgery, radiation therapy, or chemotherapy. PDT has also been evaluated for its ability to alleviate symptoms and improve survival in patients with advanced, inoperable bronchogenic cancer and endobronchial obstruction[5].

Tracheal resection with end-to-end anastomosis is the preferred treatment for tracheal tumors, as it ensures the restoration of an anatomically normal airway. However, the primary challenge of this procedure lies in the lesion's extent. Not only is it infeasible for lesions of considerable length but it also increases tension at the anastomotic site, potentially causing complications such as separation, granuloma formation, or re-stenosis at the tracheal anastomosis. Anastomotic separation is a partic-



DOI: 10.12998/wjcc.v11.i16.3915

Figure 4 Follow-up bronchoscopy view. Bronchoscopy was performed 3 mo following the photodynamic therapy. Scar tissue was visible (asterisk), and the biopsy was negative for malignancy.

ularly severe complication, and can result in dramatic airway loss with potentially fatal outcomes. Complete airway loss is rare but has a high fatality rate, often attributed to excessive tension. While study findings vary, it is widely accepted that complications related to airway separation escalate dramatically when more than 3 to 4 cm of the airway is resected[6,7]. Consequently, our objective in this case was to minimize tension. Our previous research showed that PDT was effective in controlling microscopic residual tumors in the distal trachea, and we expected similar results in this patient[8]. We made an incision in the tracheal wall, removed only the tumor, and applied PDT to the tumor bed. This method allowed us to bypass tracheal segmental resection, which carries the risk of fistulous complications at the anastomotic site.

CONCLUSION

Herein, we have presented the successful treatment of a patient with concurrent tracheal and lung cancers using a combination of surgical excision and intraoperative PDT. This approach was both safe and effective, and resulted in the complete regression of the protruding tracheal squamous cell carcinoma.

FOOTNOTES

Author contributions: Jung HS and Kim KW wrote and edited the manuscript and collected the data; Kim HJ obtained informed consent from the patient, participated as an assistant in the surgery, and contributed to the data collection; Kim KW contributed to the data analysis and provided conceptualization and supervision; All authors have read and approved the final manuscript.

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

Conflict-of-interest statement: All the authors report having 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 arrived according to the CARE Checklist (2016).

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S-Editor: Liu XF
L-Editor: Filipodia
P-Editor: Zhao S

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World Journal of Clinical Cases

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World J Clin Cases 2023 June 6; 11(16): 3921-3928

DOI: 10.12998/wjcc.v11.i16.3921

ISSN 2307-8960 (online)

CASE REPORT

Coexistence of urinary tuberculosis and urothelial carcinoma: A case report

Yu-Chi Tsai, Chiao-Ching Li, Bing-Tau Chen, Chien-Yao Wang

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Oley MH, Indonesia; Yarmahmoodi F, Iran

Received: March 30, 2023
Peer-review started: March 30, 2023
First decision: April 13, 2023
Revised: April 20, 2023
Accepted: April 27, 2023
Article in press: April 27, 2023
Published online: June 6, 2023

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Abstract

BACKGROUND

Taiwan has a high prevalence of tuberculosis and urothelial carcinoma. However, the simultaneous occurrence of both disorders in one patient is uncommon. Tuberculosis and urothelial carcinoma share some common risk factors and could demonstrate overlapping clinical manifestations.

CASE SUMMARY

Herein, we report the case of a patient who presented with fever, persistent hematuria, and pyuria. Chest computed tomography scans revealed a bilateral upper lobes cavitary lesion with fibrosis. Severe hydronephrosis of the right kidney and renal stones and cysts in the left kidney were observed. Initial microbiological testing was negative; however, a polymerase chain reaction assay of the urine confirmed a urinary tuberculosis infection. The patient was started on an anti-tuberculosis regimen. Ureteroscopy performed to resolve obstructive nephropathy revealed the incidental finding of a left middle-third ureteral tumor.

Examination after biopsy and transurethral resection of the bladder tumor indicated urothelial carcinoma. The patient underwent laparoscopic nephroureterectomy, with bladder cuff excision for the right kidney and ureter, and holmium laser ablation of the ureteral lesion to preserve the left kidney and ureter. He has remained stable after the procedures.

CONCLUSION
Although establishing a causal relationship between tuberculosis and cancer is difficult, medical personnel should consider their correlation.

Key Words: Urinary tuberculosis; Urothelial carcinoma; Fever; Hematuria; Taiwan; Case report

Core Tip: We have reported the case of a patient who presented with fever, persistent hematuria, and pyuria and was diagnosed with both urinary tuberculosis and urothelial carcinoma. Tuberculosis and urothelial carcinoma have some common risk factors such as smoking, alcohol consumption, chronic diseases, and malnutrition. Although it is difficult to establish a causal relationship between these two diseases, clinical medical personnel should consider the correlation between the two diseases.

Citation: Tsai YC, Li CC, Chen BT, Wang CY. Coexistence of urinary tuberculosis and urothelial carcinoma: A case report. *World J Clin Cases* 2023; 11(16): 3921-3928
URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3921.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3921

INTRODUCTION

Taiwan has a high prevalence of tuberculosis and urothelial carcinoma. However, the simultaneous occurrence of these disorders is uncommon in the same patient. The concurrent development of both of these diseases in the same patient could be explained by the following mechanisms: Local long-term inflammatory response, leading to the destruction of the host protective barrier, resulting in the invasion of microorganisms or cancer cells[1]. In addition, the inflammatory response damages immune cells and weakens the host's immunity.

Tuberculosis and urothelial carcinoma have some common risk factors, such as smoking, alcohol consumption, chronic diseases, and malnutrition. Although it is difficult to establish a causal relationship between these two diseases, clinical medical personnel should consider the correlation between the two. Herein, we report the case of a patient who presented with fever, persistent hematuria, and pyuria and was diagnosed with both urinary tuberculosis and urothelial carcinoma.

CASE PRESENTATION

Chief complaints

A 70-year-old man was transferred to our hospital for further management of intermittent fever, chills, and fatigue lasting for 10 d.

History of present illness

The patient experienced intermittent symptoms accompanied by severe night sweats. His body temperature was 38.5 °C, and his fever temporarily subsided after taking oral acetaminophen. He denied respiratory symptoms, such as cough, sore throat, or runny nose, and did not experience any gastrointestinal symptoms such as vomiting or diarrhea. Although the patient did not report urinary symptoms such as blood in urine, urgency, difficulty or pain during urination, or frequent voiding, he did report persistent bilateral lower back pain in the past 10 d. The patient had previously been diagnosed with lumbar herniated intervertebral disc disorder and had been undergoing rehabilitation therapy. As he believed that his current back pain was not significantly different from his previous pain, he did not pay particular attention to it.

History of past illness

The patient had developed anorexia, with a weight loss of 5.6 kg during the past year. Moreover, he had third–fourth lumbar herniated intervertebral disc disorder which had been treated with physical

rehabilitation therapy since the age of 63. He did not have any systemic disorders, such as diabetes mellitus or liver cirrhosis.

Personal and family history

The patient disclosed a smoking history of 31 pack-years and reported infrequent alcohol consumption. He worked as a bus driver and had been experiencing fatigue prior to this visit. The patient denied any recent travel history or engagement in unsafe sexual activities or drug abuse. Furthermore, he had no history of prescription medication use or underlying medical conditions.

Physical examination

During the physical examination, dull percussions were noted bilaterally in the upper back, along with the presence of rhonchi in the same region. Despite these findings, the patient did not exhibit any signs of respiratory distress. His vital signs were within normal limits, with a temperature of 36.5 °C, blood pressure of 144/87 mmHg, heart rate of 102 beats per minute, and respiratory rate of 18 breaths per minute. The patient did not display any pain or discomfort upon percussion of the bilateral kidney areas. No discharge was observed around the urethra, and there were no suspicious lumps, rashes, or wounds in the perineal or other areas of the body.

Laboratory examinations

The patient's hemogram revealed leukocytosis with neutrophil predominance. The blood electrolytes, glucose levels, and hepatic function were all within normal ranges. His serum urea nitrogen and creatinine levels were elevated. The urinal analysis found microscopic hematuria and pyuria. Detailed laboratory test results are presented in Table 1.

Imaging examinations

Chest radiography revealed patchy consolidation with fibrosis in both upper lungs (Figure 1).

MULTIDISCIPLINARY EXPERT CONSULTATION

The patient was admitted to our ward for further management of the bilateral upper lung lesions observed on chest radiography.

Initially, the patient was prescribed intravenous ceftriaxone 2 g per day after blood and sputum cultures had been obtained. On day 3 of admission, the empiric antibiotics were escalated to intravenous piperacillin/tazobactam 2.25 g every 6 h for broad-spectrum coverage as the patient was experiencing persistent fever and worsening conditions. Additionally, testing for lung lesions was performed. Chest computed tomography (CT) scans revealed fibrotic lesions surrounded by parenchymal fibrosis, calcified granuloma, calcification atelectasis, and bronchiectasis over the bilateral upper and right lower lobes. Severe hydronephrosis of the right kidney was further observed. Sequential CT scans of the abdomen revealed an upper-third ureteral stone complicated by severe hydronephrosis of the right kidney. Moreover, renal stones and cysts were observed in the left kidney with hemorrhagic changes (Figure 2).

Owing to the lack of an initial adequate microbiological clue, repeated sputum cultures and rapid serology tests, including pneumococcus urine antigen and Cryptococcus antigen serum test, were performed. However, they all demonstrated negative results. Four acid-fast stain sputum smear sets and the final tuberculosis culture results were also all negative. Sputum fungus culture yielded negative results as well.

A urologist was consulted for renal function deterioration and persistent turbid urine passage by the patient. On admission day 5, a decompressive percutaneous nephrostomy (PCN) was performed on the right kidney to correct the worsening infection and collect adequate microbiological evidence. Urine culture and cytology samples from the right kidney were collected, and acid-fast staining of the urine demonstrated positive results.

A polymerase chain reaction assay of the urine confirmed a urinary tuberculosis infection on admission day 12. The patient was initiated on empirical anti-tuberculosis regimen (isoniazid, rifampin, pyrazinamide, and ethambutol).

Ureteroscopy was performed to resolve obstructive nephropathy on admission day 15. However, during the procedure, a cauliflower-like lesion was incidentally observed over the right posterior and right lateral wall junction of the urinary bladder. A left middle-third ureter tumor was also incidentally diagnosed during the same procedure (Figure 3). After discussion with the family, a biopsy of the left ureteral tumor with double-J catheterization was performed.

Histological examination of the specimen obtained from the left middle third ureter revealed high-grade papillary pattern urothelial carcinoma with lamina propria invasion (cT1). Immunohistochemical staining was positive for CK7, CK20, and Ki67. Urothelial carcinoma of the urinary bladder was identified based on pathological evidence after transurethral resection of the bladder tumor.

Table 1 Laboratory test results

Variable	Reference range	Illness day 10, on presentation	Illness day 30, on discharge
Hemoglobin (g/dL)	12–15.5	14.9	12.4
Hematocrit (%)	34.9–44.5	43.3	37.2
White-cell count (per mm^3)	4000–11000	12710	14960
Differential count (%)			
Neutrophils	40–70	83.0	86.1
Lymphocytes	22–44	7.9	6.8
Monocytes	4–11	8.4	5.8
Basophils	0–3	0.4	0.5
Eosinophils	0–8	0.3	0.8
Platelet count ($\times10^3$ per mm^3)	135–400	253	304
Red-cell count ($\times10^6$ per mm^3)	3.90–5.03	4.71	4.12
Mean corpuscular volume (fL)	80.0–100.0	91.9	90.3
C-reactive protein (mg/dL)	< 1	16.11	7.69
Sodium (mmol/L)	136–145	132	135
Potassium (mmol/L)	3.5–5.2	3.9	4.0
Urea nitrogen (mg/dL)	8–25	20	20
Creatinine (mg/dL)	0.60–1.50	2.1	1.4
Estimated glomerular filtration rate (ml/min/1.73 m^2)	> 60	33.4	53.3
Glucose (mg/dL)	70–110		
Aspartate aminotransferase (U/L)	≤ 33	26	15
Alanine aminotransferase (U/L)	10–49	24	32
Total bilirubin (mg/dL)	0.3–1.2	0.79	0.68
Glycated Hemoglobin (%)	< 5.8	5.7	
Specimen			
Anti-human immunodeficiency virus test	Negative	Negative	
Aspergillus antigen (serum)	Negative	Negative	
Cryptococcus antigen (serum)	Negative	Negative	
Pneumococcus antigen (urine)	Negative	Negative	
Blood culture	Negative	Negative	
Sputum culture	Negative	Negative	
Sputum acid fasting smear	Negative	Negative	
Urine acid fasting smear	Negative	Positive	Negative
Urine polymerase chain reaction assay	Negative	Positive; *Mycobacterium tuberculosis*	

An integrated tumor study was conducted for comprehensive disease staging. Through a dynamic renal function scan, it was discovered that the renal function of the left kidney was intact. Meanwhile, the right kidney was non-functioning.

FINAL DIAGNOSIS

Based on clinical manifestations, laboratory examinations, imaging examination, and pathological biopsy, the patient was finally diagnosed with coexisting urinary tuberculosis and urothelial carcinoma.

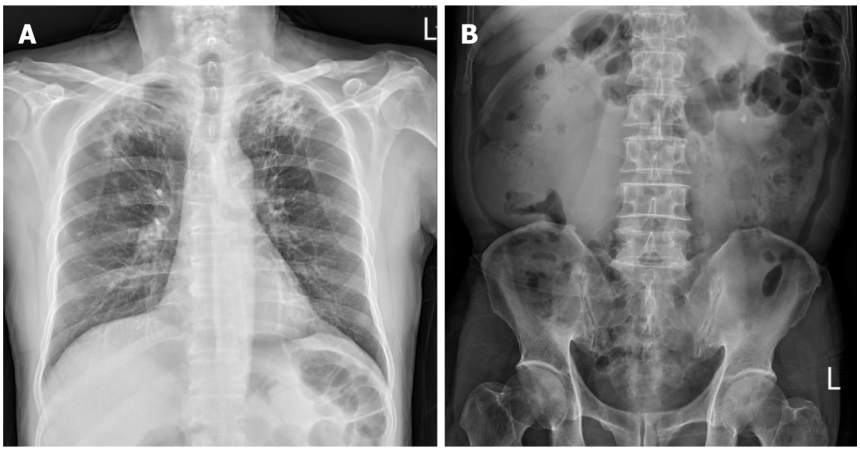

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Figure 1 Chest and abdominal radiograph. A: Chest radiograph reveals the presence of a bilateral upper-lobe cavitary lesion with fibrosis; B: Abdominal radiograph reveals a renal stone in the left kidney.

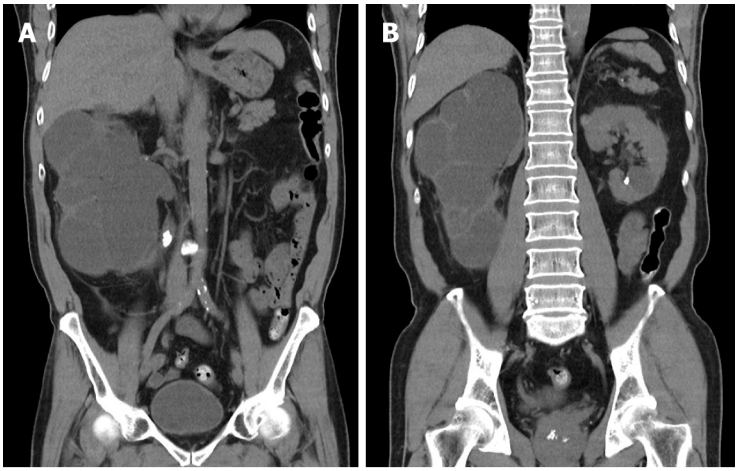

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Figure 2 Computed tomography scans. A: Computed tomography (CT) scans of the abdomen demonstrate severe hydronephrosis of the right kidney with a paper-thin cortex. Upper-third ureteral stone is noted; B: CT scans of the same area revealed a left renal stone with a cyst.

TREATMENT

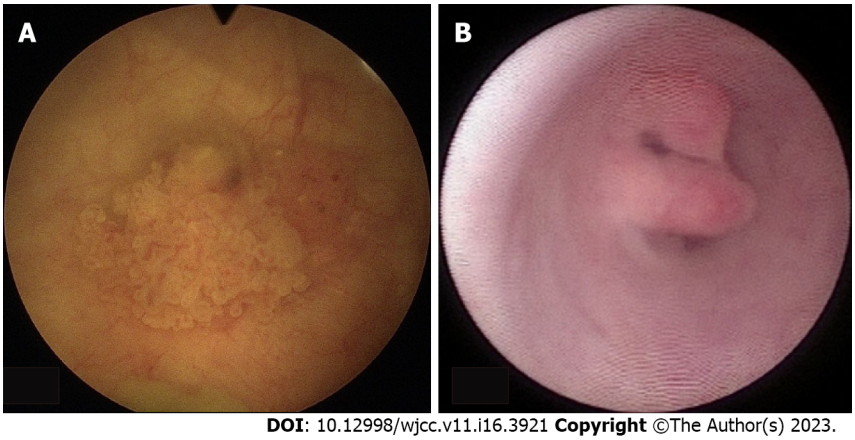
After discussion, the surgeon decided to perform laparoscopic nephroureterectomy, with bladder cuff excision for the right kidney and ureter, and to preserve the left kidney and ureter with holmium laser ablation of the ureteral lesion on admission day 25. There were no surgery-related complications. The patient was discharged on admission day 30.

OUTCOME AND FOLLOW-UP

The initial anti-tuberculosis regimen consisted of four drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) for 2 mo, followed by isoniazid and rifampin for 4 mo owing to susceptibility to the first-line therapy. One month after antibiotic treatment commencement, the patient's urine culture demonstrated no growth of the tuberculosis species. Although the patient's renal function did not fully recover, it also did not deteriorate to the extent of requiring dialysis. The patient continued regular follow-ups at our clinic.

DISCUSSION

In Taiwan, the incidence of genitourinary tuberculosis is approximately 0.19 cases per 100000 indi-



DOI: 10.12998/wjcc.v11.i16.3921

Figure 3 Photograph from ureteroscopy. A: Photograph from ureteroscopy; cauliflower-like lesions over right posterior and right lateral wall junction of the bladder are observed; B: Photograph of the patient's left ureter *via* ureteroscopy; an intraluminal bulging tumor located at the middle third of the ureteral cavity (approximately 0.8 cm) is observed. Histological examination of the lesion confirms the diagnosis of urothelial carcinoma.

viduals per year, which has been demonstrating a downward trend since 2000[2]. Moreover, Taiwan has a high incidence of upper tract urothelial carcinoma, with 3.14–3.41 cases being diagnosed in approximately 100000 people each year[3]. It is very rare for both of these disorders to coexist in the same patient.

The simultaneous occurrence of both diseases in the same patient may be explained by the fact that tuberculosis may cause a long-term local inflammatory response, which may in turn induce cellular carcinogenesis. This could be further explained by the relationship between pulmonary tuberculosis and lung cancer[4], and ulcerative lesions of intestinal tuberculosis acting as a precursor to intestinal mucosal cancer[5]. Mycobacterium tuberculosis may also promote the development of cancer by inducing a chronic inflammatory state and compromising T cell-mediated immunity[6]. However, tumor cells may also weaken the host's ability to resist the invasion of microorganisms such as mycobacteria by destroying the local infection barrier[7]. These tumor cells can also affect pathogen resistance through systemic immunosuppression[8,9].

Chen *et al*[6] have conducted a retrospective study of 45455 cancer patients and reported that tuberculosis is an independent risk factor for the development of all cancers. Hence, tuberculosis could increase the risk of specific cancers in patients[6]. A retrospective study by Lien *et al*[10] in Taiwan that analyzed national data also reported that urinary tract tuberculosis was associated with the development of urothelial carcinoma[10].

However, cancer has been recognized as a risk factor for active Mycobacterium tuberculosis infection since the 1970s. All types of cancers increase the risk of developing active tuberculosis disease, albeit to varying degrees. This could be due to intrinsic immunosuppression caused by the cancer itself, immunosuppressive effects of chemotherapy, or factors related to the patients themselves. Tuberculosis shares several disease risk factors with cancer, such as smoking[11], alcohol consumption, chronic diseases such as diabetes[3], malnutrition, and low socioeconomic status[12]. A previous study conducted in Taiwan on a large population reported that cancer was an independent risk factor for tuberculosis, with the highest risk observed 1 year before and 1 year after cancer diagnosis[13].

Although the temporal association between cancer and tuberculosis and a potential causal relationship between the two have not been established in the literature, as this may be challenging in clinical practice, clinicians should nonetheless be aware of this relationship[6,9,13].

The diagnosis and identification of a suitable treatment strategy in the present case were challenging, primarily because the patient had persistent pyuria and fever, and microbiological pathogenic evidence was lacking. To improve his condition and obtain relevant samples, we arranged decompressive PCN of the right kidney. Although the urine collected *via* PCN confirmed the tuberculosis infection, this patient already exhibited signs suggestive of urinary tuberculosis, including chest radiography resembling old pulmonary tuberculosis and persistent pyuria despite antibiotic treatment with sterile routine microbial cultures[14]. After several consecutive sets of negative urine cultures, clinicians should perhaps consider urinary tuberculosis as a differential diagnosis.

Surgery is the treatment of choice for early localized urothelial carcinoma. The mainstay of treatment for genitourinary tuberculosis is anti-tuberculosis drugs[15]. Indications for nephrectomy in case of genitourinary tuberculosis combination urothelial carcinoma include a nonfunctioning kidney, extensive disease involving the entire kidney along with hypertension and ureteropelvic junction obstruction, and renal carcinoma[16]. Considering that this patient only had unilateral residual renal function and was worried about the coexistence of potential tumors in the right kidney, he eventually chose the surgical option to remove the non-functional right kidney and is undergoing regular follow-ups to closely monitor the left urinary system that still has renal function.

CONCLUSION

The association between tuberculosis and cancer could be multifaceted. Although the causal relationship between the two has not yet been established, clinicians should be aware of the link between cancer and tuberculosis.

ACKNOWLEDGEMENTS

Yu-Chi Tsai would like to thank his wife Meng-Huang Chang for being considerate and helpful.

FOOTNOTES

Author contributions: Tsai YC and Wang CY designed this study; Li CC and Chen BT participated in the surgery; Tsai YC, Li CC, Chen BT, and Wang CY were involved in data acquisition; Tsai YC, Li CC, Chen BT, and Wang CY were involved in the statistical analysis and data interpretation; Tsai YC, Li CC, Chen BT, and Wang CY drafted the manuscript; Tsai YC made the final revisions; All authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report 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 CARE Checklist (2016), and the manuscript was prepared and revised according to CARE Checklist (2016).

Country/Territory of origin: Taiwan

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S-Editor: Li L
L-Editor: A
P-Editor: Li L

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World Journal of Clinical Cases

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

World J Clin Cases 2023 June 6; 11(16): 3929-3931

DOI: 10.12998/wjcc.v11.i16.3929

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Symmetric DWI hyperintensities in CMT1X patients after SARS-CoV-2 vaccination should not be classified as stroke-like lesions

Josef Finsterer

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ata F, Qatar; Wang MK, China

Received: February 20, 2023
Peer-review started: February 20, 2023
First decision: March 14, 2023
Revised: April 12, 2023
Accepted: April 25, 2023
Article in press: April 25, 2023
Published online: June 6, 2023

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Abstract

The interesting case report by Zhang *et al* on a 39 years-old male with Charcot-Marie-Tooth disease type 1X has several limitations. The causal relation between the two episodes of asyndesis, dysphagia, and dyspnea 37 d after the second dose of the inactivated severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) vaccine (Beijing Institute of Biological Products Co., Ltd., Beijing, China) remains unproven. SARS-CoV-2 vaccination cannot trigger a genetic disorder. It also remains unsupported that the patient had a stroke-like episode (SLE). SLEs occur in mitochondrial disorders but not in hereditary neuropathies. Because of the episodic nature of the neurological symptoms, it is critical to rule out seizures. Overall, the causal relation between vaccination and the neurological complications remains unsupported and the interpretation of symmetric diffusion-weighted imaging lesions on cerebral magnetic resonance imaging should be carefully revised.

Key Words: Stroke-like episode; Stroke-like lesion; SARS-CoV-2; Vaccination; Side effect

Core Tip: Symmetric diffusion-weighted imaging hyperintensities in charcot-marie-tooth type 1X patients after severe acute respiratory syndrome-coronavirus-2 vaccination should not be classified as stroke-like lesions.

Citation: Finsterer J. Symmetric DWI hyperintensities in CMT1X patients after SARS-CoV-2 vaccination should not be classified as stroke-like lesions. *World J Clin Cases* 2023; 11(16): 3929-3931

URL: https://www.wjgnet.com/2307-8960/full/v11/i16/3929.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i16.3929

TO THE EDITOR

We read with interest the article by Zhang *et al*[1] on a 39 years-old male with two episodes of asyndesis, dysphagia, and dyspnea 37 d after the second dose of the inactivated severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) vaccine (Beijing Institute of Biological Products Co., Ltd., Beijing, China). The individual history was positive for chronic eczema and kidney stones. The family history was positive for pes cavus in two brothers, and Charcot-Marie-Tooth (CMT) disease in one of them[1]. Neurological exam revealed chewing weakness, bulbar weakness, reduced tendon reflexes, discrete muscle wasting, and pes cavus[1]. Genetic work-up revealed the variant c.65G>A in *GJB1* which is why Charcot-Marie-Tooth 1X (CMT1X) was diagnosed[1]. Despite documentation of the genetic defect, CMT1X was interpreted as side effect of the anti-SARS-CoV-2 vaccination[1]. The study is excellent but raises concerns.

The main limitation of the study is the study type (case report). SARS-CoV-2 vaccination cannot be held responsible for the two episodes of asyndesis, dysphagia, and dyspnea from a single case. A case control or cross-sectional study is warranted to confirm a causal relationship between vaccination and the acute neurological symptoms. Therefore, we disagree with the notion that "CMT1X can occur after SARS-CoV-2 vaccination" suggesting that the vaccination caused CMT1X, that SARS-CoV-2 vaccination is a predisposing factor for CMT1X, and that there are predisposing factors for CMT1X, such as fever, high-altitude travel, or excessive physical activity[1]. CMT1X is a genetic disorder and not an infectious or immunological disease. There is no causal relation between SARS-CoV-2 and CMT1X. However, infectious or immunological disease may occasionally modify the phenotype of CMT1X.

We disagree with the use of the term "stroke-like episode" (SLE)[1]. SLE is a phenomenon predominantly occurring in primary mitochondrial disorders, particularly in mitochondrial encephalopathy, lactic acidosis, and stroke-like episode syndrome, for which SLEs are pathognomonic[2]. SLEs are the clinical correlate of a stroke-like lesion (SLL), which are transient, dynamic cerebral lesions, most commonly originating from the cortex, and not consistent with a vascular territory and have a characteristic pattern on imaging.

We also disagree that the diffusion-weighted imaging (DWI) lesions shown in Figure 2 (original article) represent SLLs[1]. SLL's have typically a dynamic course with initial expansion of the lesion and regression after a nadir has been reached. SLL's end up as white matter lesion, focal atrophy, cyst formation, laminar cortical necrosis, or toenail sign[3]. Occasionally, SLLs disappear without a residual lesion. SLLs can be identified and delineated from differential abnormalities by multimodal magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), magnetic resonance angiography (MRA) and fluor-deoxy glucose-positron emission tomography (FDG-PET). On multimodal MRI, SLLs typically present as hyperintensity on T2, fluid-attenuated inversion recovery, DWI, and perfusion-weighted imaging[4]. SLLs are hypointense on T1 and oxygen-extraction fraction MRI. MRS of SLLs typically shows a reduced N-acetyl aspartate peak and a lactate peak. MRA commonly shows dilation of arteries supplying the area of the SLL[4]. On FDG-PET, a SLL typically manifests with hypometabolism. Another argument against a SLL pretended to be shown in Figure 2, is that the lesions were symmetric. SLLs are almost always non-symmetrical. Another argument against SLLs is that these lesions did not show the typical dynamics of SLL. SLL usually expand until a nadir before they regress again and either completely disappear or remain in a lesional stage[4]. Another argument against SLLs is that they usually are associated with seizures or epileptiform discharges on electroencephalography (EEG) but the patient's individual history was negative for seizures. Lesions shown in Figure 2 do not meet these criteria. Therefore, they cannot be classified as SLLs and thus the clinical correlate cannot be a SLE.

A limitation of the study is that no EEG was recorded. SLLs are commonly associated with seizures or even triggered by seizures[5]. Furthermore, the episodic nature of the clinical manifestations aphasia and dysphagia suggest seizure activity. In addition, the transient DWI hyperintensities could be also triggered by seizures. Therefore, it is mandatory to search the history for seizures and to record an EEG.

An argument against a causal relation between SARS-CoV-2 vaccination and the cerebral lesions is the long latency of 37 days between vaccination and the MRI. Several other causes should have been ruled out. An argument for a causal relation is that DWI hyperintensities of the corpus callosum have been previously reported as side effects of SARS-CoV-2 vaccinations[6].

Because the index patient was diagnosed with a genetic disorder, it is mandatory to investigate all clinically affected and unaffected first-degree relatives for the causative variant. Family screening for the culprit variant is essential for assessing the progression and outcome of the disease and for genetic counselling.

It is not comprehensible why the previous history was not positive for pes cavus. Because pes cavus was described on the clinical neurologic exam, the patient should have noticed it already by himself. We should also know whether the patient recognised any phenotypic manifestations of hereditary neuropathy? Did he complain about paresthesias, dysesthesias, allodynia, numbness, liability to pressure palsies, or pain insensitivity? Surprisingly, clinical exam did not reveal aphasia[1]. We should know why?

It is not comprehensible why the index patient received steroids and intravenous immunoglobulins simultaneously. A possible therapeutic effect cannot be attributed to either of the two if they are given in common.

Because the cerebral lesions do not explain the bulbar symptoms, CMT1X should be considered as causative.

Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Symmetric DWI hyperintensities in CMT1X patients after SARS-CoV-2 vaccination should not be classified as SLLs.

FOOTNOTES

Author contributions: Finsterer J was responsible for everything.

Conflict-of-interest statement: There are no conflicts of interest to report.

Country/Territory of origin: Austria

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Fan JR

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