ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 December 26; 11(36): 8434-8605

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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Thrice Monthly Volume 11 Number 36 December 26, 2023

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 36 December 26, 2023

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The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCC* as 1.1; IF without journal self cites: 1.1; 5-year IF: 1.3; Journal Citation Indicator: 0.26; Ranking: 133 among 167 journals in medicine, general and internal; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
December 26, 2023

World Journal of Clinical Cases

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

World J Clin Cases 2023 December 26; 11(36): 8434-8439

DOI: 10.12998/wjcc.v11.i36.8434

ISSN 2307-8960 (online)

EDITORIAL

Post-trans-arterial chemoembolization hepatic necrosis and biliary stenosis: Clinical charateristics and endoscopic approach

Silvia Cocca, Lorenzo Carloni, Margherita Marocchi, Giuseppe Grande, Marcello Bianchini, Antonio Colecchia, Rita Conigliaro, Helga Bertani

Specialty type: Gastroenterology and hepatology

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): 0
Grade E (Poor): 0

P-Reviewer: Long X, China

Received: November 9, 2023
Peer-review started: November 9, 2023
First decision: November 22, 2023
Revised: December 1, 2023
Accepted: December 6, 2023
Article in press: December 6, 2023
Published online: December 26, 2023

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Abstract

Liver cancer is the fifth most common tumor and the second highest death-related cancer in the world. Hepatocarcinoma (HCC) represents 90% of liver cancers. According to the Barcelona Clinic Liver Cancer group, different treatment options could be offered to patients in consideration of tumor burden, liver function, patient performance status and biochemical marker serum concentration such as alpha-fetoprotein. Trans-arterial chemoembolization (TACE) is the treatment of choice in patients with diagnosis of unresectable HCC not eligible for liver transplantation, and preserved arterial supply. TACE is known to be safe and its complications are generally mild such as post-TACE syndrome, a self-resolving adverse event that occurs in about 90% of patients after the procedure. However, albeit rarely, more severe adverse events such as biloma, sepsis, hepatic failure, chemoagents induced toxicities, and post-TACE liver necrosis can occur. A prompt diagnosis of these clinical conditions is fundamental to prevent further complications. As a result, biliary stenosis could be a rare post-TACE necrosis complication and can be difficult to manage. Complications from untreated biliary strictures include recurring infections, jaundice, chronic cholestasis, and secondary biliary cirrhosis.

Key Words: Hepatocarcinoma; Trans-arterial Chemoembolization; Biliary stenosis; Multistenting

Core Tip: Multifocal hepatocarcinoma (HCC) can benefit from local treatments with curative or down-staging purposes. Trans-arterial chemoembolization (TACE) is the treatment of choice in patients with a diagnosis of HCC not eligible for surgery (resection or liver transplantation) and ablation. TACE is known to be a safe procedure but can lead to both self-limiting mild adverse events and, albeit rarely, severe hepatic and biliary damage due to extensive hepatic ischemia.

Citation: Cocca S, Carloni L, Marocchi M, Grande G, Bianchini M, Colecchia A, Conigliaro R, Bertani H. Post-trans-arterial chemoembolization hepatic necrosis and biliary stenosis: Clinical charateristics and endoscopic approach. *World J Clin Cases* 2023; 11(36): 8434-8439
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8434.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8434

INTRODUCTION

Hepatocarcinoma (HCC) is the fifth most common and the second highest death-related cancer. It represents almost the totality of liver cancers and its incidence is increasing worldwide, mostly in Eastern countries and Africa[1]. Chronic liver disease, whatever the etiology, represents the major risk factor for HCC occurrence. Ultrasound (US), abdomen magnetic resonance imaging, and serum biochemical marker evaluation represent the validated diagnostic tools for early HCC detection in patients with advanced chronic liver disease[1]. According to tumor burden, liver function, and patient features (performance status, biomarker concentration, and prognostic score value such as Albumin-Bilirubin [ALBI]) Grade and Child-Pugh/MELD scores, several treatment options could be proposed to the patient[2]. Based to the latest Barcelona Clinic Liver Cancer update, liver transplantation (LT) is the treatment of choice when Milan Criteria are met or are achieved after disease down-staging[2,3]. In the case of focal HCC, surgery or local treatments [*i.e.* radiofrequency ablation, RFA, or microwave ablation (MWA)] could be proposed in consideration of patient surgical fitness. Whereas, in the case of multiple/diffuse HCC, local approaches [*i.e.* trans-arterial chemoembolization (TACE)] or immune/chemo-therapy represent the best treatment options. Through the embolization of the feeding hepatic artery branches following the injection of multiple chemotherapy drugs, TACE robs tumors of their sustenance (*i.e.* ethiodized oil, gelatin powder, particles, and beads)[4]. The procedure is usually carried out through a right femoral approach: the catheter is advanced to the coeliac trifurcation where the common hepatic artery is catheterized and tumor arterial branches are reached up. Subsequently, chemo-agents are used to embolize neoplastic vasculature and lead to tumor necrosis. TACE is considered to be safe as well as effective for HCC, but nonvascular and vascular AE have been reported[1]. Among non-vascular complications, post-TACE syndrome presents in almost the totality of cases. Other nonvascular complications such as biloma, hepatic abscess, hepatic and renal failure, sepsis, pancreatitis, and toxicities induced by chemo-agents are possible [5,6]. Among the vascular AE, instead, post-TACE bile duct necrosis (BDN) and perforation have been reported[7].

CASE DESCRIPTION OF POST-TACE NECROSIS

We report a case of a 79-year-old woman with post-TACE hepatic hilar necrosis which resulted in serrated biliary stenosis. The patient was affected by hepatitis C virus related liver cirrhosis (Child-Pugh B7) complicated by hepatic encephalopathy, portal thrombosis, and multifocal HCC. Sustained virological response was achieved in 2016. In January 2023, for unresectable HCC recurrence in the caudate lobe, the patient underwent TACE. One month later, she was admitted to our hospital for persistent fever, abdominal pain, and jaundice. Abdominal imaging (US and CT) showed a cirrhotic liver with intrahepatic biliary dilation with solid tissue at the level of hilar bifurcation with substenosis. An endoscopic retrograde cholangiopancreatography (ERCP) and choledoscopy with Spyglass II was planned to study and characterize the biliary substenosis suitable for recurrence or necrosis and to treat the hilar stenosis. Biliary stenosis were seen during ERCP (Figure 1) and choledoscopy with Spyglass II revealed the presence of firm tissue strongly adherent to the biliary tree in the hepatic hilum (Figure 2). The histology report showed peri-bile duct tissue with necrotic changes, including coagulation necrosis and fibrinoid necrosis of the bile duct. After mechanical (Soehendra Biliary Dilation Catheter 4-6 Fr) and pneumatic dilatation (6 mm) of the intrahepatic ducts, two plastic stents (7 Fr × 15 cm) were placed in the left and right intrahepatic ducts to achieve proper biliary drainage. Moreover progressive pneumatic dilations (up to 8 mm) associated to multiple stenting replacement (up to 8.5 Fr × 12 cm) were subsequently performed to avoid jaundice recurrence and in the attempt to improve hilar stenosis. During follow-up the endoscopic treatment proved to be unsuccessful, given the persistence of biliary strictures together with the intrahepatic biliary dilation (Figure 3), suggesting permanent ischemic biliary damage. However, in light of the already compromised liver function and given the extent of the biliary damage, the patient was not eligible for other therapeutic options. The subsequent clinical, laboratory and radiological evaluations showed a stationary condition, and the patient showed no signs of obstructive jaundice at follow up.

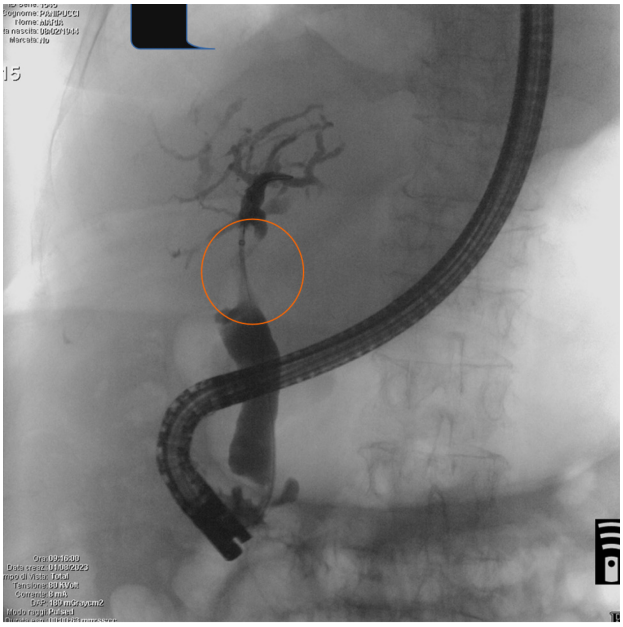

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Figure 1 Endoscopic retrograde cholangiopancreatography performed at admission to clarify the radiological findings showed a serrated biliary hilar stenosis (orange circle) and dilatation of intrahepatic bile ducts.

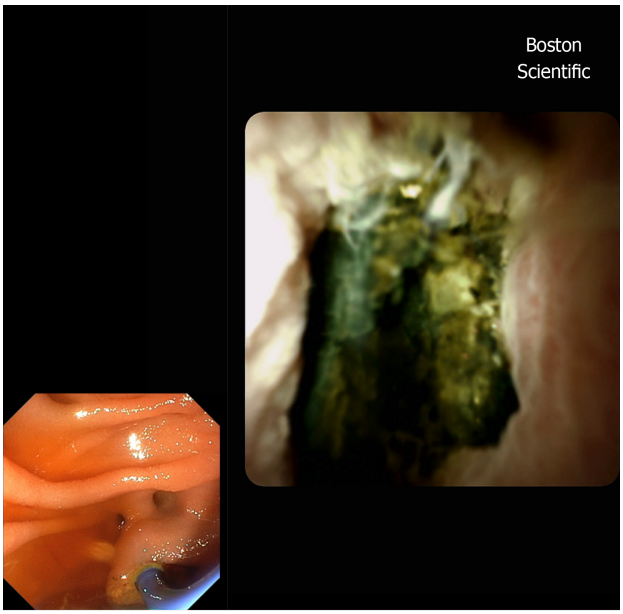

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Figure 2 Choledoscopy with Spyglass II revealed the presence of fixed tissue in the hepatic hilum causing bile duct stenosis.

CLINICAL CHARACTERISTIC OF POST-TACE NECROSIS AND SUBSEQUENT BILIARY STRICTURE

TACE is considered to be safe as well as effective for HCC, but, as already said, nonvascular and vascular AE have been reported[5]. Among the non-vascular complications, post-TACE syndrome presents in almost the totality of cases. It is characterized by fever, hypertransaminasemia, and right upper abdominal pain, but it is a clinical self-limiting condition lasting < 48 h. Beside post-TACE syndrome, other nonvascular complications such as biloma, hepatic and renal failure, sepsis, pancreatitis, and toxicities induced by chemo-agents can occur. Vascular AE include post-TACE hepatic necrosis and perforation. In particular, a rare occurrence of hepatic necrosis in a patient with a metastatic neuroendocrine tumor (NET) was reported by Micallef *et al*[4]. Kim *et al*[7] reported post-TACE duodenal perforation and esophageal ischemia in a man with unresectable HCC. Vascular thrombosis was detected on Doppler ultrasound and computed tomography scan (CT) in both reports, likely due to chemo-agents/arterial embolization induced ischemia, which probably plays a pivotal role in post-TACE necrosis and can lead to subsequent irreversible biliary stenosis.

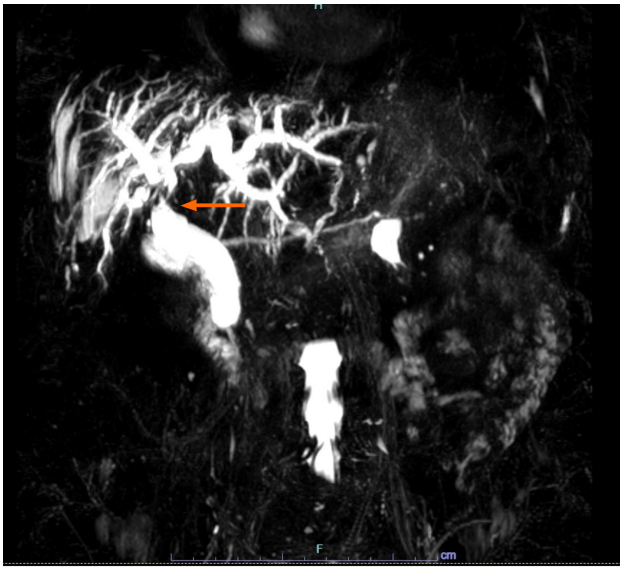

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Figure 3 Magnetic resonance imaging cholangiopancreatography showing persistence of bile duct and intrahepatic biliary dilation after endoscopic treatment.

Hepatic arteries are the only blood vessels that supply the bile ducts. When the peribiliary vascular plexus or the tiny hepatic arteries are damaged, or when all arterial blood supplies are cut off, as in the case of a transplanted liver with hepatic artery thrombosis, an ischemic bile duct injury may result. Most causes of bile duct ischemia are iatrogenic: benign biliary stricture (BBS) represents the most frequently observed post-LT biliary complication[3]. However, liver necrosis and subsequent BS is a very rare complication after TACE, as the liver parenchyma receives a dual blood supply *via* the hepatic arteries and the hepatic portal veins[2]. It has only been reported in a few cases[8,9], therefore its incidence has not been clearly estimated. In the anecdotal cases found in the literature the most common outcome was death.

TACE should be suggested in patients with unresectable HCC[2] not eligible for LT and it is considered a safe procedure. However, in the described case, we have shown how TACE could be linked to severe vascular complications such as hepatic necrosis resulting in biliary tree stenosis. Although this AE is rare and unexpected, it may result in severe sequelae (*i.e.* jaundice, sepsis). That is why it should be considered if fever and abdominal pain are not self-limiting within 48 h and/or continue after analgesics administration[4,5]. Post-TACE biliary strictures can be diagnosed when signs and symptoms of biliary obstruction (abnormal liver function tests, jaundice, abdominal pain, and cholangitis) occur and in case of biliary dilatation on imaging. Localization and confirmation of the BS ultimately depends on cholangiography, either contrast-enhanced or magnetic resonance cholangiopancreatography (MRCP)[10].

ENDOSCOPIC TREATMENT OF BENIGN BILIARY STENOSIS

Endoscopy has become the preferred option for treating BBS, of which 85% are located in the common bile duct[11]. Unacceptably high adverse event rates and poor long-term results have led to the discontinuation of BBSs therapy with a single plastic stent or uncovered SEMS[11,12]. Therefore, the use of a single plastic stent as a first line of treatment should only be considered in very specific cases before engaging definite strategies.

Endoscopic treatment consists in multiple plastic stent (MPS) placement, balloon dilation, or a combination of these two techniques. The guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) suggest inserting as many stents as feasible every 3 months for a total period of 12 months[11]. Plastic stents remain the gold standard for management of benign biliary strictures despite recent data demonstrating good and equal effectiveness of fully covered metal stents (FC-SEMS) in selected clinical scenarios[13,14]. With their larger diameters (10 mm *vs* 3.3 mm, respectively) and technical advantages—they are simpler to insert and take less time to place than MPS—they may be able to overcome some of the drawbacks of plastic stents[15]. However, using FC-SEMS presents a high risk of stent migration (around 9%), which varies significantly depending on the cause of the stenosis[14].

Technically speaking, hepatic and hilary strictures represent greater challenges for endoscopists. Percutaneous transhepatic cholangiography is one of the extra treatments that may be needed for the management of these strictures [10,11]. These kind of strictures are more common in individuals with primary sclerosing cholangitis (PSC). Short-term stents were not better than balloon dilatation in the first and only randomized trial of individuals with PSC with a prominent intrahepatic or hilar stricture, and they might even be harmful. Consequently, a very high rate of treatment-related adverse events, such as cholangitis, post-ERCP pancreatitis, and cholecystitis, necessitated the study's termination. Therefore, due to its ability to lower cholestasis, balloon dilatation ought to be the first treatment option for benign intrahepatic and hilar strictures[15,16].

CONCLUSION

For patients with intermediate-stage HCC with maintained liver function, TACE is currently the recom-mended type of treatment. It is a safe procedure that involves inserting synthetic materials and chemotherapy into a blood artery that feeds a tumor in order to interrupt it's blood supply and trap the chemotherapy inside the tumor. However, TACE is associated with vascular and non-vascular adverse events. Non-vascular complications are biloma, hepatic and renal failure, sepsis, pancreatitis, and toxicities induced by chemo-agents; these adverse events are rare but extremely severe and can lead to patient death. The most common vascular AE is post-TACE syndrome which includes self-limiting fever, hypertransaminasemia, and right upper abdominal pain; post-TACE necrosis and perforation have been reported as well, and represent rare but severe vascular AE. We reported the first case of a severe biliary stricture induced by extensive post-TACE hepatic necrosis. Ischemic bile duct injury may occur when small hepatic arteries or the peribiliary vascular plexus are injured, or when all arterial blood supplies are interrupted, for example in transplanted liver with hepatic artery thrombosis. The clinical and biochemical examination (abnormal liver function tests, jaundice, abdominal discomfort, and cholangitis) together with biliary dilatation on imaging are part of the diagnostic workup of post-TACE biliary strictures. Cholangiography—either contrast-enhanced or MRCP—is eventually necessary for the localization and confirmation of the BS[10]. Endoscopic balloon dilation and multistenting treatment either with plastic or metallic stents represents the treatment of choice; however, in case of serrated stenosis, endoscopic treatment can be unsuccessful and may require radiological permanent biliary drainage or a surgical treatment.

BDN is a stage that precedes overt biloma. When treated promptly, most intrahepatic bilomas have an excellent outcome. Patients who develop bilomas following TACE have a mortality incidence of between 5% and 10%[17]. Therefore, early detection of BDN and biloma on imaging and extra careful management might be mandatory to improve patient prognosis after repeated TACE for liver tumors.

FOOTNOTES

Author contributions: Cocca S contributed to conceptualization and writing - original draft; Carloni L, Marocchi M, Bertani H, Bianchini M, Colecchia A contributed to contributed to writing - review & editing; Bertani H contributed to supervision; Marocchi M and Grande G contributed to review and figures editing; Conigliaro R contributed to supervision and conceptualization; All authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors declare no conflicts of interest.

Country/Territory of origin: Italy

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

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World Journal of Clinical Cases

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

World J Clin Cases 2023 December 26; 11(36): 8440-8446

DOI: 10.12998/wjcc.v11.i36.8440

ISSN 2307-8960 (online)

MINIREVIEWS

Perioperative nursing care for hip arthroplasty patients with concomitant hypertension: A minireview

Chang-Yue Ji, Li-Ru Yang

Specialty type: Nursing

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: Pădureanu V, Romania; Pratap T, India

Received: September 21, 2023
Peer-review started: September 21, 2023
First decision: October 9, 2023
Revised: October 18, 2023
Accepted: December 8, 2023
Article in press: December 8, 2023
Published online: December 26, 2023

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Abstract

Hip replacement (HA) is mainly indicated for the elderly, who generally suffer from various underlying diseases such as hypertension. This article provides a review of the key points of perioperative nursing care for patients with hypertension undergoing HA. It analyzes the key points of care during the perioperative period (preoperative, intraoperative, and postoperative) and proposes directions for the development of perioperative nursing care for HA. The prognosis for patients can be improved through the modification of traditional medical approaches and the application of new technologies and concepts.

Key Words: Hip arthroplasty; Hypertension; Perioperative nursing care; Intelligent Device; Quality of life; Future research

Core Tip: Patients suffering from femoral neck and intertrochanteric fractures are frequently treated with an orthopedic rehabilitation surgery called hip arthroplasty (HA). Comorbidities challenge perioperative nursing care, specifically in older individuals, who comprise most HA patients. Postoperative rehabilitation may offer an avenue to enhance patients' quality of life with HA. The essential components of perioperative nursing care for patients with HA are covered in this in-depth review.

Citation: Ji CY, Yang LR. Perioperative nursing care for hip arthroplasty patients with concomitant hypertension: A minireview. *World J Clin Cases* 2023; 11(36): 8440-8446
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8440.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8440

INTRODUCTION

The aging population in China has increased the number of patients with severe hip socket or femoral head injuries leading to hip joint pain, functional impairments, and even hip joint deformities over the years[1]. Hip arthroplasty (HA) involves replacing a damaged hip socket or femoral head with an artificial joint, restoring the structural integrity and function of the patient's hip joint. Recent studies have identified that patients with hip joint dysfunction who require HA are generally over 50 years of age, and many of them have complex medical histories (Figure 1). Moreover, older patients with underlying medical conditions are at great risk of postoperative complications including infection, joint dislocation, deep vein thrombosis (DVT), ectopic ossification, wound complications, fractures, and nerve injuries. In severe cases, mortality is a possible risk. Therefore, Perioperative nursing care is crucial. Research data indicates that perioperative care for patients undergoing HA can promote patient recovery, enhance the functional recovery of the affected limb, reduce the occurrence of joint dislocation, and decrease the incidence of complications and adverse events[2,3]. The study[4] examined 100000 patients who underwent HA and demonstrated significant correlations between patient education level, economic status, and the incidence of postoperative infections. Similarly, in a study of approximately 17000 patients who underwent HA, Stisen *et al*[5] observed that those with higher education levels had significantly higher Harris hip scores, a measure of hip dysfunction, 1 year after a primary or revision HA than those with lower education levels. Patient outcomes are associated with various factors, including perioperative rehabilitation. Therefore, strengthening perioperative rehabilitation and nursing care for patients may significantly impact postoperative recovery, including hip joint function rehabilitation, complication reduction, and quality of life improvement. This research reviewed relevant literature content, using databases such as Web of Science, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang Medical Database for retrieval. During the search, keywords such as 'hip joint', 'hypertension', 'perioperative care', and 'hip replacement' were set for the search, and approximately 400 pieces of literature were retrieved. When selecting literature, articles from suitable core journals were first screened based on the accuracy and reliability of the information, then reference literature relevant to this review was selected, and the retrospective method was used to broaden the scope of the search and obtain more related information. Finally, after reading the literature, a total of 60 pieces of literature were included. This comprehensive review examines the research progress in perioperative nursing care for patients with concomitant hypertension who underwent HA, including the preoperative, perioperative, and postoperative periods. This study aimed to further improve patients' quality of life following HA.

PREOPERATIVE NURSING CARE

Psychological rehabilitation guidance

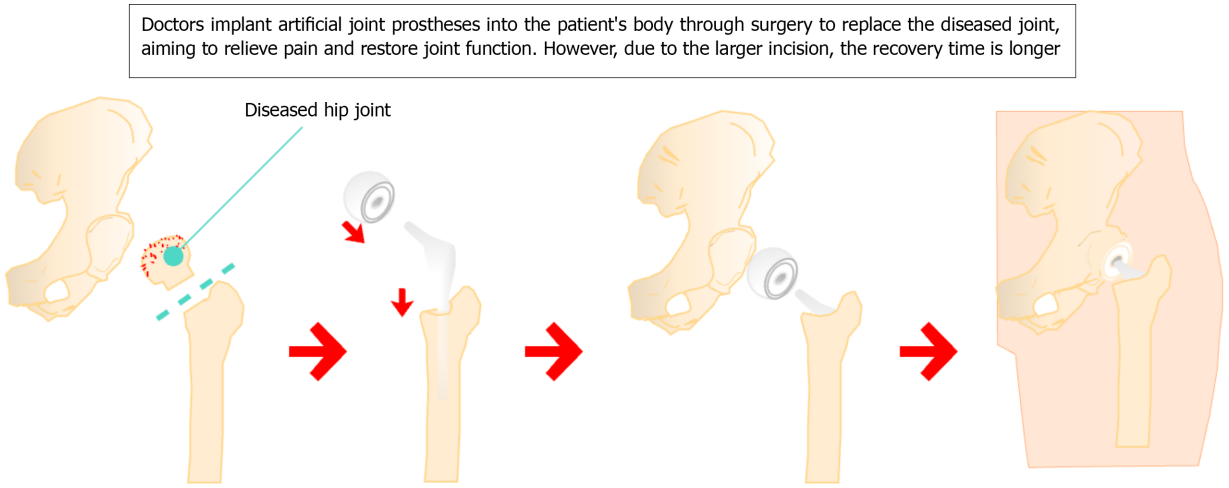
As hip joint-related diseases have a long course, patients often experience anxiety, restlessness, sleep disturbances, and other psychological issues due to daily life inconveniences and chronic pain caused by the joint dysfunction. In severe cases, increased blood pressure may also occur[6]. Several studies have discovered that preoperative anxiety and/or depression assessment and psychological care interventions, including explaining the surgical process and principles to patients, emphasizing the importance and necessity of the surgery to alleviate patients' fear, and addressing their emotional changes and psychological needs, can effectively prevent negative emotions before and after surgery, stabilize blood pressure, and reduce the incidence of postoperative complications[7-9].

Preoperative medication intervention

Due to the extent of surgical incision in HA, prophylactic antibiotics should be administered preoperatively[10]. Therefore, adverse reactions to antibiotics should be closely monitored as part of the preoperative nursing care. Antihypertensive medications may be used preoperatively to maintain blood pressure within the target range and reduce any associated surgical risks[11]. Postoperatively, the body continues to be under stress, which can easily lead to elevated blood pressure and an increased risk of cardiovascular accidents. Therefore, close monitoring of the patient's blood pressure and emotional fluctuations is necessary. Proper documentation and supervision should be implemented to ensure patient compliance with postoperative antihypertensive medications under healthcare professionals' guidance[12].

Sleep and dietary interventions

Studies have demonstrated that sleep disorders increase the risk of elevated blood pressure[12,13]. Therefore, improving the sleep quality of patients undergoing HA, especially those with hypertension, should be a key focus in clinical nursing care. Sleep therapy techniques, such as relaxation, smiling hypnosis, reverse induction sleep, and tension shaking induction, can improve sleep quality, help control blood pressure, and reduce postoperative complications[14-16]. Moreover, guiding patients to adhere to a low-sodium, low-cholesterol, low-sugar, high-protein, and high-calcium diet may be beneficial for controlling blood pressure and improving sleep, as a well-recognized positive correlation exists



DOI: 10.12998/wjcc.v11.i36.8440 **Copyright** ©The Author(s) 2023.

Figure 1 Hip arthroplasty.

between sodium intake and blood pressure[17,18].

Preoperative rehabilitation training

Most HA surgeries are elective procedures. Hence, patients generally have sufficient time for preoperative preparation and postoperative rehabilitation. Engaging patients in appropriate upper and lower limb muscle contraction exercises before surgery can improve cardiopulmonary function[19,20]. The two main exercises commonly performed are as follows: (1) Quadriceps femoris muscle contraction exercise: continuous contraction of the quadriceps femoris muscle for approximately 5 s while keeping the limb still, followed by a brief pause and repeat; and (2) Upper limb strength training aims to restore upper limb strength and enable patients to better utilize their walking aids postoperatively. Family members should also be instructed on precautions to enhance the patient's postoperative recovery, such as elevating tables and chairs at home to facilitate the patient's rehabilitation after discharge.

INTRAOPERATIVE NURSING

During HA, intraoperative nursing staff should assist the anesthesiologist in managing the patient throughout surgery. Patients should be positioned comfortably using soft pillows and head support to facilitate anesthesia and ensure smooth surgical progress. Owing to the extensive trauma caused by hip replacement surgery, various factors during the procedure, such as significant bleeding, anesthesia induction, and changes in patient positioning, can impact the patient's hemodynamics. From the nursing perspective, preparing various rescue medications and emergency measures in case of potential hemodynamic changes during surgery is necessary[21].

POSTOPERATIVE NURSING

Multiple studies have demonstrated that early rehabilitation training after HA is closely related to successful recovery of hip joint function and improvement of quality of life[22-24]. Due to the significant surgical trauma associated with hip replacement surgery, prolonged and multidimensional nursing and rehabilitation training is required to ensure optimal surgical outcomes.

Postoperative medication intervention

After HA, the patient's body continues to be in a state of stress. This imposes significant pressure on the cardiovascular system[25]. Hence, close postoperative observation of the patient's blood pressure and emotional fluctuations is necessary. Rational use of antihypertensives and analgesics may be required to stabilize the patient's blood pressure within the target range and prevent cardiovascular accidents. In recent years, the development of various pain management techniques, including preemptive analgesia, preventive analgesia, and regional administration, has rendered a relatively pain-free postoperative state possible for patients. During the postoperative analgesic phase, pain assessment techniques such as the visual analog scale can be used to evaluate the patient's pain level, which is beneficial for postoperative rest and functional exercise[26].

Prevention of lower limb DVT

Lower limb DVT after hip replacement surgery is relatively common[27,28]. The affected limb should be immobilized

during the early postoperative period after HA administration to mitigate the chances of DVT. Oral medications, such as aspirin and warfarin, should be administered to prevent thrombotic complications. In contrast, intravenous fluid therapy or venous infusion pumps may be employed to reduce the occurrence of thrombotic complications and prevent all other associated risks[29]. Additionally, during the bed rest period, the patient should be monitored regularly for changes in blood circulation, hip joint edema, and hematoma. Massages of the hip and lower limb muscles after surgery should be performed as part of the nursing process to promote lower limb blood circulation and prevent the formation of thrombosis[30].

Guidance for postoperative lower limb functional rehabilitation activity

Older patients often experience decreased movement coordination of their lower limbs and hip dislocation following HA due to age-related decline in muscle functions[31]. Consequently, maintaining the correct body positioning of the patient during the early postoperative period is essential. During early postoperative transfers, nursing staff should strive to keep the patient's body in a neutral position, with the affected limb not deviating or crossing the body's midline, Furthermore, forward tilting in the sitting position should also be avoided. Care should be taken to prevent falls or injuries during transfer, which could lead to adverse outcomes[32,33].

Functional training should involve foot-specific exercises guided by healthcare professionals, including dorsiflexion and plantar flexion movements, ankle joint flexion and extension exercises, and stretching and contraction exercises of the affected limb muscles. Studies have demonstrated that patients who received early rehabilitation training after HA had significantly improved hip joint and related tissue function. This effectively enhanced the early-stage rehabilitation and patients' quality of work and life[34,35]. In the midterm postoperative period, guidance should be provided for rehabilitation activities, such as position transfers, getting out of bed, and walking exercises for the hip joint[36]. Once the patient can stand and walk, they can be guided to perform further activities, such as straight-leg lifting, sliding board exercises, and sitting position transfers. Healthcare professionals should encourage patients to engage in pain-free rehabilitation exercises for the knee and hip joints, including strengthening exercises for hip flexion and abduction. Achieving a flexion angle of ≥ 90° and an abduction angle of not less than 40° is recommended. Individualized rehabilitation care plans should be developed to enhance the effectiveness of postoperative rehabilitation exercises and promote the recovery of hip joint function[37].

DEVELOPMENT DIRECTION OF PERIOPERATIVE NURSING FOR HA

In recent years, the development of biomechanics, information technology, and intelligent devices has provided new theoretical support and technical means of perioperative nursing in HA[38-41]. As displayed in Table 1, various factors can influence patient prognosis following HA. Moreover, a large body of clinical evidence highlights the importance of perioperative nursing in patient outcomes[42,43]. Coupled with traditional medicine and new treatment concepts, multidimensional nursing, where patient care addresses the patient's physical but also psychosocial, social, and spiritual needs, can improve prognosis and quality of life.

Enhancement of patient compliance with intelligent devices

In the past, due to a lack of standardized guidelines and evidence-based medicine, patient compliance with maintaining correct body positioning and movements after HA was poor, which often led to adverse outcomes, such as hip dislocation[44-46]. In a recent biomechanical study of 30 volunteers, Sah *et al*[47] used validated wearable sensors to measure the relevant angles during typical daily activities. The study identified that the angles while walking and going up and down the stairs were less than 90°. The average transition from sitting to standing was 103.0°, while the average maximum transition when rising from the toilet was 112.6°. Furthermore, the average transition when squatting initially was 120.0°, and the average transition when tying shoelaces was 126.1°. These data can be used to educate patients after HA to improve compliance and prevent hip dislocation.

Enhancement of comprehensive treatment effects with traditional medicine

As previously mentioned, HA is associated with significant surgical trauma and a lengthy recovery period. Two studies have demonstrated that compared to conventional orthopedic care and health education, the implementation of early rehabilitation and traditional Chinese medicine significantly improved hip joint function and self-care ability in patients following HA[48,49]. Wu *et al*[50] also demonstrated a reduced incidence of lower limb venous thrombosis in patients after HA through early rehabilitation guidance and traditional Chinese medicine treatment. Additionally, specific Chinese herbal formulas, such as Shu Jin Huo Xue Tang, combined with ingredients such as Xixin and Dingxiang, can significantly promote blood circulation in the lower limbs, effectively prevent muscle atrophy, and reduce the formation of venous thrombosis in the lower limb[51-53]. The aforementioned results indicate that nursing care that combines traditional medical treatment, such as acupuncture and herbal medicine, and traditional orthopedic care may significantly improve patient outcomes and, thus, should be further researched and promoted.

Development of comprehensive nursing programs with new technologies and concepts

With the development of information technology and digital healthcare, various interactive patient-medical rehabilitation technology platforms are available in China. Patients can consult and communicate with healthcare professionals through video conferences, official WeChat accounts, online consultation platforms, and other media. Healthcare professionals can provide education to patients using these platforms, thereby improving access to care and, thus, improving patient

Table 1 Factors influencing the prognosis of hip arthroplasty

Influencing factors	Ref.	Conclusion
Economic and educational level	Bhandari *et al*[4]	Patients with high education levels have low postoperative infection rates and favorable prognoses
Education level	Stisen *et al*[5]	The Harris hip scores at 1 yr after primary and revision hip arthroplasty were significantly higher in the high-educated group compared to the low-educated group
Whether to adhere to hip dislocation precautions during the first 6 wk after surgery	Theaker *et al*[35]	Early postoperative rehabilitation training can improve patient outcomes
Early rehabilitation guidance combined with syndrome differentiation	Liu *et al*[48]	Early rehabilitation guidance combined with syndrome differentiation nursing can improve outcomes in elderly patients
Early rehabilitation guidance combined with traditional Chinese medicine treatment based on syndrome differentiation	Wu *et al*[50]	Early rehabilitation guidance combined with traditional Chinese medicine treatment based on syndrome differentiation can reduce the incidence of lower limb venous thrombosis after hip arthroplasty

outcomes[54]. Fast-track surgery (FTS) rehabilitation involves preoperative education, intraoperative coordination, and comprehensive postoperative care, allowing personalized nursing plans based on each patient's conditions[55,56]. Research has demonstrated that implementing the FTS concept can significantly reduce hospitalization time, improve patients' postoperative Harris scores, and lead to a favorable prognosis[57].

CONCLUSION

HA can alleviate the pain caused by hip joint disease, improve the function of the hip joint, and help patients enhance their quality of life and survival in the future. However, postoperative care after HA is also a crucial part of the recovery period, which can promote postoperative recovery and reduce the incidence of complications and adverse events. In addition to following the routine orthopedic nursing and rehabilitation process, the care of patients with hypertension undergoing HA should focus on managing the blood pressure and pain during the perioperative period to prevent cardiovascular accidents and emotional distress, such as anxiety and restlessness. Furthermore, a personalized perioperative rehabilitation program for each patient is desirable and should be developed by incorporating new theories and technologies to improve patient outcomes. Further research to explore innovative approaches and interventions for optimizing patient care and rehabilitation after HA, especially for patients with hypertension, is warranted. Future studies could explore the use of intelligent devices, the benefits of traditional medicine, and the application of new concepts and technologies to enhance comprehensive nursing strategies. By continuously improving and tailoring the care provided to these patients, healthcare professionals can contribute to favorable patient outcomes and an improved quality of life.

FOOTNOTES

Author contributions: Ji CY reviewed the literature and contributed to the manuscript drafting; Yang LR reviewed the manuscript; all authors approved the final version.

Conflict-of-interest statement: All authors declare no potential conflicts of interest for this article.

Country/Territory of origin: China

ORCID number: Li-Ru Yang 0009-0007-5523-4663.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

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World J Clin Cases 2023 December 26; 11(36): 8447-8457

DOI: 10.12998/wjcc.v11.i36.8447

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Evaluation of response to gemcitabine plus cisplatin-based chemotherapy using positron emission computed tomography for metastatic bladder cancer

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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): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Pavlidis TE, Greece

Received: September 22, 2023
Peer-review started: September 22, 2023
First decision: November 9, 2023
Revised: November 10, 2023
Accepted: December 6, 2023
Article in press: December 6, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

The purpose of the present study was to examine retrospectively the contribution of ^{18}Fluorodeoxyglucose positron emission tomography computed tomography (^{18}FDG-PET/CT) to the evaluation of response to first-line gemcitabine plus cisplatin-based chemotherapy in patients with metastatic bladder cancer.

AIM

To evaluate the response to Gemcitabine plus Cisplatin -based chemotherapy using ^{18}FDG-PET/CT imaging in patients with metastatic bladder cancer.

METHODS

Between July 2007 and April 2019, 79 patients underwent ^{18}FDG-PET/CT imaging with the diagnosis of Metastatic Bladder Carcinoma (M-BCa). A total of 42 patients (38 male, 4 female) were included in the study, and all had been administered Gemcitabine plus Cisplatin-based chemotherapy. After completion of the therapy, the patients underwent a repeat ^{18}FDG-PET/CT scan and the results were compared with the PET/CT findings before chemotherapy according to European Organisation for the Research and treatment of cancer criteria. Mean age was 66.1 years and standard deviation was 10.7 years (range: 41–84 years).

RESULTS

Of the patients, seven (16.6%) were in complete remission, 17 (40.5%) were in partial remission, six (14.3%) had a stable disease, and 12 (28.6%) had a progressive disease. The overall response rate was 57.1 percent.

CONCLUSION

^{18}FDG-PET/CT can be considered as a successful imaging tool in evaluating response to first-line chemotherapy for metastatic bladder cancer. Anatomical and functional data obtained from PET/CT scans may be useful in the planning of secondline and thirdline chemotherapy.

Key Words: Metastatic bladder cancer; Response to chemotheraphy; Positron emission tomography computed tomography; ^{18}FDG-PET/CT

Core Tip: ^{18}Fluorodeoxyglucose positron emission tomography computed tomography can be considered as a successful imaging tool in evaluating response to first-line chemotherapy for metastatic bladder cancer. Anatomical and functional data obtained from positron emission tomography computed tomography scans can be useful in the planning of second and third-line chemotherapy.

Citation: Öztürk H, Karapolat İ. Evaluation of response to gemcitabine plus cisplatin-based chemotherapy using positron emission computed tomography for metastatic bladder cancer. *World J Clin Cases* 2023; 11(36): 8447-8457
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8447.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8447

INTRODUCTION

Bladder cancer is the ninth most common cancer all over the world with 380.000 new cases annually. Ration of male: female patients is 3.8:1[1]. According to database of Surveillance, Epidemiology and End Results, no significant change has occurred over the last 30 years in the number of patients dying of bladder cancer[2]. 10% to 15% of the patients with bladder cancer are metastatic at the time of diagnosis. The local recurrence rate after a radical cystectomy is 30% in muscle-invasive bladder carcinoma, and the rate of metastatic disease is even higher, at 60%[3,4]. Metastases are the main cause of death in this disease, and despite all therapies, 50% of patients with local disease develop metastasis within two years[5]. Metastatic bladder carcinoma is associated with extremely poor prognosis. Systematic chemotherapy is the standard therapy for metastatic disease.

Bladder transitional cell carcinoma (TCC) are usually chemosensitive tumors but response to a single agent is limited. Cisplatin, cyclophosphamide and vinblastine, cisplatin, doxorubicin and cyclophosphamide and methotrexate, vinblastine, adriamycin and cisplatin (M-VAC) induced 12% to 78% overall response rate (ORR)[6]. The combination of gemcitabine with cisplatin (GC) has become the first-line chemotherapy and has further improved results with higher ORR (57%) and complete remission (CR) (15% to 21%)[7].

Diagnosing occult metastases in bladder cancer is still a challenge, and there is much more need for a diagnostic test for monitoring response to therapy and predicting residual disease in patients after chemotherapy. ^{18}Fluorodeoxyglucose positron emission tomography computed tomography (^{18}FDG PET/CT) is the most important imaging modality in this regard. The re-staging of bladder cancer still constitutes a challenge using conventional techniques such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy, with success rates approximately 70 percent in literature[8]. It has been proposed that ^{18}FDG-PET/CT can provide additional diagnostic knowledge in the clinical management of bladder cancer[9]. We used the GC-based chemotherapy protocol described by European Association of Urology (EAU) in our patients, and the ^{18}FDG-PET/CT findings from before and after treatment were recorded[10].

The purpose of the present study was to examine retrospectively the contribution of ^{18}FDG-PET/CT to the evaluation of response to first-line gemcitabine plus cisplatin-based chemotherapy in patients with metastatic bladder cancer. An accurate primary staging of the disease is particularly important for the planning of second-line chemotherapy protocols and the determination of complete and incomplete response at this stage of the disease. The histological findings or the clinical and radiological workup (US, CT, MRI and bone scintigraphy) were used as a standard reference. There are a few number of studies in literature evaluating ^{18}FDG-PET/CT in the detection of residual disease and the evaluation of response to therapy after GC-based chemotherapy in patients with metastatic bladder carcinoma.

MATERIALS AND METHODS

A total 10553 ^{18}FDG-PET/CT scans were performed in the Nuclear Medicine Department of Sifa University and Tinaztepe University, Izmir, Turkey between July 2007 and April 2019. In this group of patients, 79 patients underwent ^{18}FDG-PET/CT because of metastatic bladder cancer. The PET/CT findings of 42 patients before and after first-line chemotherapy were recorded.

Table 1 Characteristics of patients and disease

Characteristics	No. %
Gender	
Male	38 (90.4)
Female	4 (9.6)
Age (yr)	
Median	66.1
Range	41-84
Primary site	4 (9.6)
Bladder	38 (90.4)
Bladder, ureter, renal pelvis	4 (9.6)
Site of metastasis	
Lymph node	65 (53.2)
Bone	30 (24.6)
Lung	26 (21.3)
Liver	10 (8.1)
Soft tissue	10 (8.1)
Other[1]	3 (2.4)

[1]Adrenal gland, penile.

Thirty-eight (90.4%) of these patients were male and 4 (9.6%) were female. Mean age was 66.1 years and standard deviation was 10.7 years (range: 41–84 years). Written informed consents was obtained from all patients.

All (100%) patients had data on histological sub-types of muscle-invasive bladder cancer (high-grade TCC) based on pathological investigations. In the patients, the primary tumor was confined within the bladder in 38 (90.4%) of the patients, whereas four patients (9.6%) had bladder tumors and concomitant upper tract urothelial carcinoma (UTUC). Baseline characteristics of the patients are summarized in Table 1.

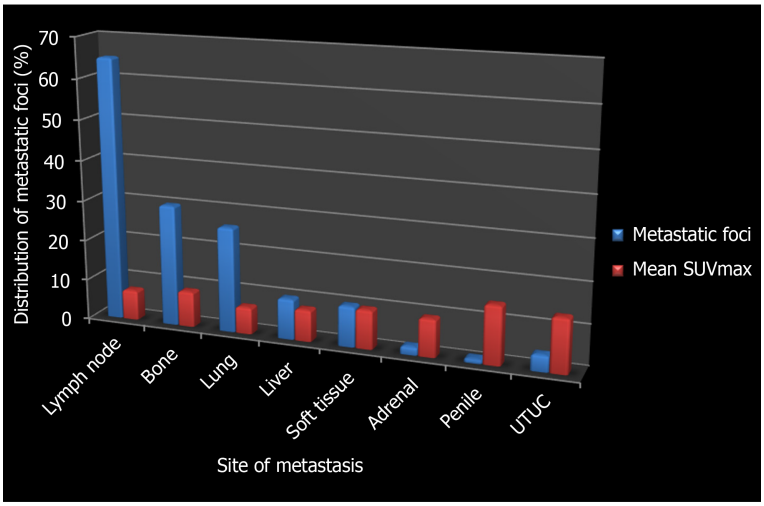
Imaging and interpretation of data

370 MBq of 18F FDG injected intravenously after at least six hours of fasting and when blood glucose level was lower than 200 mg/dL. One hour after 18F FDG injection, a total body CT scan without IV contrast agent and whole-body 3D PET acquisition with 8 bed positions of 3 min of emission scan time, covering the area from the vertex to the proximal thigh, each using a dedicated PET/CT scanner (HI-REZ Biograph 16, SIEMENS) which provides an in-plane spatial resolution of 4.8 mm, an axial field view of 16.2 cm. The PET data were reconstructed using a Gaussian filter with an ordered-subset expectation maximization algorithm (3 iterations, 8 subsets), re-oriented in transverse, coronal and sagittal planes.

PET scans were analyzed visually and semi-quantitatively using SUV_{max} measurement. One experienced nuclear medicine expert reviewed blindly and independently the FDG PET/CT scans regardless of as positive or negative for a primary tumour site. It was thought that ingestion of any radioactive substance that deviated from the physiological distribution was in favor of the spread of the disease.

RESULTS

A total of 144 metastatic foci in 42 patients with metastatic bladder carcinoma were evaluated using [18]FDG-PET/CT before chemotherapy, which 65 (53.2%) foci of lymph node's metastasis (mean SUV_{max}: 7.4), 30 (24.6%) foci of bone's metastasis (mean SUV_{max}: 8.8), 26 (21.3%) foci of lung's metastasis (mean SUV_{max}: 6.6), 10 (8.1%) foci of liver's metastasis (mean SUV_{max}: 7.8), 10 (8.1%) foci of soft tissue's metastasis (mean SUV_{max}: 9.6), two (1.6%) foci of adrenal's metastasis (mean SUV_{max}: 9.3) and one (0.8%) foci of penile's metastasis (SUV_{max}: 14.4) were detected. Additionally, four (3.2%) foci of contomitant UTUC were also detected (mean SUV_{max}: 13.3). The distribution of metastatic foci and mean SUV_{max} are summarized in Figure 1. The patients underwent second [18]FDG-PET/CT scan after gemcitabine plus cisplatin-based chemotherapy to allow an evaluation of response to chemotherapy. The mean time interval between the two [18]FDG-PET/CT scans was 6 months (range: 3–14 mo), and the same chemotherapy protocol was used in all patients during this period. Responses to chemotherapy were evaluated using the criteria of the European Organisation for the Research and



DOI: 10.12998/wjcc.v11.i36.8447

Figure 1 Distribution of metastatic foci and mean SUV_{max}. SUV: Standardised uptake value.

treatment of cancer (EORTC), which it was found that seven patients (16.6%) were in complete remission, 17 (40.5%) were in partial remission, 6 (14.3%) had a stable disease and 12 (28.6%) had a progressive disease (Figure 2). The overall response rate (ORR) was 57.1%.

DISCUSSION

Recurrent and metastatic bladder TCC has a poor prognosis. An accurate re-staging is crucial for the justification of additional toxic and expensive therapy. There is still only limited data on the benefits of [18]FDG-PET/CT in the identification of recurrences and new metastases after first-line chemotherapy for metastatic bladder cancer, and evaluating responses to therapy in cancer patients is still just as challenging as before. The reason for this is that; with current imaging techniques it is not possible to detect with absolute accuracy after chemotherapy to what extent of metastatic focus has been affected by the chemotherapeutics. In 1976, Moertel and Hanley reported that a decrease of 50 percent or more in tumor size must be regarded as a complete response to chemotherapy, which was accepted by world health organization in 1979[11]. Evaluation of response to chemotherapy based solely on anatomic criteria was added to the response evaluation criteria in solid tumors (RECIST) criteria in 2000, in which a decrease < 30 percent or an increase of < 20 percent was defined as a response to chemotherapy, although the RECIST criteria have undergone two modifications since then, one in 2009 and the other in 2010[12]. False negative results caused by the use of anatomic criteria in evaluating response to chemotherapy have resulted in the incorporation of functional/metabolic criteria into the assessment. The EORTC criteria were published in 2009, followed by the PET Response Criteria in Solid Tumors criteria in 2009 [12]. The present study has been conducted based on the EORTC criteria, which are summarized in Table 2.

High uptake of FDG in cancerous lesions of the transitional carcinoma was first demonstrated by Harney *et al*[13] in rats. Drieskens *et al*[14] found that metabolism-based anatomical information gathered by the addition of FDG-PET to CT provided high diagnostic accuracy in pre-operative staging of invasive transitional cancers particularly invasive bladder carcinoma. Nowadays, FDG-positron emission tomography combined with computed tomography (FDG-PET/CT) is an established standard for pre-operative staging and detecting metastatic lesions of bladder cancer[15-17].

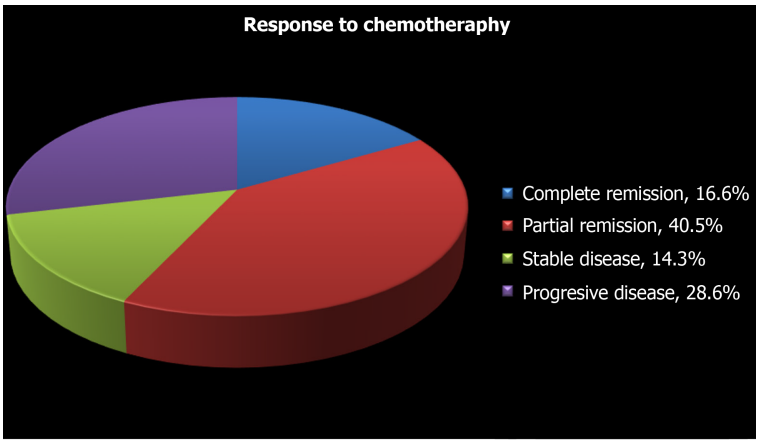
The accumulation of FDG in metastatic cells is closely related to such transport proteins as GLUT-1 and hexokinase enzyme activities. However, P-glycoprotein (MDR-1) expression, metallothionein over-expression, altered p53 expression MRP (multi-drug resistance-associated protein) mRNA induction and epidermal growth factor receptor over-expression in metastatic bladder cancer are all considered to be potential predictors of response to chemotherapy[18]. Accordingly, FDG accumulation and response to chemotherapy cannot be evaluated only with GLUT-1 and hexokinase enzyme activities in tumor cells without elucidating the molecular biologic basis of the disease, and so it is obvious that this area requires further research (Figure 3).

Why is therapy planning in cases of metastatic bladder cancer using [18]FDG-PET/CT imaging so important? What contribution does [18]FDG-PET/CT make in decisions to continue with second-line chemotherapy after initial chemotherapy treatment? Figure 4 shows the metabolic activity of cancer before an anatomic visualization of the tumor as a general rule, applicable for all cancers, and this stage is extremely important in diagnosis, staging, targeted therapy and the planning of radiotherapy. In order to spare the patient from additional toxic therapies, the detection of occult metastases and the evaluation of response to chemotherapy are only possible if there is a thorough understanding of the molecular/functional findings. This figure outlines the importance of molecular imaging, and the represented data is particularly important in the planning of treatments.

Table 2 Response criteria as defined by response evaluation criteria in solid tumors, world health organization, and the research and treatment of cancer

	RECIST	WHO	EORTC
Complete remission	Disappearance of all disease	Disappearance of all disease	Complete resolution of FDG uptake within the tumor volume
Partial remission	Decrease ≥ 30% in the sum of the greatest dimension of all measurable disease	Decrease ≥ 50% in the sum of the cross products	A reduction of a minimum of 15%-25% in tumor FDG SUV after one cycle of chemotherapy, and greater than 25% after more than one treatment cycle
Stable disease	Decrease < 30% and increase < 20% in the sum of the greatest tumor dimensions	Decrease < 50% and increase < 20% in the sum of the cross products	Increase of less than 25% or a decrease of less than 15% in tumor FDG SUV and no visible increase in extent (20% in the longest dimension)
Progressive disease	Increase ≥ 20% in the sum of the greatest tumor dimensions	Increase ≥ 50% in the sum of the cross products	Increase in FDG tumor SUV of greater than 25% within the tumor region, or increase of extend of FDG uptake (20% in the longest direction) or appearance of new lesions

RECIST: Response evaluation criteria in solid tumors; WHO: World health organization; EORTC: Research and treatment of cancer; FDG: F-2-fluoro-2-deoxyglucose; SUV: Standardised uptake value.



DOI: 10.12998/wjcc.v11.i36.8447

Figure 2 Rate of response to chemotheraphy.

Recent Studies suggest that solid organ metastasis from bladder cancer, particularly metastasis to the liver, is an independent risk factor resulting from poor prognosis. There is a correlation between the Karnowsky score and disease specific survival, and so the detection of solid organ and occult metastases with high accuracy and the detection of residual active disease after therapy using ^{18}FDG-PET/CT contribute significantly to survival figures.

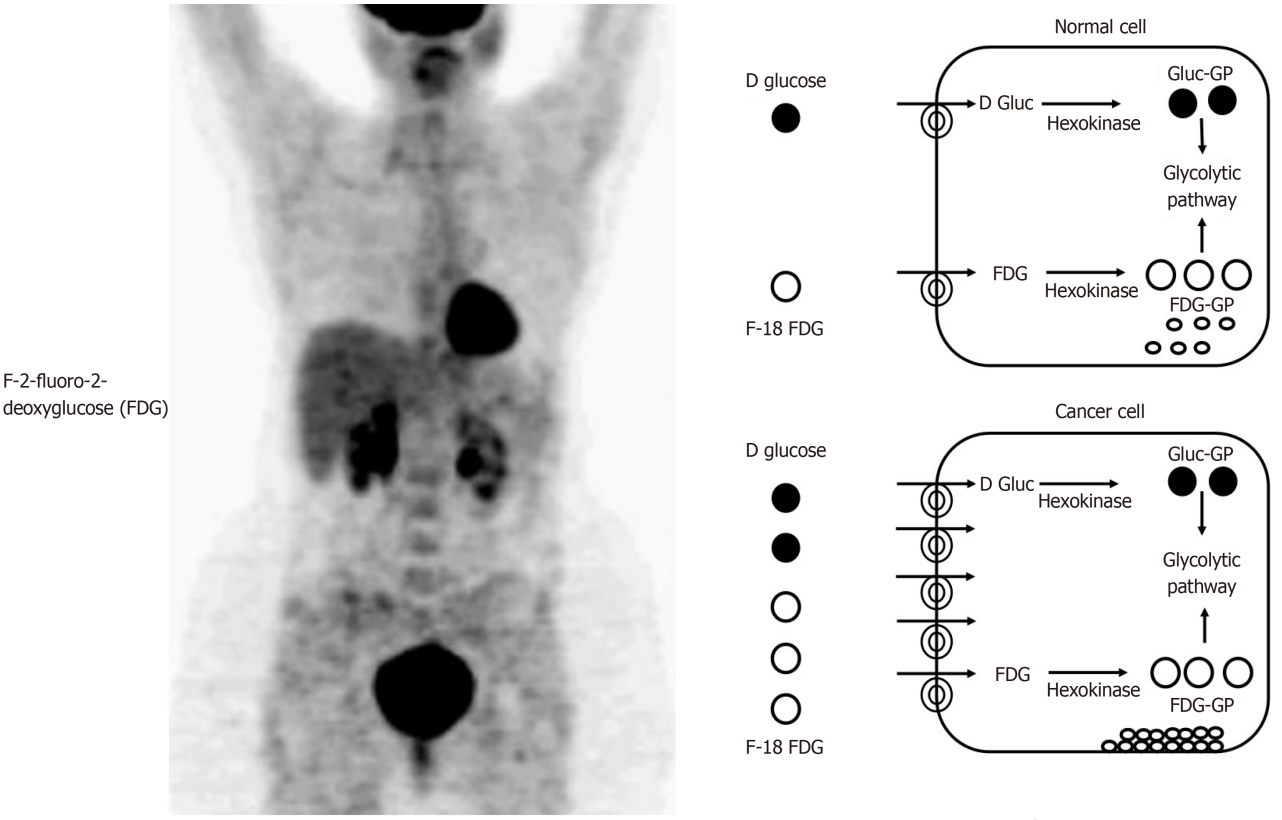
Bladder TCC are chemosensitive tumors. In metastatic disease, chemotherapy is the only therapeutic option. Imaging studies of metastatic urogenital malignancies are the main part of initial staging, response assessment and follow-up after systemic therapy. In particular, the clinically important question of the most accurate method to monitor therapeutic response during cytotoxic therapy or treatment with molecular approaches has been much neglected[19]. The mean ORR for metastatic bladder cancer after GC-based chemotherapy ranges between 40 and 70 percent in literature, and similar rates were reported by Bellmunt *et al*[20] in a study of 637 patients in 2007 and by Bamias *et al*[21] in a study of 175 patients in 2011. The mean ORR was 57.1 percent in the present study, which falls within the range of values in literature. Second or third-line chemotherapy is used in cases where the disease proves to be resistant to cisplatin-based chemotherapy; although there is no consensus on this issue[22]. In a recent published case study, the authors obtained a CR with FOLFOX4 chemotherapy in a metastatic urothelial cancer patient, after failure of GC combination[23]. As shown in Table 3, a precise re-staging is pivotal in the planning of second and third-line chemotherapy.

Metastasis may also appear in normal-sized lymph nodes. In bladder cancer, primary lymphatic drainage is to the internal iliac, common iliac and retroperitoneal lymph nodes. Therefore, metastasis occurs in these areas. Conventional CT is wrong 30% of the time. Conventional CT is wrong 30% of the time[24]. The functional and metabolic datas of PET/CT provide both accurate staging and evaluating of response to therapy higher sensitivity. In a population-based study in 2023, Patients with muscle-invasive bladder carcinoma (MIBC) who underwent pre-treatment staging with FDG-PET/CT were more often staged as lymph node positive, regardless of cT stage[25]. In a recent study by Voskuilen *et al*[26], FDG-PET/CT provides important incremental staging information, which potentially influences clinical management in 18% of MIBC patients, but leads to false positive results as well. In a study by Lodde *et al*[27], ^{18}FDG-PET/CT provided 100 percent PVV and specificity, compared to CT (33% *vs* 57%) in the detection of lymph node metastases, indicating the

Table 3 Treatment recommendations in metastatic baldder carcinoma

First line treatment			Second and third line treatments
Patients eligible to cisplatin	Unfit patients	Cisplatin sensitive disease	Cisplatin refractory disease
MVAC, HD-MVAC, GC, and DD-GC	GCa and MCAVI	Cisplatin based doublet not used in first line	Vinflunine, Paclitaxel-gemcitabine, and all actives drugs not used

MVAC: Methotrexate-vinblastine-doxorubicin-cisplatin; HD: High dose; GC: Gemcitabin-cisplatin; DD: Dose dense; MCAVI: Methotrexate-carboplatin-vinblastine; GCa: Gemcitabine plus carboplatin;



DOI: 10.12998/wjcc.v11.i36.8447

Figure 3 Illustrates the metabolic relationship between F-2-fluoro-2-deoxyglucose and cancer cells. D-glucose: The d-isomer of Glucose is d-glucose; Gluc-GP: Glucose- Glycogen phosphorylase (GP); FDG-GP: F-2-fluoro-2-deoxyglucose - Glycogen phosphorylase (GP); FDG: F-2-fluoro-2-deoxyglucose.

superiority of [18]FDG-PET/CT over standard CT in detecting lymph node metastasis. In a study by Taguchi *et al*[28], found that liver metastases represented the highest risk to survival when compared to other metastates. In their study, all liver metastases died within 9.3 months of diagnosis after being unresponsive to chemotherapy. This and other studies in literature suggest that the precise recognition of metastases is vitally important in predicting survival, evaluating response to chemotherapy and determining the most appropriate therapy.

Precise evaluations of metastases after chemotherapy are also particularly important. In a study by Lehmann *et al*[29] of 44 patients, a 28 percent five-year survival rate was reported in patients with metastatic bladder carcinoma. Furthermore, in a recent study conducted in 2014, Mertens *et al*[30] evaluated the relationship between [18]FDG-PET/CT results and mortality in patients with MIBC (n = 211), in which the median follow-up period was 18 mo. Disease-specific survival was 50 mo in the PET-negative patients, and this rate decreased to 16 mo in the PET-positive patients. The presence of extravesical disease was found to be an independent prognostic factor in mortality in PET-positive patients.

Kibel *et al*[17] studied 43 patients with T2-3N0M0 stage urothelial cancer and reported a sensitivity of 70 percent, specificity of 94 percent, a positive predictive value of 78 percent and negative predictive value of 91 percent for [18]FDG PET/CT. They found occult metastatic disease in 7 of 42 patients, and concluded that pre-operative [18]FDG-PET/CT may affect decisions related to treatment prior to a radical cystectomy. The same study also evaluated the relationship between PET findings and survival, finding a rate of 24-mo recurrence-free survival of 24 percent in patients with positive PET findings and 55 percent in patients with negative PET findings. Drieskens *et al*[14] provided valuable data on the prognosis of patients showing a longer median survival rate after negative results from a PET examination compared to patients with positive results for bladder cancer.

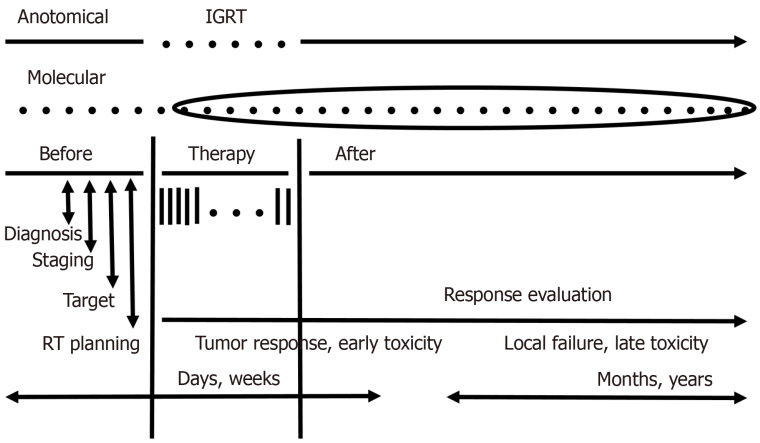


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Figure 4 Role of molecular imaging in oncology. IGRT: Image-Guided Radiation Therapy.

Additionally, based on an observation of 276 patients who had undergone cisplatin-based chemotherapy, Herr *et al*[31] concluded that those recording a complete or partial response to chemotherapy and those with limited nodal or a solitary visceral metastasis would be most likely to benefit from metastasectomy. The study also concluded that surgery should be avoided in the event of multiple liver metastases, metastases involving more than one visceral site or abdominal organ, or in cases of bone metastases, especially involving the pelvis or axial skeleton[31,32].

Drieskens *et al*[14] reported 60, 88 and 78 percent sensitivity, specificity and accuracy respectively for ^{18}FDG-PET/CT in the detection of metastatic disease in 55 patients with MIBC. Apolo *et al*[16] evaluated 135 metastatic lesions in 47 patients with metastatic disease, recording 88 percent sensitivity and 87 percent specificity in an organ-based analysis. In this study, ^{18}FDG-PET/CT detected malignant disease in 40 percent more patients when compared to such conventional techniques as CT and MRI; furthermore, the results of ^{18}FDG-PET/CT imaging brought about a change in the treatment plan of 68 percent of the patients. The authors found that ^{18}FDG-PET/CT provides data of sensitivity and specificity for the detection of metastatic Bladder Cancer, and provides the diagnostician with more detailed diagnostic information than that supplied by CT/MRI alone. In the present study, 132 metastatic foci in 42 patients were evaluated.

In a series of 46 patients studied by Liu *et al*[33], ^{18}FDG-PET/CT registered a sensitivity of 77 percent and a specificity of 97 percent in the detection of metastatic disease in patients who had not undergone chemotherapy. In a recent study by van Ginkel *et al*[34], The percent of sensitivity, specificity and accuracy of FDG-PET/CT was 36, 93 and 77 in turn, versus 12, 97 and 74 of CT only in MIBC. In a study by Moussa *et al*[35], On a patient-based analysis, PET-CT, and CT showed a sensitivity of 40.3% and 13.4%, respectively, a specificity of 79.5% and 86.7%, respectively, positive predictive value (PPV) of 61.4% and 45%, respectively, and negative predictive value of 62.3% and 55.4%, respectively in MIBC.

In a systemic review and meta-analysis by Lu *et al*[15], a sensitivity of 89 percent and a specificity of 82 percent were reported in the detection of metastatic lesions in cases of bladder cancer. In the meta-analysis, ^{18}FDG-PET/CT scans provided sufficient diagnostic accuracy for the staging and re-staging of patients with MIBC and metastatic cancer; however, the ^{18}FDG-PET/CT scans achieved a less than sufficient diagnostic performance in the detection of primary bladder cancer on the bladder wall. In this regard, the study found that the method may lack sufficient data for the "T" stage of the bladder and for the identification of detrusor lesions due to the urinary excretion of FDG, although the method may be used for staging purposes and for the detection of metastatic disease.

The existing studies in literature measuring the diagnostic performance of ^{18}FDG-PET/CT in cases of metastatic bladder cancer are summarized in Table 4.

Jadvar *et al*[36] evaluated the diagnostic performance of ^{18}FDG-PET/CT in patients with MIBC retrospectively and reported that the method led to a change in the clinical management of 17 percent of the patients. The aim of the present retrospective study has been to evaluate response to therapy in patients with metastatic bladder carcinoma after primary chemotherapy using ^{18}FDG-PET/CT, allowing informed decisions to be made related to follow-up treatment programs and a precise re-staging prior to the planning of additional toxic therapy. In this regard, the method more accurately determines the response to chemotherapy when compared to conventional methods. Although this falls outside the scope of the study, it is suggested that there may be a theoretical benefit in deciding in favor of a salvage cystectomy.

Metastatic transitional cells show a high affinity to FDG due to high glucose utilization, and progressive and hypermetabolic behavior. In the present study, the mean SUV_{max} for lymph nodes was 7.4, the mean SUV_{max} for visceral metastases was 6.6–7.8 and the mean SUV_{max} for bone metastases was 8.8.

In a metastatic lesion, the FDG uptake is dependent upon several factors. A strong relationship exists between FDG uptake and the number of cancer cells – a decreased FDG uptake points to a decrease in the number of viable tumor cells, while an increase in FDG uptake points to an increase in the number of viable tumor cells and tumor growth. Diagnoses of metastatic cancer are often established after the lesion reaches 10–100 grams in weight or a 10^{10}–10^{11} cell population, however the resolution of current PET/CT systems in cancer imaging ranges between 0.4 and 1.0 cm in diameter, corresponding to a tumor weight of 0.1–0.5 and 1.0 gr, and a cell number of 10^{8}–10^{9}. By using PET/CT, a diagnosis of metastatic bladder cancer can be established before the 100-fold increase occurs in the number of malignant cells (2 logarithms), meaning that a response to cancer therapy can be determined before a 100-fold decrease has occurred in the number of

Table 4 Diagnostic performance of [18]Fluorodeoxyglucose positron emission tomography computed tomography studies in the literature

Ref.	Modality	*n*	Status of the BCa	Sensitivity, %	Specifity, %
Drieskens *et al*[14]	FDG-PET/CT	55	Metastatic BCa	60	88
Apolo *et al*[16]	FDG-PET/CT	47	Metastatic BCa	88	87
Liu *et al*[33]	FDG-PET/CT	55	Metastatic BCa	77	97
Lu *et al*[15]	FDG-PET/CT	-	Metastatic BCa	89	82

Average values from meta-analysis of 4 individual positron emission tomography/computed tomography studies. BCa: Bladder cancer; FDG-PET/CT: Fluorodeoxyglucose positron emission tomography computed tomography.

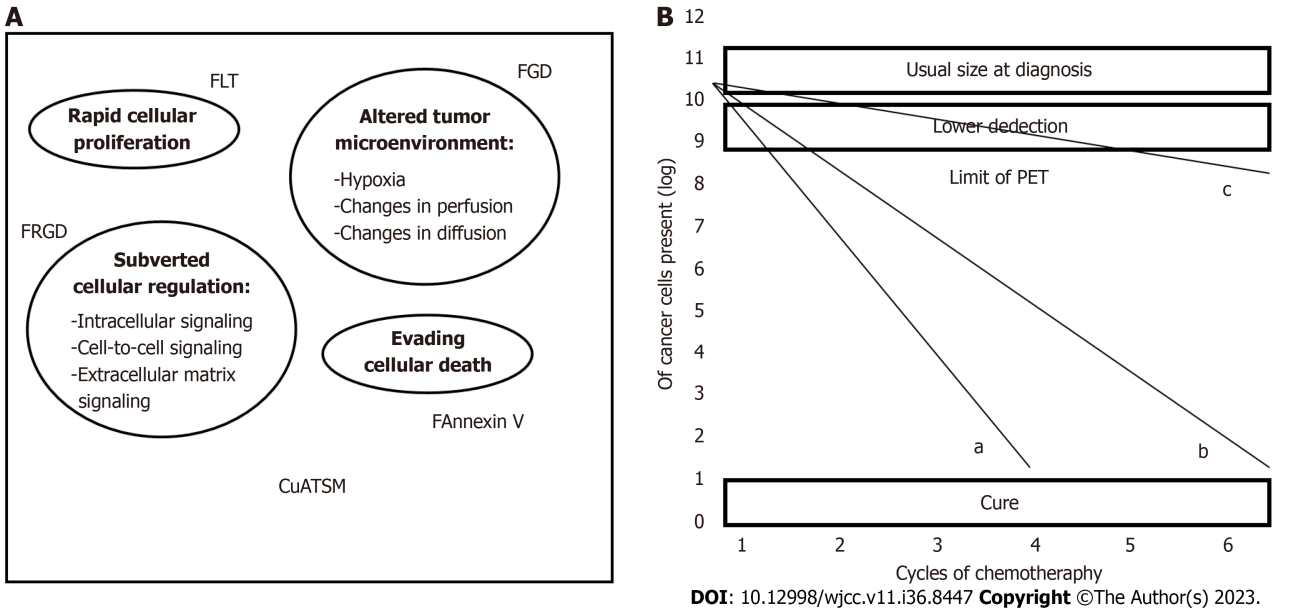

Figure 5 Shows the relationship between F-2-fluoro-2-deoxyglucose and tumor cells. A: Molecular imaging targets in oncology; B: Relationship between the death of tumor cells – number of viable tumor cells and F-2-fluoro-2-deoxyglucose positron emission tomography. FDG: Fluorodeoxyglucose; FLT1: Fms-related tyrosine kinase 1; FRGD: frgD gene; F Annexin V: [18]F using N-succinimidyl-4-[18]F-fluorobenzoic acid; Cu-ATSM: Copper(II)-diacetyl-bis(N(4)-methylthiosemicarbazone.

malignant cells (2 logarithms). After therapy, negative findings from [18]FDG-PET/CT imply a lack of cancer cells or a lack of lesions harboring more than 10^7 cells. FDG-PET/CT cannot differentiate between a minimal tumor load and the lack of a tumor; however, a completely negative PET/CT scan after post-therapy indicates a good prognosis, while positive findings in PET/CT indicate the presence of a residual tumor (in the absence of inflammation). Figure 5 shows the relationship between FDG and tumor cells.

Limitations

Disease-specific limitations: The lack of information on why known active TCC cells fail to uptake FDG as to become visible on the detector, negative predictive which has not yet reached 100%, and the lack of data on a sufficient number of patients in literature can be regarded as disease-specific limitations.

Technical limitations: Diagnostic failures in [18]FDG-PET/CT are associated mostly with the lungs and liver, as PET technologies may fail to identify small lung metastases measuring less than 5 mm, even when used in conjunction with CT in the correction of anatomical location and attenuation. It is unclear if this observation of a decline in sensitivity is caused by pulmonary motion artifacts or by the low metabolic activity of the lung metastases. Respiratory gate and time-of-flight technologies might help detect motion artifacts and improve diagnostic correctness by reducing the smearing effect, and may provide a good spatial resolution, offering higher accuracy and more precise calculation of SUV[37].

Study limitations: The retrospective design of the study, the relatively small number of patients and the lack of histological correlation can be regarded as the limitations of the study.

CONCLUSION

^{18}FDG-PET/CT seems to be a considerably successful and applicable diagnostic tool in the evaluation of response to therapy after first-line chemotherapy for metastatic bladder cancer. The addition of metabolic/functional data to the anatomical findings may allow greater accuracy in the diagnosis. The re-staging of the disease is of particular importance in the planning of second- and third-line chemotherapy protocols, as all possible additional chemotherapy protocols will increase morbidity and mortality in a patient with impaired performance status after having undergone first-line chemotherapy. It is suggested that the presented method will allow a better explanation of the requirement for additional chemotherapy protocols to both the patient and their relatives, although further studies are required in order to standardize additional therapy protocols.

ARTICLE HIGHLIGHTS

Research perspectives

More sensitive scanning methods are needed such as positron emission tomography (PET)/magnetic resonance imaging (MRI), metabolic-based imaging.

Research conclusions

Use PET/computed tomography (CT) more for accurate staging regardless of whether fluorodeoxyglucose (FDG) is excreted from the urinary tract. PET/CT can be standart in muscle-invasive bladder carcinoma

Research results

Restaging with high accuracy can protect patients from secondary or even tertiary chemotheraphy. Of the patients, seven (16.6%) were in complete remission, 17 (40.5%) were in partial remission, six (14.3%) had a stable disease, and 12 (28.6%) had a progressive disease. The overall response rate was 57.1 percent. Imaging techniques that detect every behavior of the tumor will increase the success of future treatment. This study is an example of this. In fact, PET-MRI may become the standard instead of PET/CT in the future. Their contributions to the overall research in this field, and the problems that remain to be solved; There is still only limited data on the benefits of ^{18}Fluorodeoxyglucose positron emission tomography computed tomography (^{18}FDG PET/CT) in the identification of recurrences and new metastases after first-line chemotherapy for metastatic bladder cancer, and evaluating responses to therapy in cancer patients is still just as challenging as before. The reason for this is that; with current imaging techniques it is not possible to detect with absolute accuracy after chemotherapy to what extent of metastatic focus has been affected by the chemotherapeutics.

Research methods

The research method is data analysis.

Research objectives

To contribute to the literature in this field. We believe that, this study will guide in the future. We see that data pool is beeing increased in this field.

Research motivation

Urooncology and Nuclear Medicine departments study as multidisciplinary. Scientific data is discussed in the council and outputs are produced.

Research background

The purpose of the present study was to examine retrospectively the contribution of ^{18}FDG-PET/CT to the evaluation of response to first-line gemcitabine plus cisplatin-based chemotherapy in patients with metastatic bladder cancer. An accurate primary staging of the disease is particularly important for the planning of second-line chemotherapy protocols and the determination of complete and incomplete response at this stage of the disease.

FOOTNOTES

Author contributions: Öztürk H participated in the design of the study and performed the statistical analysis; Karapolat İ carried out the nuclear medicine studies; Öztürk H and Karapolat İ drafted the manuscript; Öztürk H conceived the study, and participated in its design and coordination; all authors read and approved the final manuscript.

Institutional review board statement: There is no need approval. The research method is data analysis.

Informed consent statement: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study. Additional information consent was obtained from all patients for which identifying information is

included in this article.

Conflict-of-interest statement: All the authors declare that they have no competing interests. Financial support has not been received.

Data sharing statement: No additional data are available.

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

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World Journal of Clinical Cases

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World J Clin Cases 2023 December 26; 11(36): 8458-8474

DOI: 10.12998/wjcc.v11.i36.8458

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Functional magnetic resonance imaging study of group independent components underpinning item responses to paranoid-depressive scale

Drozdstoy Stoyanov, Rositsa Paunova, Julian Dichev, Sevdalina Kandilarova, Vladimir Khorev, Semen Kurkin

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: Mazza M, Italy; Shariati MBH, Iran

Received: September 26, 2023
Peer-review started: September 26, 2023
First decision: November 9, 2023
Revised: November 10, 2023
Accepted: December 5, 2023
Article in press: December 5, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Our study expand upon a large body of evidence in the field of neuropsychiatric imaging with cognitive, affective and behavioral tasks, adapted for the functional magnetic resonance imaging (MRI) (fMRI) experimental environment. There is sufficient evidence that common networks underpin activations in task-based fMRI across different mental disorders.

AIM

To investigate whether there exist specific neural circuits which underpin differential item responses to depressive, paranoid and neutral items (DN) in patients respectively with schizophrenia (SCZ) and major depressive disorder (MDD).

METHODS

60 patients were recruited with SCZ and MDD. All patients have been scanned on 3T magnetic resonance tomography platform with functional MRI paradigm, comprised of block design, including blocks with items from diagnostic paranoid (DP), depression specific (DS) and DN from general interest scale. We performed a two-sample *t*-test between the two groups-SCZ patients and depressive patients.

Our purpose was to observe different brain networks which were activated during a specific condition of the task, respectively DS, DP, DN.

RESULTS

Several significant results are demonstrated in the comparison between SCZ and depressive groups while performing this task. We identified one component that is task-related and independent of condition (shared between all three conditions), composed by regions within the temporal (right superior and middle temporal gyri), frontal (left middle and inferior frontal gyri) and limbic/salience system (right anterior insula). Another component is related to both diagnostic specific conditions (DS and DP) *e.g.* It is shared between DEP and SCZ, and includes frontal motor/language and parietal areas. One specific component is modulated preferentially by to the DP condition, and is related mainly to prefrontal regions, whereas other two components are significantly modulated with the DS condition and include clusters within the default mode network such as posterior cingulate and precuneus, several occipital areas, including lingual and fusiform gyrus, as well as parahippocampal gyrus. Finally, component 12 appeared to be unique for the neutral condition. In addition, there have been determined circuits across components, which are either common, or distinct in the preferential processing of the sub-scales of the task.

CONCLUSION

This study has delivers further evidence in support of the model of trans-disciplinary cross-validation in psychiatry.

Key Words: Paranoid-depressive scale; Functional magnetic resonance imaging; Cross-validation; Group independent component analysis; Schizophrenia; Depression

Core Tip: There have been identified five independent components, on the level of brain signals, which are significantly modulated by clinical diagnostic scales adapted to functional magnetic resonance imaging paradigm. Those results may help potentially to define patterns of activations which differ between patients with depression and patients with schizophrenia.

Citation: Stoyanov D, Paunova R, Dichev J, Kandilarova S, Khorev V, Kurkin S. Functional magnetic resonance imaging study of group independent components underpinning item responses to paranoid-depressive scale. *World J Clin Cases* 2023; 11(36): 8458-8474

URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8458.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8458

INTRODUCTION

Schizophrenia (SCZ) and depressive disorders constitute 4% on populational level and are considered severe mental disorders of global health, social and economic burden[1]. Their causal structure and pathogenetic mechanisms remain a controversial topic due to a variety of methodological constraints in psychiatry research[2,3]. One of those critical constraints is the lack of valid biological markers of disease.

Objective biomarkers have been a critical challenge for the field of psychiatry, where diagnostic, prognostic and theranostics assessments are still based on subjective narratives[4]. The lack of objective biomarkers produces an explanatory gap between disciplines concerned with mental health. On one hand, psychopathology operates with idiographic knowledge and subjective evaluations incorporated into clinical assessment inventories, and on the other hand, it is considered to be a medical discipline and, as such, uses medical intervention methods (*e.g.*, pharmacological, electroconvulsive treatment repetitive transcranial magnetic stimulation, transcranial direct current stimulation), and therefore is supposed to operate with the language and methods of nomothetic networks[5].

Yet, there exists a gap between those two kinds of knowledge, which contributes to one major challenge before their integration. As a consequence, the idiographic assessments were provisionally "quantified" into "structured clinical scales" to in some way resemble nomothetic measures. Instead of fostering data merging and integration, this approach further encapsulates the clinical psychiatric methods, as all other, biological tests (molecular, neuroimaging) are performed separately, only after the clinical assessment has provided diagnosis. By contrast, in other fields of medicine, diagnosis is mandatory co-produced by convergence of biological and clinical evaluation. We expect that neither biological measures nor subjective reports should be considered separately, but contribute to the incremental validity of each other, *i.e.* regarded as complementary approaches. In this way they can perform better in clinical practice and substitute each other in some clinical situations (like *e.g.* troponin or electro-cardiography can substitute radiological tests in some emergency cases).

Translational cross-validation of clinical assessment instruments and functional magnetic resonance imaging (MRI) (fMRI) is an attempt to address the gap[4]. It is in line with the emerging attempt to bring together viable imaging data and non-imaging variables, or behavioral components into joint analysis, beyond traditional approaches[6].

Our studies expand upon a large body of evidence in the field of neuropsychiatric imaging with cognitive, affective and behavioral tasks, adapted for the fMRI experimental environment. There is sufficient evidence that common networks underpin activations in task-based fMRI across different mental disorders[7].

For instance a common behavioral test (which is used as computer adapted test in clinical reality), is monetary incentive task. It has been applied in studies of the reward processing in clinical populations with specific pattern of hypo-and hyper-activation in SCZ and depression[8-11].

Emotional processing, working memory and reward processing were investigated in various mental disorders with common and distinct signatures of neural circuits' dysfunctions with reactive, regulation and compound fMRI stimuli[12, 13].

A most recent meta-analysis revealed that subjects with depression are reported to have greater activation in the anterior cingulate gyrus, insula, and middle frontal gyrus (MFG) for positive emotional stimuli, whereas activation in the MFG, inferior frontal gyrus, and insula is found to be greater for negative emotional stimuli[14].

In a systematic review by Cusi *et al*[15] social cognition in terms of facial emotion recognition and processing has been reported to be altered in major depressive disorder (MDD).

Neural correlates of N-back task performance have been consistently reported as correlates of working memory impairments as trans-diagnostic target in different psychiatric disorders, such as SCZ, MDD, bipolar disorder (BD) and attention-deficit and hyperactivity disorder[16]. Other working memory tasks have been implemented over the past years to investigate shared and distinct fMRI response in SCZ and MDD[17]. Working memory, cognitive control, prediction error have been studied in SCZ, depression and BD[12,18,19].

Although some of the above mentioned studies implement fMRI tasks with possible clinical use, the results, which address directly the translation between clinical evaluation tools and functional MRI are scarce.

Therefore we decided to explore the fMRI signatures behind the performance on clinical diagnostic self-assessment scales with established reliability and validity[3], whereby diagnostic fMRI tasks are regarded as more "naturalistic" stimuli[20].

Previous results of classical statistical parametric mapping (SPM) analysis, Depression Scale and Paranoid-Depression Scale. In our previous studies, we have managed to adapt clinical assessment tools to fMRI paradigms (stimuli) and to explore the real-time blood-oxygenation level dependent signals underpinning item responses[21]. Most prominently we have used two self-assessment tests, which are designed to capture two core syndromes in clinical psychopathology: Depressive and paranoid. The two syndromes are captured by the von zerssen depression specific (DS) and paranoid-depressive scales (PD-S). The assumption of our earlier studies was to establish translational validity of the constructs and thereby of the clinical states, without any claims at nosological validity. The depression scale was tested in a population of patients with depression compared to healthy controls. DS stimuli as contrasted to neutral items (DN) scale items yielded in patients with depression significant residual activations in right supramarginal gyrus, left MFG, triangular part of the left inferior frontal gyrus, and middle temporal gyrus, among others. The left precuneus activation was found to correlate with the patients' DS score[22]. Paranoid-depressive scale was administered in a group of patients with depression compared to patients with SCZ. Initial results indicated that patients with SCZ demonstrate significant activations in a number of regions [right angular gyrus (AG)], left posterior cingulate and precuneus, right transverse temporal gyrus) during responses to paranoid *vs* depressive scale items which differ topologically from those found in patients with major depression (left middle cingulate and right superior temporal gyrus[23]. Further more comprehensive study[24] reported by means of direct comparison significant activations during paranoid items processing in left precuneus and posterior cingulate gyrus and right AG. Further investigations, using multivariate analysis on a similar sample revealed high discriminatory power of the PD-S as task-related functional MRI paradigm both independently[25] and in combination with other, structural and resting state MRI modalities[26].

As one step further in the implementation of our paradigm, we have decided to use independent component analysis (ICA). The method is less focused on voxel-wise analysis, like SPM, and more on identification of temporally coherent spacial networks corresponding to task performance in task-based fMRI[27]. In that context this approach appears to be much more sensitive to capture the fluctuation in the fMRI signal during more complex cognitive-affective tasks, including verbal self-assessment.

Further group ICA was introduced was developed in order to assess independent patterns of network modulation (activation and deactivation) on group level[28].

Group ICA is more agnostic and explorative as compared to general linear model (GLM), essentially multivariate approach, which provides certain degree of freedom in the data interpretation and inferences beyond the constraints of the GLM[29].

In that regard, group ICA on fMRI data with the depression scale adapted to an fMRI task/paradigm[30] confirmed differences in the preferential networks processing diagnostic *vs* off blocks between patients and controls in anterior cingulate cortex and MFG. In that same study, diagnostic conditions from D-S as contrasted to neutral conditions from interest scale have yielded differential activity of right superior frontal gyrus and right middle cingulate cortex in the comparison of patients with depression and healthy controls.

In this context, the aim of the current study is to investigate whether there exisst common and specific neural circuits, which underpin differential item responses to depressive, paranoid, and DN in patients, respectively, with SCZ and MDD. The lead hypothesis is that the item responses to the two scales during fMRI session in patients suffering from the two main spectra of mental disorders may be cross-validated by means of group independent components analysis.

MATERIALS AND METHODS

Subjects

In total, 60 patients participated in this study: 33 with depressive episode and 27 with SCZ. Initially diagnostic assessment was performed by a board certified psychiatrists using mini international neuropsychiatric interview[31]; after that patients with depression were appraised with Montgomery-Asberg Depression Rating Scale[32], and patients with SCZ with The Positive and Negative Syndrome Scale[33]. We excluded patients with past medical history of concomitant mental conditions, neurological diseases of systemic and organic kind, traumatic incidents with loss of consciousness, or metal implants that interfere with MRI signal. All subjects signed a written informed consent in accordance to the Declaration of Helsinki. Our study was approved by the Medical University of Plovdiv Ethical Committee (2/19.04.2018).

Methods

MR scanning: Patients were scanned on a 3T MRI system (GE Discovery 750w), starting with a high resolution structural scan (Sag 3D T1 FSPGRsequence), slice thickness 1 mm, matrix 256 × 256, relaxation time (TR) 7.2 ms, echo time (TE) 2.3, and flip angle 12o, followed by a functional scan (2D EPI sequence), with slice thickness 3 mm, matrix 64 × 64, TR 2000 ms, TE 30 ms, and flip angle 90.

fMRI task: The paradigm was comprised of three different active conditions and a resting condition, with a summed duration of 11 min 44 s presented in a standart block design. Each active block went on for 32 s and consisted of four text statements of 8 s each. The statements for the DS and the paranoia specific (PS) blocks relied on the von Zerssen subscales for depression and paranoia, accordingly, while the DN blocks, was inspired from a questionnaire concerning general likes and interests. Four answers ("completely true", "mostly true", "somewhat true", "not true") with their respective response buttons (upper left, lower left, lower right, upper right) were presented under the questions. Four blocks of each type were rotating between the three active conditions (DS, DN, PS) and the rest condition, when we displayed a cross for fixation. The sequence of conditions may be summarized as DS_rest_DN_rest_PS_rest_DS.

Image processing: The SPM 12 software[34] was used for the processing the functional data. The images were realigned, co-registered with the structural ones, normalized to Montreal Neurological Institute (MNI) space, and smoothed with a 8 mm full-width-at-half-maximum Gaussian kernel.

ICA: To determine the brain networks that were activated in response to the task, a group ICA[35-37] was performed using FMRI toolbox (GIFT) software[38]. Individual ICA component maps were calculated using the Infomax algorithm. All subjects were analyzed simultaneously for the group ICA, and principal component analysis was used for compression. Because the number of components actually determines the spatial scale of the results (fewer number of the components results in larger brain networks), the number of components in the study was set to 50. The number of components recommended by GIFT based on the data reduction method was about 30, but we increased it to 50 for extra spatial precision[34,36]. Moreover, such number of components is a typical choice in many studie[39-42].

A GLM of the activity was constructed for the components by using a single-regression technique with three regressors to evaluate the components which were modulated by the task. The regressors were coded for the three active conditions (DS, DN, and PS). Regression of 50 components resulted from ICA analysis, each indicating the modulation for a particular task. There were single regression analyses for each of 3 conditions and 50 components with the false discovery rate (FDR) correction. The resulting beta values were then used in calculating two-sample t-tests in between-subjects design (SCZ *vs*. depressive) to identify significant effects at the FDR corrected $P < 0.05$. Thus, we determined the components which were modulated by the task and changed significantly between SCZ and depressive groups of patients.

We extracted the list of the regions which corresponded to the component activity in MNI and Talairach coordinates by means of "Write Talairach Table" function in GIFT with the following parameters: Threshold-3.5 to ensure $P < 0.01$ while mostly following manual recommendation and the distance between the contiguous voxels-4 mm, considering smoothing with a 8 mm FWHM Gaussian kernel, as half-width window distance between voxels of smoothed volume could be considered same structure[43].

Statistical analysis

For the statistical analysis of the demographic and clinical characteristics of the participants we used IBM SPSS 22.0 for Windows. The level of significance was set to $P < 0.05$ for all tests. Differences in mean values of continuous variables were tested with Independent Samples Kolmogorov test and the Pearson Chi-Square test was used for categorical ones.

RESULTS

Demographic and clinical characteristics

The two patient groups did not differ significantly in their sex, education level, and age, also in their age at onset, illness duration and episode duration for the respective condition as shown in the Table 1.

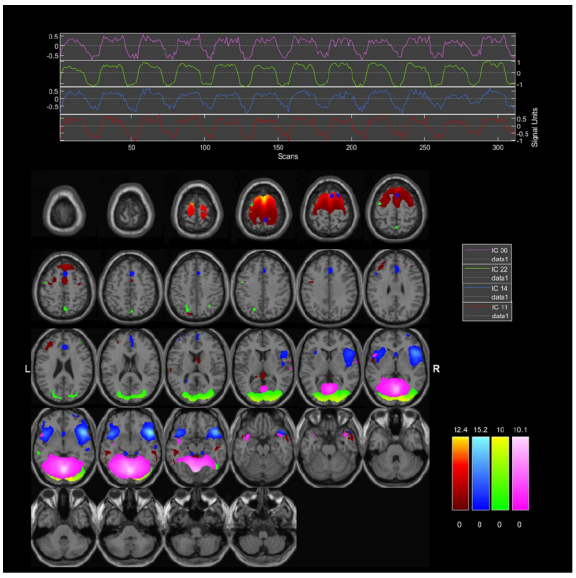
ICA results

We performed a two-sample *t*-test for the regressor beta-weights of all independent components between the two groups-

Table 1 Demographic and clinical characteristics for the groups, mean ± SD

Variable	Depressive (*n* = 33)	SCZ (*n* = 27)	Significance corrected
Sex (M/F)	9/24	14/13	0.357[1]
Education (primary/secondary/higher)	2/15/15	1/19/7	1
Age	43.8 ± 11.837	39.58 ± 13.950	1
Age at onset	32.48 ± 11.775	26.96 ± 9.313	1
Illness duration (mo)	125.612 ± 89.914	151.54 ± 110.431	1
Current episode duration (wk)	20.193 ± 35.929	13.417 ± 14.788	1
Total intracranial volume, TIV	1.3854 ± 0.1209	1.4146 ± 0.1145	1
Total MADRS score	29.78 ± 5.785		
Total PANSS G score		24.74 ± 9.86	
Total PANSS P score		17.79 ± 7.16	

[1]Bonferroni-corrected Pearson Chi-Square. MADRS: Montgomery Asberg depression rating scale; PANSS: Positive and negative sympstoms scale; SCZ: Schizophrenia; TIV: Total intracranial volume.



DOI: 10.12998/wjcc.v11.i36.8458

Figure 1 Map of the components, significantly modulated by the depression specific condition.

SCZ patients and depressive patients. Our goal was to identify different brain networks, which were activated during a specific condition of the task (respectively, DS, PS, or DN) and differed between SCZ and depressive groups. For the DS condition the significant components were -11, 14, 22, 36 (Tables 2 and 3, Figure 1). For the PS condition, the significant components were –11, 14, 23, 38 (Tables 4 and 5, Figure 2). For the DN condition, the significant components were –12, 14, 23 (Tables 6 and 7, Figure 3).

DISCUSSION

This study demonstrated several significant results in the comparison between SCZ and DEP groups while performing a task with diagnostically specific (for depression and paranoia) and DN stimuli. On the level of independent components, we identified one component (C14) that is task-related and independent of condition (shared between all three conditions), another component (C11) that is related to both diagnostically specific conditions (DS and PS) and it is shared between DEP and SCZ, one paranoia-specific component linked only to the PS condition (C38), and two components (C22 and C36) significantly correlated with the depression-specific condition. Finally, component 12 appeared to be unique for the neutral condition.

Table 2 Significant components that were found between schizophrenia and depressive groups for depression condition

Component	*P* value	T value
Component 11	0.004249717	2.976318
Component 14	0.008079258	2.7432945
Component 22	0.0059576669	2.8551928
Component 36	0.021446516	2.3640435

Table 3 Detailed description of the Talairach tables corresponding to the significant components that were found between schizophrenia and depressive groups for depression condition

Component	Area	Brodmann area	Volume (cc)	MNI coordinates	Loading
	Left inferior parietal lobule	40	1.7	(-42, -52, 58)	-
	Left inferior frontal gyrus	44, 45, 46	2.4	(-56, 22, 16)	-
	Left middle frontal gyrus	8, 10, 46	2.4	(-40, 22, 50)	-
	Paracentral lobule	5, 6	1.2	(4, -42, 60)	-
11					
	Right superior frontal gyrus	6, 8	8.1	(4, 0, 72)	+
	Left middle frontal gyrus	6	3.7	(-22, 10, 68)	+
	Right medial frontal gyrus	6	2.4	(6, -18, 72)	+
	Left precentral gyrus	4, 6	2.1	(-28, -16, 72)	+
	Left sub-gyral	21	2.2	(-42, 4, -20)	-
	Right superior temporal gyrus	22, 38, 41, 42	2.4	(40, 10, -24)	-
	Left clmen		1.2	(-2, -46, -12)	-
	Left middle frontal gyrus	6, 8, 9	2.2	(-28, 32, 50)	-
	Left middle Ttemporal gyrus	21	1.1	(-50, 4, -20)	-
	Left inferior frontal gyrus	9, 44, 45, 46	1.5	(-50, 12, 14)	-
14					
	Right inferior frontal gyrus	13, 45, 47	10.4	(46, 18, -8)	+
	Right superior temporal gyrus	21, 22, 38	6.3	(50, 18, -8)	+
	Right insula	13, 22	4.9	(40, 14, -4)	+
	Right precuneus	7, 19, 31, 39	2.9	(38, -78, 38)	-
	Left parahippocampal gyrus	19, 30, 36, 37	1.5	(-20, -50, -10)	-
22					
	Right cuneus	17, 18, 19, 23, 30	9.2	(14, -94, -2)	+
	Right lingual gyrus	17, 18, 19	7.4	(10, -92, -2)	+
	Right middle occipital gyrus	18, 19	8.1	(24, -94, 2)	+
	Right sub-gyral		2.7	(22, -94, -6)	+
	Right cuneus	17, 18, 19	3.6	(2, -92, 8)	-
	Right middle occipital gyrus	18, 19	2.2	(12, -92, 14)	-
36					
	Left lingual gyrus	18, 19, 30	10.8	(-4, -70, -4)	+
	Left Culmen		5.9	(-6, -66, -8)	+
	Left fusiform gyrus	19, 37	1.5	(-20, -70, -12)	+

	Left parahippocampal gyrus	19, 30, 36, 37	3.3	(-18, -54, -8)	+
	Left cuneus	18, 23, 30	1.5	(-4, -68, 4)	+
	Left sub-gyral	37	7.2	(-28, -70, -8)	+

MNI: Montreal neurological institute.

Table 4 Significant components that were found between schizophrenia and depressive groups for paranoid specific condition

Component	*P* value	T value
Component 11	0.0032496235	-3.0704975
Component 14	0.025153517	-2.2985475
Component 23	0.008092356	-2.7426922
Component 38	0.034015527	-2.1712631

Table 5 Detailed description of the Talairach tables corresponding to the significant components that were found between schizophrenia and depressive groups for paranoid specific condition

Component	Area	Brodmann area	Volume (cc)	MNI coordinates	Loading
	Left sub-gyral	21	2.2	(-42, 4, -20)	-
	Right superior temporal gyrus	22, 38, 41, 42	2.4	(40, 10, -24)	-
	Left culmen		1.2	(-2, -46, -12)	-
	Left middle frontal gyrus	6, 8, 9	2.2	(-28, 32, 50)	-
	Left middle temporal gyrus	21	1.1	(-50, 4, -20)	-
	Left inferior frontal gyrus	9, 44, 45, 46	1.5	(-50, 12, 14)	-
14					
	Right inferior frontal gyrus	13, 45, 47	10.4	(46, 18, -8)	+
	Right superior temporal gyrus	21, 22, 38	6.3	(50, 18, -8)	+
	Right Iinsula	13, 22	4.9	(40, 14, -4)	+
	Left inferior parietal lobule	40	1.7	(-42, -52, 58)	-
	Left inferior frontal gyrus	44, 45, 46	2.1	(-56, 22, 16)	-
	Left middle frontal gyrus	8, 10, 46	2.4	(-40, 22, 50)	-
	Paracentral lobule	5, 6	1.2	(4, -42, 60)	-
11					
	Left inferior parietal lobule	40	1.7	(-42, -52, 58)	+
	Left inferior frontal gyrus	44, 45, 46	2.4	(-56, 22, 16)	+
	Left middle frontal gyrus	8, 10, 46	2.4	(-40, 22, 50)	+
	Right paracentral lobule	5, 6	1.2	(4, -42, 60)	+
	Right superior frontal gyrus	6, 8	8.1	(4, 0, 72)	+
	Left middle frontal gyrus	6	3.7	(-22, 10, 68)	+
	Right medial frontal gyrus	6	2.4	(6, -18, 72)	+
	Left precentral gyrus	4, 6	2.1	(-28, -16, 72)	+
	Left middle frontal gyrus	8, 9, 10, 11, 47	4.3	(-36, 26, 42)	-
	Left superior frontal gyrus	6, 8, 9, 10	4.9	(-14, 26, 62)	-

23					
	Right inferior frontal gyrus	9, 13, 44, 45, 46	12.1	(54, 18, 28)	+
	Right middle frontal gyrus	6, 8, 9, 10, 46	14.1	(52, 16, 32)	+
	Right sub-gyral		6.7	(46, 16, 24)	+
	Right precentral gyrus	3, 6, 9, 13, 43, 44	13.8	(48, 22, 38)	+
	Right postcentral gyrus	1, 2, 3, 43	6.1	(60, -8, 22)	+
	Right insula	13	3.3	(46, 8, 12)	+
	Right superior frontal gyrus	6, 8	6.0	(16, 28, 62)	-
	Right middle frontal gyrus	6, 8, 10, 11, 47	1.5	(24, 24, 60)	-
	Left inferior frontal gyrus	13, 44, 45, 46, 47	1.1	(-50, 38, -8)	-
38					
	Left middle frontal gyrus	6, 8, 9, 10, 46	18.4	(-50, 10, 44)	+
	Left precentral gyrus	4, 6, 9	8.6	(-46, 20, 38)	+
	Left inferior frontal gyrus	6, 9, 45, 46, 47	4.4	(-52, 8, 36)	+
	Left postcentral gyrus	1, 2, 3, 4, 40	1.9	(-56, -12, 48)	+
	Left superior frontal gyrus	6, 8, 9, 10	4.3	(-40, 16, 54)	+
	Left medial frontal gyrus	6, 8, 9, 32	2.9	(-2, 16, 48)	+

MNI: Montreal neurological institute.

Component 14 shares significant clusters modulated by all three conditions, therefore it has limited contribution to the differential diagnostic pattern. It is mainly built up by regions within the temporal (right superior and middle temporal gyri), frontal (left middle and inferior frontal gyri) and limbic/salience system right anterior insula (rAI). According to our results, patients with both diagnoses are processing the information by increasing the activity in those regions and on the other hand, independent of the content of the stimuli, the emotional component is always there even in the DN statements. Moreover this could be explained with the semantic processing of emotional words[44,45] which are likely to have comparable subjective valence for both patients' groups, regardless of the diagnostic-specific content. This component encompasses Brodmann areas (BA) 22, 42, 44, 45 and 47 mainly related to language processing[46,47], as well as BA 46 which corresponds to the dorsolateral prefrontal cortex (PFC) (DLPFC) involved in sustained attention and working memory[48,49]. Moreover, the involvement of the left DLPFC has been linked to higher demands in planning which might be the case of our task with four different response options[50].

Another significant cluster within component 14 appears to be located within the rAI which is involved in a variety of cognitive, affective, and regulatory processes, including interoception, emotional reactions, and empathy[51]. Interoceptive processing is suggested to be linked primarily to the function of rAI which is simultaneously part of the salience network (SN) along with anterior cingulate cortex[52]. The crucial role of the SN as a switch between internally default mode network (DMN) and externally (central executive network) oriented attention is found to be disrupted in both SCZ and DEP[12,53-55]. Notably, in our recent effective connectivity study the alterations of the self-inhibitory connection of the AI emerged as a feature of both mood disorders and SCZ[56].

The second important finding in the present study is that Component 11 is significantly modulated by both diagnostic conditions, DS and PS, thereby contributing to a diagnostic pattern. The brain areas within this component are mainly focused in frontal motor/language (BA 4, 6, 8, 10, 44, 45, 46) and parietal regions (BA 40). Dysregulations in those areas relate to the pathogenesis of both diagnoses-depression and SCZ[57] and it is expected to be significant in both conditions. Increased activation in Superior frontal gyrus is reported to relate to the different stages of depression[58].

BA 10 or rostral PFC is involved in working memory, episodic memory, and multiple-task coordination[59] while areas 4, 6, and 8 are related to motor planning. Notably, BA 8 demonstrates increased activation with increasing uncertainty in decision-making[60] which might be the case in both patient groups when assessing and responding to diagnostic-specific statements. Interestingly, this component includes supramarginal gyrus (BA 40) which is well known for being part of the mirror neuron system, involved in tool use tasks, and visual word recognition as well[61-63].

Notably, both C14 and C11 include clusters of DLPFC (BA 46) where various dysfunctions in task-related fMRI have been found in both SCZ and DEP[64-66]. Most studies link the dysfunction to impaired cognitive control which is a manifestation of both pathologies[12,67]. Moreover, on a metabolic level, significant relationship between left DLPFC N-acetilaspartate/creatine ratio and cognitive deficits in patients with first episode psychosis was found[68]. In addition, the role of the left DLPFC in depression is supported by the successful use of this area as a target for transcranial magnetic stimulation in treatment resistant depression[69].

Table 6 Significant components that were found between schizophrenia and depressive groups for diagnostically neutral condition

Component	*P* value	T value
Component 12	0.013277254	2.5546326
Component 14	0.004986471	-2.9193653
Component 23	0.047710834	-2.0228125

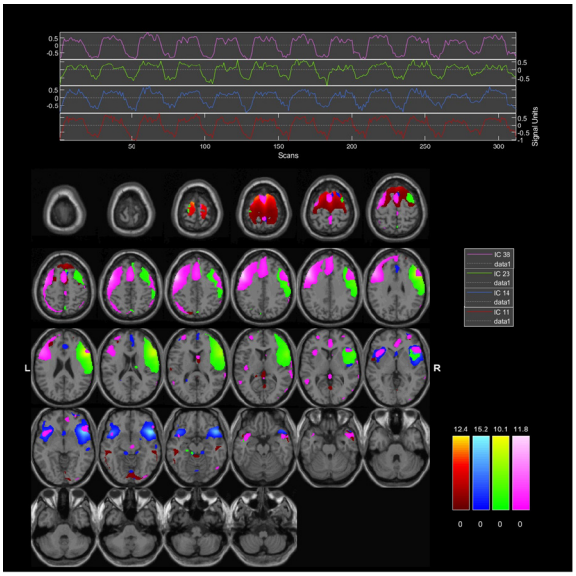


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Figure 2 Map of the components, significantly modulated by the paranoid specific condition.

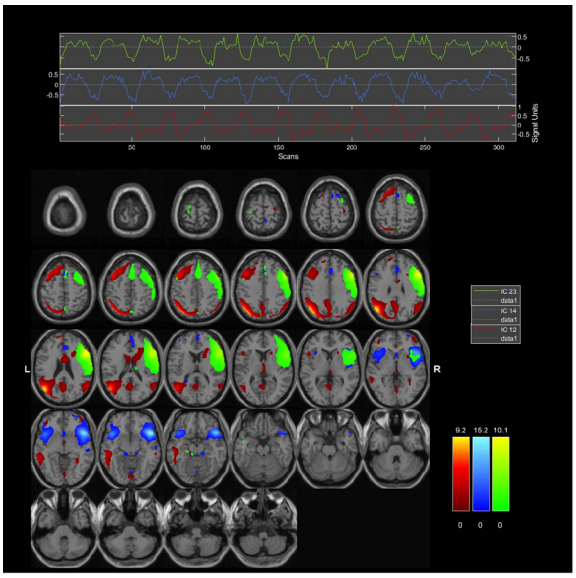

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Figure 3 Map of the components, significantly modulated by the neutral items condition.

Another finding of our study was the significant difference between SCZ and DEP in regard to component 38 demonstrating an association with the paranoid-specific items (stimuli). Most of its regions are within the frontal areas of the brain including distributed sensory-motor networks (BA 1, 2, 3, 4, 6), and all three sub-divisions of the PFC [DLPFC-BA 8, 9, 46; ventrolateral PFC (VLPFC)-BA 45, 47; and orbitofrontal (OFC)-BA 10, 11]. Notably, within this component, the involvement of the well-known language areas BA 44 and 45 extends to a less studied BA 47 which is proposed to be part of the "frontal language production system"[70] as well as part of the VLPFC traditionally associated with emotion

Table 7 Detailed description of the Talairach tables corresponding to the significant components that were found between schizophrenia and depressive groups for paranoia specific condition

Component	Area	Brodmann area	Volume (cc)	MNI coordinates	Loading
Component 12					
	Left superior temporal gyrus	13, 21, 22, 38, 41, 42	6.1	(-64, -16, 6)	-
	Right medial frontal gyrus	6, 8, 32	1.5	(4, 14, 48)	-
	Right precuneus	7	3.8	(30, -54, 50)	-
	Right middle frontal gyrus	6	2.6	(34, 0, 58)	
	Left angular gyrus	39	2	(-50, -66, 32)	+
	Left middle temporal gyrus	19, 21, 37, 39	7.6	(-50, -66, 28)	+
	Left supramarginal gyrus	40	3.5	(-50, -62, 32)	+
	Left inferior parietal lobule	7, 39, 40	4.4	(-44, -70, 38)	+
	Left superior temporal gyrus	22, 39	2.8	(-50, -62, 28)	+
	Left precuneus	7, 19, 31, 39	6.7	(-42, -74, 36)	+
	Left superior parietal lobule	7	2	(-36, -74, 44)	+
	Left middle frontal gyrus	6, 8, 9, 10, 11	8.4	(-44, 16, 50)	+
Component 14					
	Left sub-gyral	21	2.2	(-42, 4, -20)	-
	Right superior temporal gyrus	22, 38, 41, 42	2.4	(40, 10, -24)	-
	Left culmen		1.2	(-2, -46, -12)	-
	Left middle frontal gyrus	6, 8, 9	2.2	(-28, 32, 50)	-
	Left middle temporal gyrus	21	1.1	(-50, 4, -20)	-
	Left inferior frontal gyrus	9, 44, 45, 46	1.5	(-50, 12, 14)	-
	Right inferior frontal gyrus	13, 45, 47	10.4	(46, 18, -8)	+
	Right superior temporal gyrus	21, 22, 38	6.3	(50, 18, -8)	+
	Right insula	13, 22	4.9	(40, 14, -4)	+
Component 23					
	Left middle frontal gyrus	8, 9, 10, 11, 47	4.3	(-36, 26, 42)	-
	Left superior frontal gyrus	6, 8, 9, 10	4.9	(-14, 26, 62)	-
	Right inferior frontal gyrus	9, 13, 44, 45, 46	12.1	(54, 18, 28)	+
	Right middle frontal gyrus	6, 8, 9, 10, 46	14.1	(52, 16, 32)	+
	Right sub-gyral		6.7	(46, 16, 24)	+
	Right precentral gyrus	3, 6, 9, 13, 43, 44	13.8	(48, 22, 38)	+
	Right postcentral gyrus	1, 2, 3, 43	6.1	(60, -8, 22)	+
	Right insula	13	3.3	(46, 8, 12)	+

MNI: Montreal neurological institute.

regulation and cognitive reappraisal. Moreover, the left VLPFC is proposed to be responsible for the semantic process of generating and selecting appraisals according to emotion regulation[71].

The OFC is involved in controlling and correcting reward- or punishment-related behavior, and in emotions[72]. Both structural and functional alterations have been found across a number of psychiatric disorders[73], including SCZ[74] and DEP[75]. Of note, shared impairment of OFC functional connectivity was found spanning across psychotic and mood disorders with a gradient in the extent of alterations from SCZ through BD to MDD[76]. In addition, resting-state effective connectivity between OFC and precuneus was found to demonstrate differential diagnostic properties in our recent study on SCZ and DEP[77].

Most of the regions are within the frontal areas of the brain, with DMN and central attention networks (CEN) involved as crucial hubs. Studies on the matter have shown significant aberrations in connectivity between the two networks[78], with increased intraconnectivity, while the insula does not display adequate activation, suggesting there may be a circle of a positive feedback mechanism between the two in schizophrenic patients[79]. Furthermore, medial PFC is a region, which is associated with high-level executive functions and decision-associated processes[80]. Those functions are impaired in patients with SCZ and it is established that they have disrupted function[81,82]. It is evident that there is significant activation of the postcentral somatosensory cortex, which is consistent with studies documenting increased connectivity between the thalamus and said brain region[83,84].

Components 22 and 36 are both significantly modulated by the depression specific condition in SCZ as compared to DEP and thereby contribute to a differential diagnostic pattern. They include clusters within the DMN such as posterior cingulate and precuneus, several occipital areas, including lingual and fusiform gyrus, as well as parahippocampal gyrus (PHG). PHG has a key role in cognition and memory[85] and is linked to the influence of emotions on these processes [86]. Having in mind the clinical presentation of depression, it is not surprising that this brain region has been implicated in the pathogenesis of the disorder[87]. Research demonstrates that there is an increased involvement of PHG when presenting negative/disgusting stimuli to patients with MDD[88]. Moreover, whole-brain functional connectivity revealed that the most discriminative connections between patients with depression and healthy individuals were concentrated in the DMN, visual cortex, and affective network and that the PHG has a high discriminative role in terms of the diagnose[89].

Precuneus is known to be a key hub of the DMN, and as such, it plays a crucial role in self-referential processing, including episodic memory and mental imagery. Studies have shown that the precuneus is a potential biomarker associated with MDD[90], further validating the theory of DMN activity alteration in depressive patients, which is also consistent with our findings[77,91].

The last component which is present in more than one condition is C23, as it appears to be modulated by both PS and DN conditions. The regions within this component are mostly located in the frontal (bilateral DLPFC, OFC, and right VLPFC, pre- and postcentral regions-BA 1, 2, 3, 6, 8, 9, 10, 11, 44, 45, 46) and insular cortex (rAI). The involvement of the SN in this component that is shared between PS and DN conditions might be interpreted as evidence that the DN statements are processed by the patients with SCZ as emotionally laden or referential stimuli, as expressed in more detail elsewhere[92].

Component 12 is also significantly higher in SCZ but only in the DN task condition. There are a variety of frontal, temporal, and parietal regions within C12 which are associated with different brain networks-DMN (precuneus, AG, medial PFC), CEN, language (semantic) network. Given the nature of the task, it is expected to see regions connected with language processing, working memory and attention. However, the Medial frontal gyrus, as region of conducting complicated processes, decision making[75] also yields in the component. What is more, it is negatively correlated. This finding proposes the idea that even if the stimuli is on the neutral side, for the patients it has meaningful interpretation and is beyond their rational control.

Apart from its contribution to the DMN, AG has been described as a "core facility used by different subsystems to access concepts when interfacing perception-to-recognition-to-action[92]". According to the authors, the AG should be seen as cross-modal integrative hub attributing meaning to an event within a context, based on prior expectations, and aimed at an intended action. As part of the semantic network, AG is engaged in reading and comprehension, and in schizophrenic patients' severity of formal thought disturbances was correlated with a disruption of the left semantic network[93]. Interestingly, subjects with SCZ demonstrate and abnormal asymmetry of the AG (left smaller than right) as compared to healthy controls (left larger than right) which might have contributed to the present results[94].

It is noteworthy that there are common, shared and distinct regions from all components, which seem to form disrupted brain networks, which process the task conditions in different ways between the two nosological groups. The main disrupted networks are-DMN, CEN and SN, with an executive summary presented on Table 8.

This adds evidence to the model of translational validation, established in our earlier work with case-control design [76]. Complementary to the already reported distinct (or specific) circuit, processing depressive scale in depressed patients, we have discovered a specific network processing paranoid items in the current specificity study. The latter includes left superior frontal gyrus and its continuation-the left medial frontal gyrus. Superior frontal gyrus is liked to self-awareness[94]. The disturbances of self-awareness are core phenomenological manifestations of psychosis[95]. Our findings are consistent with the findings of other authors about dysregulations of functional connectivity in the same region associated with SCZ[96] as well as with our own previous studies[24].

The shared circuits which process DP and DS including components from the fronto- parietal network[97] are likely to reflect the convergence of psychosis and affective disorders on the level of the underlying neural mechanisms.

We assume that the activated insula in both conditions (DS and DP) reflects the impaired role of switching the functions between DMN and CEN[78]. In contrary to many studies which yield decreased function of the insula in our study we find an increased function of the regions. We hypothesize that the increased function of the insula may compensate the disruptions in the other two networks-DMN and CEN, as a higher level of control. That assumption is in line with other studies, which report abnormal regulations of the task-positive and task-negative networks[98] as well as reduced suppression of DMN during semantic processing in SCZ.

Limitations

This study has several limitations. The first is the relatively small sample size. However the current practice of fMRI studies states that the sample size we use is sufficient for the analysis we are conducting. Szucs and Ioannidis[99] conclude that highly cited clinical fMRI studies (with patient participants) had median sample size of 14.5 subjects. Moreover, Desmond and Glover[100] state that for a liberal threshold of 0.05, about 12 subjects were required to achieve

Table 8 Circuits preferentially processing paranoid and depressive scale [regions activated ("þ")/deactivated ("−") by the condition]

Brain region	Brodmann areas	Activated (+) deactivated (-)
Common circuit for all conditions		
Right inferior frontal gyrus	13, 45, 47	+
Right superior temporal gyrus	21, 22, 38	+
Right insula	13, 22	+
Left inferior parietal lobule	40	-
Left inferior frontal gyrus	44, 45, 46	-
Left middle frontal gyrus	8, 10, 46	-
Paracentral lobule	5, 6	-
Shared circuit, between conditions DS and DP		
Left inferior parietal lobule	40	
Right paracentral lobule	5, 6	
Right medial frontal gyrus	6	
Left middle frontal gyrus	8, 9, 10, 11, 47	
Left superior frontal gyrus	6, 8, 9, 10	
Shared between DP and DN		
Right sub-gyral	[1]	+
Distinct (appear in one component), condition DS		
Right cuneus	17, 18, 19, 23, 30	+
Right lingual gyrus	17, 18, 19	+
Right middle occipital gyrus	18, 19	+
Right cuneus	17, 18, 19	
Right middle occipital gyrus	18, 19	
Left lingual gyrus	18, 19, 30	+
Left culmen		+
Left fusiform gyrus	19, 37	+
Left parahippocampal gyrus	19, 30, 36, 37	+
Left cuneus	18, 23, 30	+
Left sub-gyral	37	+
Distinct (appear in one component), condition DP		
Left postcentral gyrus	1, 2, 3, 4, 40	+
Left superior frontal gyrus	6, 8, 9, 10	+
Left medial frontal gyrus	6, 8, 9, 32	+

[1]Subcortical area.

Distinct neutral items (DN)-no distinct circuit, specific for DN is reported, which supports the assumption, that the items from that scale are diagnostically neutral. DP: Diagnostic paranoid; DS: Depression specific; DN: Neutral items.

80% power at the single voxel level for typical activations. At more realistic thresholds, that approach those used after correcting for multiple comparisons, the number of subjects doubled (24 subjects) to maintain this level of power. Also, under ongoing grant funding, our group plans to expand the sample and to outsource independent replication studies. The second limitation is methodological, as GIFT is considered to be liberal approach to brain imaging data analysis when compared to SPM more stringent techniques. The third limitation is the absence of a healthy control group. It is entailed from the assumption that in this design, we explore rather specificity, *i.e.*, differences across disorders. This is not in dissonance with the overall research rationale and is complemented with a study of sensitivity under another research project[23,24]. Although current treatment is sometimes considered as a potential confound, the effects of medication in

depression have been reported in most recent voxel-based meta-analysis as having limited impact. In other terms alterations are likely to persist regardless to the medications status of the patients[101].

CONCLUSION

This study has delivered evidence in support of the model of trans-disciplinary validation in psychiatry. The model has been previously tested using the same PD-S with classical SPM analysis and with multivariate linear method, which provide other perspectives on the same methodological concern[102]. In summary, that methodological question is whether and to what extent is it possible to cross-validate neuroimaging state-dependent biomarkers with clinical state-dependent assessment scales. Although we are still far away from the ultimate answer to such question, nevertheless this is a piece of progress towards better attunement between brief clinical tests used in everyday practice and fMRI as a potential external validator. Further replications are called for in order to advance in this line of investigation.

ARTICLE HIGHLIGHTS

Research background

The background of this study is comprised of earlier contributions of our group. Those contributions include studies of the functional magnetic resonance imaging (fMRI) correlates of the item responses to paranoid and depressive self-assessment scales. Those were studies on patients with depression, schizophrenia (SCZ), and healthy controls, by means of statistical parametric mapping and multivariate linear method.

Research motivation

The research motivation for the current study is to investigate the modulation of the fMRI signals by the diagnostic specific task (paranoid-depressive scale) with more complex toolbox. The group independent component analysis for FMRI toolbox (GIFT).

Research objectives

The primary objective of the study were to reveal the modulation of fMRI signals by diagnostic specific scales item responses in two clinical populations: Patients with SCZ and depression. The secondary objective was to investigate the difference in those signatures across the groups.

Research methods

The methods include clinical assessment, fMRI, statistical methods and GIFT.

Research results

The results indicate that there exist different neural circuits, which are modulated by paranoid and depressive diagnostic specific tasks. There are reported differences in the modulation of those circuits between patients with SCZ and depression.

Research conclusions

The methodology of GIFT is appropriate for translation of functional MRI findings into clinical utility.

Research perspectives

There are perspectives in the application the same methodology to other clinical assessment scales, *e.g.* for state and trait anxiety as well as for independent replications of the current findings.

FOOTNOTES

Author contributions: Stoyanov D designed the research study and wrote the manuscript; Stoyanov D and Kandilarova S performed the research; Paunova R, Kurkin S and Khorev V analyzed the data; all authors have read and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Medical University of Plovdiv.

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

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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

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World Journal of Clinical Cases

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World J Clin Cases 2023 December 26; 11(36): 8475-8485

DOI: 10.12998/wjcc.v11.i36.8475

ISSN 2307-8960 (online)

EVIDENCE-BASED MEDICINE

Mendelian randomization provides evidence for a causal effect of serum insulin-like growth factor family concentration on risk of atrial fibrillation

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Specialty type: Cardiac and cardiovascular systems

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): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ong H, Malaysia

Received: October 1, 2023
Peer-review started: October 1, 2023
First decision: November 16, 2023
Revised: November 10, 2023
Accepted: December 7, 2023
Article in press: December 7, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Atrial fibrillation (AF) is one of the most common persistent arrhythmias among adult cardiovascular diseases. It is important to identify potential risk factors for AF. Members of the insulin-like growth factor (IGF) family exert a variety of effects on various cell types in the context of the pathogenesis of cardiovascular diseases, and previous population-based studies indicate associations between IGF family members and AF. However, the causal effects of IGF family members in AF have not been evaluated.

AIM

In the current study two-sample Mendelian Randomization (MR) was used to assess genetic relationships between IGF family members and AF.

METHODS

MR was performed based on genome-wide association study (GWAS) datasets, and concentration levels of 14 IGF family members were retrieved. An initial MR analysis was conducted to identify single nucleotide polymorphisms potentially associated with IGF serum concentrations. A GWAS meta-analysis including 60620 AF cases and 970216 control participants of European ancestry was then conducted to identify AF causal effects. Two-sample MR packages were used to perform MR analysis in R. MR-Egger, weighted median (WM), and inverse variance weighted (IVW) methods were used.

RESULTS

In two-sample MR assessments there were lower levels of circulating IGF binding protein 3 in both WM [odds ratio (OR) 0.964, 95% confidence interval (CI) 0.940–0.960, P = 0.006] and IVW (OR 0.968, 95%CI: 0.947–0.987, P = 0.001) analyses. Higher serum levels of IGF2 receptor were associated with AF (OR 1.045, 95%CI: 1.016–1.076, P = 0.039). In reverse MR analysis conducted to investigate casual effects, elevated levels of circulating CYR61 were associated with AF (OR 1.060, 95%CI: 1.005–1.119, P = 0.031).

CONCLUSION

The results of the present study provide novel insights into the pathogenesis of AF, and the implications of serum IGF family member concentrations when assessing the risk of AF. The study generated evidence on the potential roles of developmental pathological effects in the pathogenesis of AF. Further observational and experimental studies are critically needed.

Key Words: Atrial fibrillation; Genome-wide association study; Insulin-like growth factor binding protein 3; Insulin-like growth factor family; Mendelian randomization

Core Tip: Due to the high prevalence of atrial fibrillation (AF), and adverse outcomes related to it, it is important to identify risk factors associated with development of the condition. Insulin-like growth factor (IGF) family members exert a variety of effects on various cell types in the context of the pathogenesis of cardiovascular diseases, and previous population-based studies indicate associations between IGF family members and AF. However, the causal effects of IGF family members in AF have not been evaluated. The results of the current study provide novel insights on the pathogenesis of AF, and implications of serum IGF family member concentrations when assessing the risk of AF. The study generated evidence on the potential roles of developmental pathological effects in the pathogenesis of AF. Further observational and experimental studies are critically needed.

Citation: Lin S, Tang J, Li X, Wu G, Lin YF, Li YF. Mendelian randomization provides evidence for a causal effect of serum insulin-like growth factor family concentration on risk of atrial fibrillation. *World J Clin Cases* 2023; 11(36): 8475-8485
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8475.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8475

INTRODUCTION

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice worldwide. It recently ranked as the persistent arrhythmia with the highest prevalence in the elderly population. The risk of AF increases with age, with a sharp increase between the ages of 60 and 69 years, and progressive increases from 70–79 years and 80–89 years. The phenotypes of AF are heterogeneous[1], and it is a major public health problem in both developing and developed countries.

Heart failure and metabolic disorders such as diabetes and obesity have been identified as contributing to the pathogenesis of AF, and these associations have been extensively documented. With regard to the exact mechanisms underlying AF, predominant theories center on structural remodeling induced by external stressors, including hemodynamic stressors and inflammation. Structural remodeling is commonly recognized as comprising three key components; fibroblast activation, myocardial fibrosis, and collagen deposition[2]. Given the fundamental pathophysiological mechanisms involved in AF development, which include hemodynamic stress, inflammation, and myocardial fibrosis, numerous studies have explored potential associations between biomarkers reflecting pathobiological processes and AF onset. A relationship between circulating natriuretic peptide (NP) concentrations and incident AF has been well-established in various cohorts, including the Framingham Offspring Study, Cardiovascular Health Study, and the CHARGE-AF Consortium, among others[3-5]. In addition to NPs, C-reactive protein has been recognized for its significant role in systemic inflammation and the prediction of AF[5,6]. Furthermore, several biomarkers associated with fibrosis have been investigated as potential indicators of the onset of incident AF[7-9].

Developmental aspects of AF have been documented in clinical and translational studies. Early myocardium development and its interaction with large vessels, particularly pulmonary veins, has been considered a major contributor to AF onset. Atrial fibrosis is regarded as another of the primary mechanisms underlying AF. Localized atrial fibrosis leads to abnormal calcium processing in atrial myocardium, thereby inducing re-entry and electrical disturbances, establishing a molecular and mechanical basis for AF. Thus, factors present in circulation that are implicated in atrial myocardial fibrosis should be regarded as potential contributors to AF.

The peptidic hormone insulin-like growth factor (IGF) family comprises two ligands (IGF1 and IGF2), two receptors (IGF1R and IGF2R), seven high-affinity binding proteins (IGFBPs 1–7), a substantial group of IGFBP proteases, and a novel category of proteins known as low-affinity IGFBP-related proteins (IGFBP-rPs). It has been well established that the

family plays pivotal roles in growth and development, regulating processes such as proliferation, differentiation, metabolism, and cell survival in various tissues. It is also associated with metabolic disorders, including hypertension, obesity, and stroke. Recent research indicates that reduced IGF1 Levels are linked to an elevated risk of cardiovascular disease-associated mortality. To date no population-based study has investigated associations between AF morbidity and members of the IGF family, such as IGF1 and IGFBP3[10]. In experimental rat models Wang *et al*[3] demonstrated that IGF1 was associated with atrial fibrosis and participated in AF. It has also been reported that IGF1 and IGFBPs are involved in diabetes, which exacerbates interstitial fibrosis in the atria. These associations have been seen in both animal studies[11,12] and human studies[13].

The above-described associative observations were primarily derived from conventional observational studies, which are susceptible to sample size limitations, reverse causation bias, and confounding factors[14]. It is often challenging to draw definitive conclusions given these considerations and the inherent heterogeneity between different studies, rendering it difficult to conduct causal effect analyses based on these prior studies. Additionally, conventional studies often have limitations with respect to the number of variables that can be observed. Consequently, investigations into the causal effects of all members of the IGF family on the risk of AF are limited.

To mitigate the influences of reverse causality and potential confounding factors from environmental and social sources, the current study used a Mendelian randomization (MR) methodology. The approach relies on genetic variants strongly and exclusively associated with the phenomenon of interest, so-called instrumental variables, to establish causal associations. Two-sample MR analysis was conducted to investigate genetic relationships between IGF family members and AF. The aim was to determine whether IGF family members could be considered contributors to AF.

MATERIALS AND METHODS

Study design

This study was design to assess the causal effects of IGF family members in the risk of AF. The related traits of IGF family members had been identified, and fourteen IGF family members traits included: IGF1, IGF1-sR, IGF-IIR, IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5, IGFBP6, IGFBP7, IGF-LR1, CTGF, WISP1 and CYR61. Besides, three traits had been retrived for genetic association of AF, including ebi-a-GCST006414, UKB-b-536, and finn-b-I9_AF. First, the effects of fourteen IGF family members and their serum concentration were evaluated to identify the potential single nucleotide polymorphisms (SNPs) as one sample MR analysis. Then two-sample MR analysis had been completed among AF traits to measure the causa effects of IGF family members in AF pathogensis in the largest sample size trait (ebi-a-GCST006414). Then, further confirmation had been performed among three AF traits to validate the results. After that, the reverse MR analysis to rule out the bias in analysis to evaluate the causal effects of AFs in regulating the expression of circulating IGF family members' proteins. And there was no existed protocol.

Genome-wide association studies summary data of AF and IGF family

We acquired the genome-wide association studies (GWAS) summary data for AF from a comprehensive combination of sources, including the Nord-Trøndelag Health Study, the deCODE cohort, the MGI cohort, the DiscovEHR collaboration cohort, the AFGen Consortium, and the United Kingdom Biobank resource[15]. This dataset encompassed a total of 60620 AF cases and 970216 control participants. The identification of atrial fibrillation events within the summary dataset was based on diagnostic codes, self-reports, operation codes, or causes of death. Additionally, we utilized GWAS summary datasets from the FinnGen Biobank and the UK Biobank as duplications.

To identify SNPs associated with IGF family members, we extracted and selected data from the latest and largest genome-wide association studies (GWAS) available in the UK Biobank resource, the KORA cohorts[16], and the INTERVAL study[17]. These genetic associations were adjusted for age, sex, and body mass index. All the GWAS datasets we selected are presented in Table 1.

Genetic correlation analysis

We utilized LDSC (v1.0.1, https://github.com/bulik/Ldsc) software to assess the genetic correlations between AF and each member of the IGF family. LDSC is a robust approach for conducting genetic correlation analyses of complex diseases or traits. It allows for the discrimination between true polygenetic effects and potential mixed biases, encompassing implicit associations and demographic stratification. When a genetic association demonstrates both statistical and quantitative significance, it provides confirmation that the overall phenotypic association is not solely attributable to environmental confounding factors. In this study, we examined the linkage disequilibrium (LD) between AF and each IGF family member, employing the European 1000 G reference panel as the reference dataset. To establish statistical significance, we applied a stringent Bonferroni correction, setting the significant association threshold at $P > 0.00357$ (0.05/14). P values falling within the range of 0.00357 to 0.05 were considered suggestive of significance[18].

Mendelian randomization analysis

In the present study, we employed MR analysis to assess the potential causal relationship between each member of the IGF family and AF. We conducted the analysis using the inverse variance weighted (IVW) method and initially identified significant IGF family members through ldSC analysis, which were subsequently included in further analyses. For each IGF family member, we selected SNPs strongly predictive of exposure at the genome-wide significance level ($P < 5 \times 10^{-8}$). To minimize potential pleiotropy, we excluded SNPs associated with multiple cytokines. Additionally, we retained SNPs

Table 1 All genome-wide association study datasets selected in this article

Trait	GWAS id	Sample size	Number of SNPs
Atrial Fibrillation	ebi-a-GCST006414	1030836	33519037
Atrial Fibrillation	ukb-b-536	337199	10894596
Atrial Fibrillation	finn-b-I9_AF	-	16379794
IGF-1	prot-c-2952_75_2	-	501428
IGF-I sR	prot-c-4232_19_2	-	501428
IGF-IIR	prot-c-3676_15_3	-	501428
IGFBP-1	prot-c-2771_35_2	-	501428
IGFBP-2	prot-c-2570_72_5	-	501428
IGFBP-3	prot-c-2571_12_3	-	501428
IGFBP-4	prot-c-2950_57_2	-	501428
IGFBP-5	prot-c-2685_21_2	-	501428
IGFBP-6	prot-c-2686_67_2	-	501428
IGFBP-7	prot-c-3320_49_2	-	501428
IGF-LR1	prot-a-1455	3301	10534735
CTGF	prot-c-2975_19_2	-	501428
WISP-1	prot-c-3057_55_1	-	501428
CYR61	prot-a-758	3301	10534735

GWAS: Genome-wide association study; SNPs: Single nucleotide polymorphisms.

with low linkage disequilibrium ($r^2 < 0.1$) to avoid the confounding effects of correlated SNPs. However, it should be noted that despite these efforts, none of the SNPs associated with IGF family members showed significant associations with AF in the harmonized GWAS datasets. Consequently, we adopted a more stringent cutoff ($P < 1 \times 10^{-5}$) to select SNPs predicting IGF family members. We reported the number of included SNPs, along with effect estimates, confidence intervals, and *P* values.

MR estimates were derived using the IVW method and the MR-Egger method, both implemented under a random-effects model. To assess the robustness of our IVW results, we conducted tests for heterogeneity, multiple validity tests, and sensitivity analyses using weighted median estimation and MR–Egger regression. The TwoSampleMR packages[19] (version 0.5.6) in R (version 4.0.4) were utilized for performing the MR analysis. The statistical significance level was set at $P < 0.05$.

RESULTS

Causal effects of serum IGF family member concentrations on the risk of AF

Fourteen molecules were included in the first one-sample MR to identify SNPs potentially influencing their serum concentrations; IGF1 (prot-c-2952_75_2), IGF1-sR (prot-c-4232_19_2), IGF2R (prot-c-3676_15_3), IGFBP1 (prot-c-2771_35_2), IGFBP2 (prot-c-2570_72_5), IGFBP3 (prot-c-2571_12_3), IGFBP4 (prot-c-2950_57_2), IGFBP5 (prot-c-2685_21_2), IGFBP6 (prot-c-2686_67_2), IGFBP7 (prot-c-3320_49_2), IGF-LR1 (prot-a-1455), CTGF (prot-c-2975_19_2), WISP1 (prot-c-3057_55_1), and CYR61 (prot-a-758). Of the 14 IGF family members with serum concentrations reported in published studies, 13 were associated with more than one genomewide significant SNP site. Detailed information after clumping of LD-independent SNPs as exposure are presented in Supplementary material. All F-statistics were above 10, indicating that the results were less likely to be affected by weak instrument bias.

In the first one-step MR analysis the MR-Egger method and the IVW method were used. More than one significant SNP was identified at the genome-wide level ($P < 0.001$), and these SNPs were used to calculate causal associations with AF. In pooled data analysis three molecules were associated with AF. Lower levels of circulating IGF1 were negatively associated with AF onset [odds ratio (OR) 0.918, 95% confidence interval (CI) 0.849–0.993, MR-Egger analysis]. IGFBP3 was negatively correlated with AF prevalence in both WM analysis (OR 0.964, 95%CI: 0.940–0.960, $P = 0.006$) and IVW analysis (OR 0.968, 95%CI: 0.947–0.987, $P = 0.001$). Higher serum IGF2R was positively correlated with AF pathogenesis in MR-Egger analysis (OR 1.045, 95%CI: 1.016–1.076, $P = 0.039$). Other IGF family members were not significantly associated with the risk of AF (Figure 1).

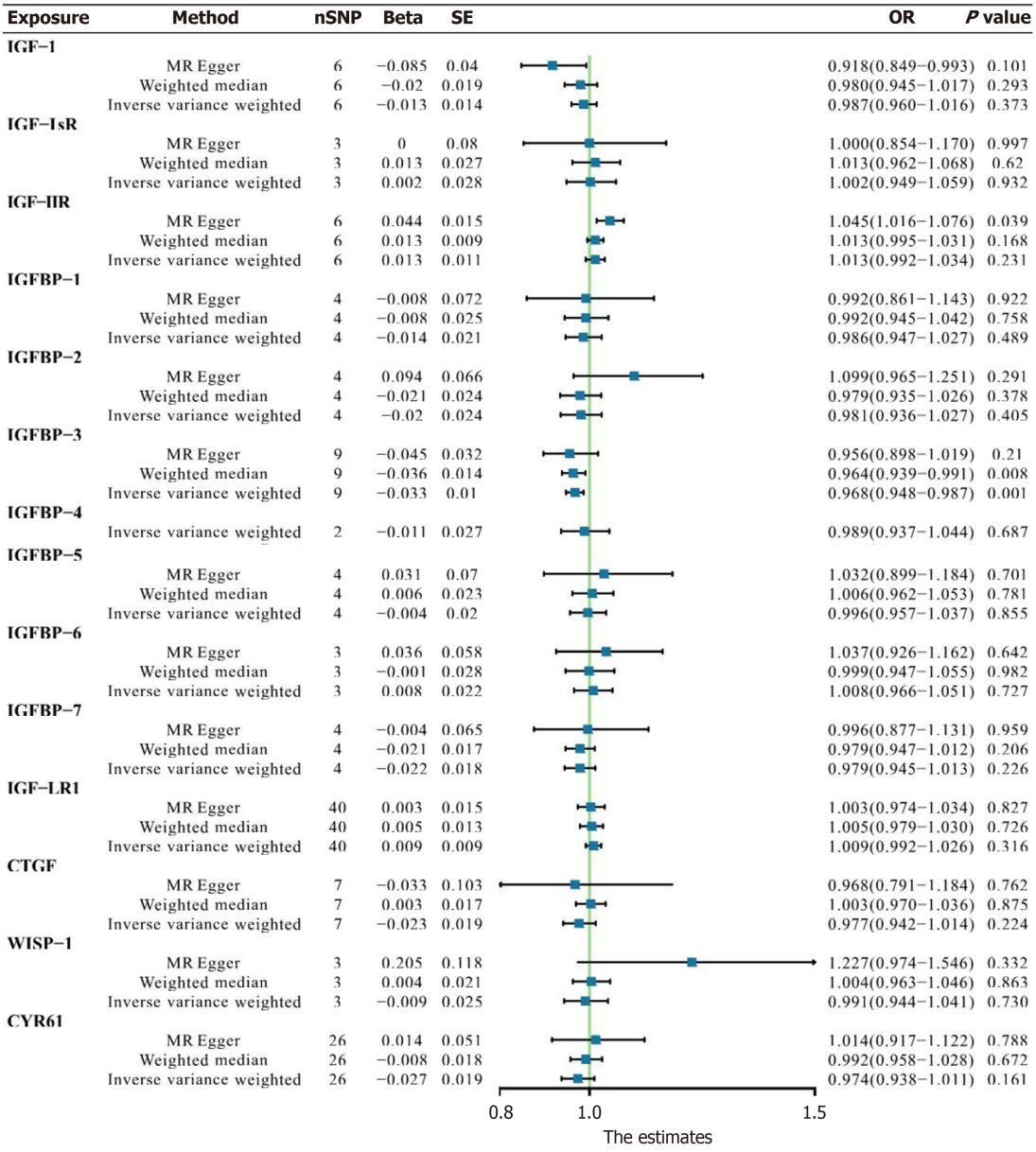

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Figure 1 Causal effect estimates of insulin-like growth factor family members on atrial fibrillation outcomes.

In IGF1 and IGF2R assessments, neither finn-b-19_AF (OR 0.873, 95%CI: 0.652–1.169, P = 0.414 and OR 0.976, 95%CI: 0.912–1.045, P = 0.528, respectively) nor ukb-b-964 (OR 0.994, 95%CI: 0.988–0.999, P = 0.154 and OR 1.000, 95%CI: 1.000–1.001, P = 0.167, respectively) yielded any significant results in MR-Egger or IVW analyses. The significant negative correlation between IGFBP3 and AF was confirmed in finn-b-19_AF trait analysis (OR 0.950, 95%CI: 0.907–0.955, P = 0.029), indicating that lower serum IGFBP3 contributes to AF (Figure 2).

Evaluation of causal effects of IGF family member expression on AF

Analyses were conducted to identify causal associations between serum IGF family member levels and AF. There was no convincing evidence of genetic associations between IGF family member expression and AF. In basic IVW analysis based on the ebi-a-GCST006414 trait, CYR61 was significantly positively correlated with AF (OR 1.060, 95%CI: 1.005–1.119, P = 0.031, Figure 3). In a more detailed validation test however, CYR61 was not positively correlated with finnb19_AF or ukb-b-964 traits as determined *via* any analysis methods (Figure 4).

DISCUSSION

In this study two-sample MR analyses using multiple GWAS datasets was conducted to assess relationships between individual IGF family members and AF. Results indicated that genetically determined lower levels of IGF1 and IGFBP3, as well as genetically determined higher levels of IGF2R, contribute to increased risk of AF. The presence of AF was

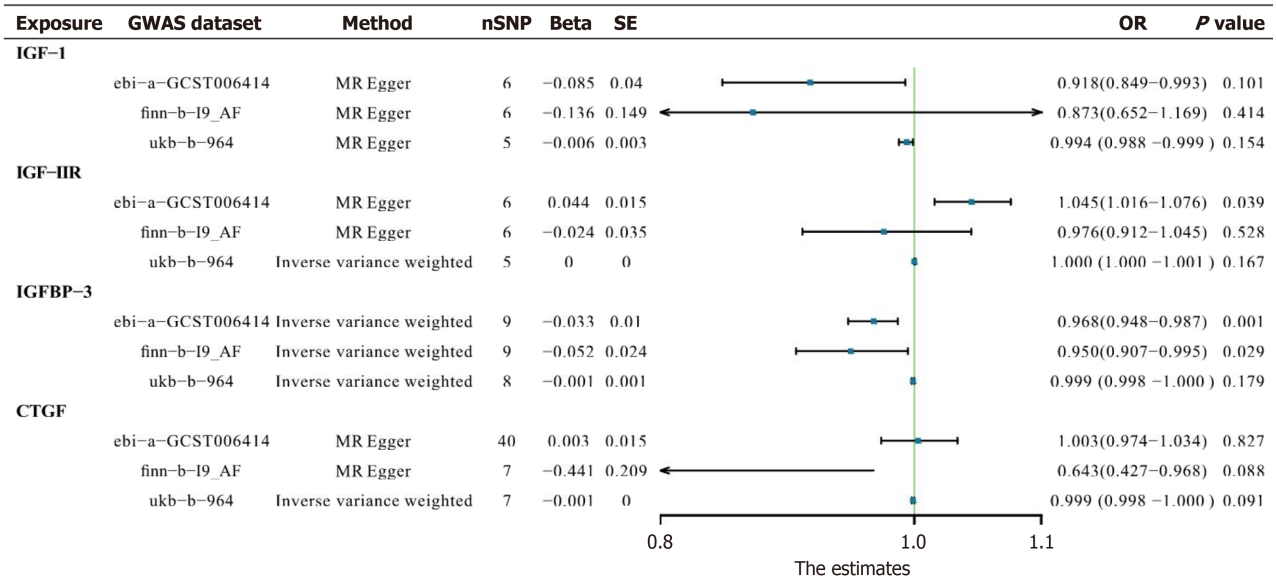

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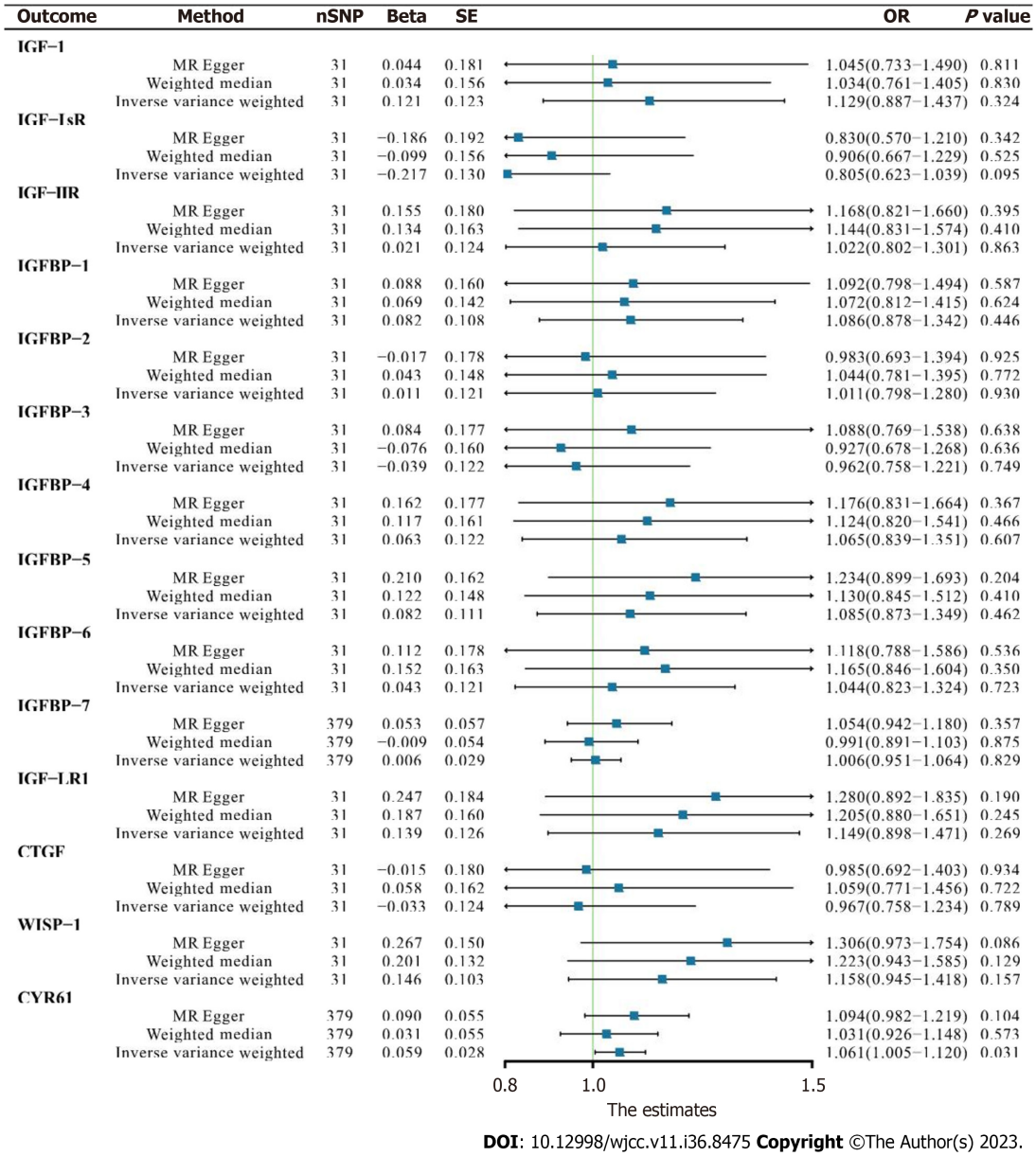
Figure 2 Detected associations between genetically predicted insulin-like growth factor family members and risk of atrial fibrillation in different genome-wide association study datasets.

genetically associated with elevated CYR61 levels. To the best of our knowledge the current study is the first comprehensive MR analysis systematically investigating associations between multiple IGF family members and AF.

In the present study a genetically determined decrease in circulating IGF1 was associated with an increased incidence of AF, a finding consistent with previously published MR analyses[20] and observational trials[10,21]. IGF1, a 70-amino acid peptide, is primarily synthesized in the liver and regulated by hypothalamic growth hormone-releasing hormone and pituitary growth hormone[22]. Notably IGFBP3—the most abundant binding partner of IGF1—was significantly positively associated with AF. Numerous studies have identified effects of IGF1 on the cardiovascular system, linking abnormalities in IGF1 levels to elevated risks of cardiovascular diseases, including atherosclerosis, hypertension, and coronary artery disease. Furthermore, IGF1 levels are age-dependent, peaking during puberty and declining throughout the remainder of life. IGFBP3, like IGF1, exhibits growth hormone-dependent regulation. Recent *in vivo* studies indicate that fetal growth restriction in mice leads to IGF1 deficiency and an increased risk of adult cardiovascular diseases. Moreover, intrauterine administration of additional IGF1 can mitigate the risk of adult cardiovascular diseases in a mouse fetal growth restriction model[23]. These effects are reportedly mediated by a deficiency in the mTORC1 pathway[24], a downstream component of the IGF1 pathway[25]. Studies in elderly populations have revealed significantly lower mean serum levels of IGF1 (P = 0.02) and IGFBP3 (P = 0.03) in AF patients than in non-AF participants[21]. A population-based study yielded similar results, further suggesting that low IGF1/IGFBP3 ratios are associated with a higher prevalence of AF[10]. Therefore our findings align with previous research suggesting that insufficient levels of IGF1 and IGFBP3 throughout life, particularly during periods of higher circulating IGF1 and growth hormone, significantly contribute to the onset of AF. These biomarkers hold potential for the prevention of AF.

In addition to IGF1 and IGFBP3, in the current study elevated levels of IGF2R were associated with AF. IGF2R, also known as the cation-independent mannose-6-phosphate receptor, comprises a substantial N-terminal extracellular region, a single membrane-spanning region, and a small cytoplasmic tail. Its primary role is to regulate circulating and tissue levels of IGF2 by targeting it for lysosomal degradation, thereby modulating IGF2 activity[26]. Both IGF2 and IGF2R have been implicated in placental and fetal growth and development. SNPs within IGF2R have been linked to increased risks of growth abnormalities, reduced growth rates during the first 3 years of life, and certain cancers[27-29]. Recent research suggests that an unfavorable intrauterine environment can induce epigenetic changes in the IGF2/H19 and IGF2R genes, subsequently altering the expression of IGF2 and IGF2R[30,31]. In animal studies fetal myocardial levels of IGF2 and IGF2R increased in response to reduced placental substrate supply in lambs[32]. In mice inactivation of the maternal IGF2R allele resulted in excessive growth and perinatal lethality, a phenotype that could be rescued with an IGF2 null allele[33]. Notably, protein abundance was inversely associated with relative left ventricle weight in models with reduced placental function, whereas it exhibited a positive correlation in the control group. This suggests that the IGF2R signaling pathway may be pathologically activated, leading to ventricular hypertrophy[32].

Previous reports have discussed the potential benefits of suppressing the IGF2R signaling pathway, such as protecting against myocardial cell apoptosis and preventing the progression of heart failure[34]. The present study provides the first indication of a potential correlation between IGF2R and AF, underscoring the potential for fetal pathological effects on the occurrence of adult cardiovascular diseases, including AF. Notably however, our literature review did not identify any observational studies investigating relationships between IGF2R and AF. Further research is therefore warranted, to investigate IGF2R as a potential biomarker of AF, and to deepen our understanding of its role in AF pathogenesis.

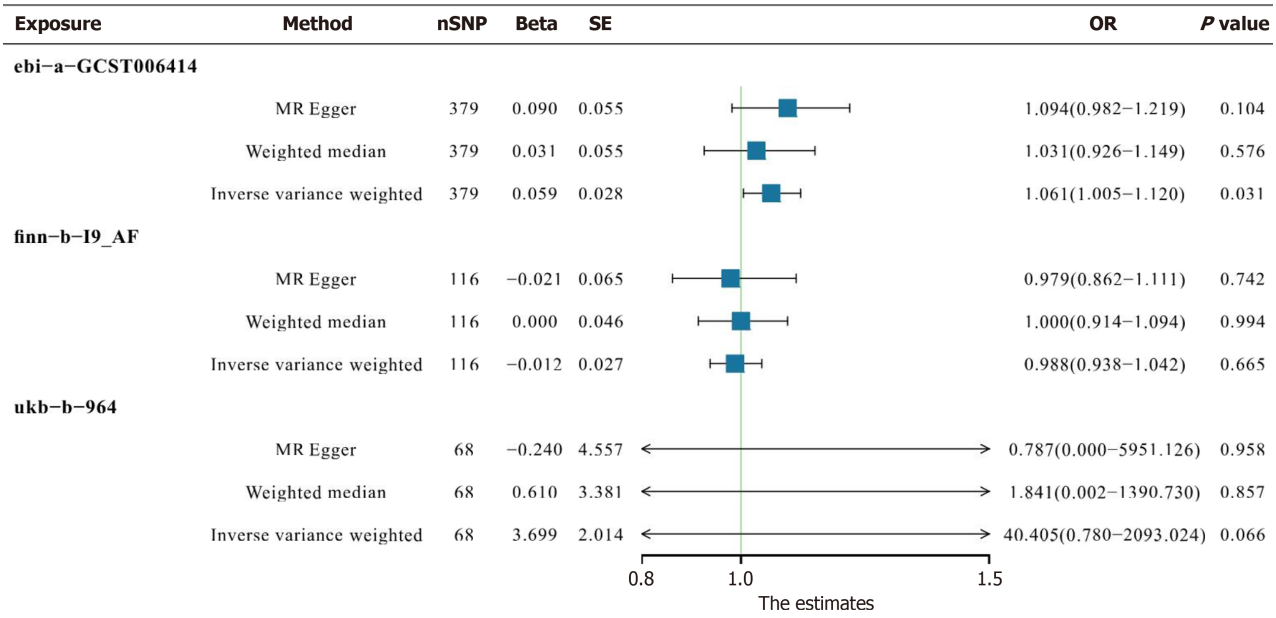


DOI: 10.12998/wjcc.v11.i36.8475

Figure 3 Causal effect estimates of atrial fibrillation on insulin-like growth factor family members outcomes.

In the present study there was a correlation between AF and alterations in CYR61 Levels in circulation. CYR61, also known as cellular communication network factor 1 (CCN1), belongs to the CCN family of matricellular proteins and plays pivotal roles in angiogenesis, inflammation, and the repair of fibrotic tissue[35-37]. Observational studies have consistently indicated significant increases in CYR61 within atherosclerotic lesions rich in vascular smooth muscle cells. Such studies have also identified CYR61 increases in the cardiomyocytes of individuals with ischemic cardiomyopathy, and STelevation in myocardial infarction patients[38-40]. Furthermore, the addition of CYR61 to the reference GRACE risk score led to improved risk stratification for all-cause mortality, surpassing the predictive capacity of high-sensitivity troponin T in subsequent analyses[40]. In the current study a preliminary CYR61-related result suggested that AF may induce increased CYR61 expression, but more detailed investigations did not confirm this. Thus a causal association between AF and CYR61 was not convincingly demonstrated. Notably however, levels of circulating CYR61 may assist the functional assessment of cardiovascular diseases.

The present study investigated associations between fourteen IGF family members and AF, and identified potential relationships with respect to three of them. Bidirectional analysis indicated that AF may influence CYR61. The use of MR analysis and large European GWAS datasets in the study conferred a substantial advantage with respect to reduced susceptibility to inverse causality, confounding, and biases inherent in the use of small sample sizes. The study also had some limitations. Primarily, the use of a higher significance threshold ($P < 1 \times 10^{-5}$) for SNP selection from GWAS datasets on IGF family members was necessitated by the limited number of IGF family members that yielded at least one genome-wide significant SNP when using the conventional threshold of $P < 5 \times 10^{-8}$. Thirteen IGF family members exhibited multiple genome-wide significant SNPs under the $P < 1 \times 10^{-5}$ threshold. A combined GWAS dataset was used for AF and atrial flutter, precluding distinction between these two arrhythmia subtypes. Due to unavailability of relevant datasets for



DOI: 10.12998/wjcc.v11.i36.8475

Figure 4 Associations between genetically predicted CYR61* and risk of atrial fibrillation in different genome-wide association study datasets. *CYR61: Cysteine rich angiogenic inducer 61; AF: Atrial fibrillation.

each specific AF subtype, the study focused solely on associations between IGF family members and AF onset. We were unable to stratify our results based on different AF phenotypes. Given the multifaceted nature of AF pathogenesis, ascertaining the precise roles played by the identified IGF family members in AF pathogenesis remains elusive. The results of the current study emphasize the urgent need for further observational and experimental studies.

CONCLUSION

Based on GWAS summary datasets derived from AF and circulating IGF family members, we identified causal relationships between three IGF family members and AF *via* MR analysis. IGFBP3 was negatively correlated with AF prevalence in both WM analysis and IVW analysis. The study results provide novel insights into AF pathogenesis and the implications of serum IGF family member concentrations with respect to AF risk. Further observational and experimental studies are critically required.

ARTICLE HIGHLIGHTS

Research background

The etiology of atrial fibrillation is still unknown, and insulin-like growth factor had been suspected to be involved in atrial fibrillation.

Research motivation

The relationship between insulin-like growth factor and atrial fibrillation had not be well addressed.

Research objectives

This study was carried out to evaluate the causal effect of serum insulin-like growth factor family concentration on risk of atrial fibrillation.

Research methods

Mendelian Randomization analysis was performed based on genome-wide association study datasets of insulin-like growth factor family concentration and atrial fibrillation.

Research results

Lower levels of circulating insulin-like growth factor binding protein 3 was associated with atrial fibrillation.

Research conclusions

The study generated evidence on the potential roles of developmental pathological effects in the pathogenesis of atrial fibrillation.

Research perspectives

Further observational and experimental studies are critically needed.

FOOTNOTES

Co-corresponding authors: Yi-Fei Li and Gang Wu.

Author contributions: Lin S, Tang J and Li X collected the data; Lin S performed the MR analysis; Wu G, Lin YF and Li YF conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content; Wu G, Lin YF and Li YF were responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: China

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

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World Journal of Clinical Cases

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World J Clin Cases 2023 December 26; 11(36): 8486-8497

DOI: 10.12998/wjcc.v11.i36.8486

ISSN 2307-8960 (online)

SYSTEMATIC REVIEWS

Significance of fostering the mental health of patients with diabetes through critical time intervention

Chiedu Eseadi, Amos Nnaemeka Amedu, Henry Egi Aloh

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): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Qureshi W, India; Setiawati Y, Indonesia

Received: October 18, 2023
Peer-review started: October 18, 2023
First decision: November 2, 2023
Revised: November 23, 2023
Accepted: December 12, 2023
Article in press: December 12, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Critical time intervention (CTI) is an evidence-based model of practice that is time-limited and aims to provide support for most susceptible individuals during a transition period.

AIM

To examine the significance of fostering the mental health of diabetes patients through CTI using the scoping review methodology.

METHODS

As part of the scoping review process, we followed the guidelines established by the Joanna Briggs Institute. The search databases were Google Scholar, PubMed, Scopus, PsycINFO, Reference Citation Analysis (https://www.referencecitation-analysis.com/), and Cochrane Library. From these databases, 77 articles were retrieved with the aid of carefully selected search terms. However, 19 studies were selected after two reviewers appraised the full texts to ensure that they are all eligible for inclusion, while 54 papers were excluded.

RESULTS

This study revealed that diabetic patients who had experienced homelessness were at higher risk of being diagnosed with mental illness and that social support services are impactful in the management of the comorbidity of diabetes and mental health problems. In addition, this review reveals that CTI is impactful in enhancing the mental health of homeless patients during the transitional period from the hospital through social support services.

CONCLUSION

CTI is a promising intervention for alleviating mental health symptoms in homeless patients. Empirical studies are needed across the globe, involving both hospitalized and community-based patients, to determine how clinically effectively CTI is in managing the mental health of diabetics.

Key Words: Comorbidity; Critical time intervention; Diabetes; Homeless patients; Mental illness

Core Tip: Evidence suggests that diabetic patients who have experienced homelessness are at higher risk of being diagnosed with mental illness, and that social support services are impactful in the management of the comorbidity of diabetes and mental health problems. Studies on the effectiveness of critical time intervention (CTI) among patients with diabetes are limited. Available studies have shown that CTI is a promising intervention for alleviating mental health symptoms in homeless patients.

Citation: Eseadi C, Amedu AN, Aloh HE. Significance of fostering the mental health of patients with diabetes through critical time intervention. *World J Clin Cases* 2023; 11(36): 8486-8497
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8486.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8486

INTRODUCTION

Diabetes can cause other health problems and complications, both physically and psychologically. Diabetes is a chronic disorder of metabolism that has become a major health concern worldwide. It is characterized by absolute deficits in insulin secretion; chronic hyperglycemia; and abnormal carbohydrate, lipid, and protein metabolism[1]. Glucose levels in the blood are elevated in people with diabetes[2]. In the literature, diabetes has been classified into four types: Type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes (GD), and other diabetes associated with certain specific conditions such as pathologies or disorder[3,4]. TID is insulin-dependent diabetes, which constitutes 5%-10% of all diabetic cases. T1D is an autoimmune disorder distinguished by T cell-mediated degeneration of pancreatic β cells, ultimately resulting in insulin depletion and hyperglycemia[5]. The pathogenesis of T1D is influenced by both genetic and environmental factors, and the pancreatic β cell-specific autoimmunity development rate is rapid in infants and children. T2D is non-insulin-dependent diabetes that constitutes about 90%–95% of diabetes cases. The characteristics of T2D are abnormalities in insulin secretion, β cell dysfunction, and insulin resistance[6]. T2D is often undiagnosed because it progresses very slowly asymptomatically over the years until the appearance of classic symptoms connected with severe hyperglycemia such as weight loss, growth impairment, polyuria, and polydipsia at the advanced stage. The pathogenesis of T2D is complex and involves multiple unknown and known features such as a combination of genetic predisposition and strong environmental influences. T2D is prevalent in older adults and is linked to obesity, inactivity, adoption of modern lifestyles, and a family history of diabetes[3]. GD is a type of diabetes linked to pregnancy, which is diagnosed between the second and third trimesters excluding undetected T2D. GD is characterized by an increase in blood glucose levels in the third trimester of pregnancy. Ninety percent of diabetes and its complications in such a period are attributed to GD, with a prevalence varying from 1% to 14%[7]. The risk of GD is linked to older age, previous pregnancy with a large baby, obesity, and a history of impaired glucose tolerance and is associated with a high lifetime risk of developing T2D[3]. Other types of diabetes associated with peculiar conditions such as pathologies or many disorders are those stemming from monogenic defects in β cell function, genetic abnormalities in insulin action, and exocrine pancreatic pathologies, among other conditions[8].

Diabetic patients may feel insecure in terms of their mental health. As a result, they monitor their blood glucose excessively, worry about complications, and constantly monitor their personal and work lives. When diabetes and mental illness coexist, the prognosis is often poor[9]. Complex interventions are often required for chronic and comorbid illnesses. Medications are in most cases less effective at treating all facets of diabetes and mental illness together[10]. As a chronic disease, it can impair daily function and mobility, which are more prevalent in homeless people than in homeowners[11]. Having diabetes can be physically and emotionally difficult, both for those with the disease and their families. As a result, people living with it must manage the disease continuously.

There are a number of mental health issues, such as anxiety and depression, which can affect diabetic patients. Diabetes has been linked to mental health complications such as psychotic disorders and complications distinctive to diabetic patients[12]. A number of terms were also utilized to describe the mental health problems connected with diabetes. For example, “diabetes distress” describes the negative emotions experienced by people with diabetes, as well as the burden of managing it, which explains the feelings of despair and emotional turmoil that are specifically related to diabetes, particularly the need for continued monitoring and care, ongoing concerns regarding complications, and the potential for professional and personal relationships to be eroded[13]. A condition known as psychological insulin resistance is characterized by an unwillingness to accept insulin therapy, leading to a delay in starting treatment[14]. Knowledge of the relationship between diabetes and mental health is crucial in that psychiatric and diabetes-specific psychosocial problems

are associated with diminished participation in self-management activities that can decrease the quality of life and care for victims and their families. Complications related to diabetes and mortality in the early stages are associated with psychiatric disorders in diabetic patients[15]. In addition to depression, anxiety, and eating disorders, individuals with T1D or T2D are at increased risk of these conditions[16]. For example, depression rates across the lifespan are twice as high for diabetics as for the general population. It was predicted that diabetic patients have poorer mental health generally, and in a variety of mental health dimensions in particular[17]. In addition, studies in the past have shown that diabetes is linked to severe depressive disorder, anxiety, bipolar disorder[18], schizophrenia[19], personality disorders[20, 21], stress, trauma, abuse and neglect[22,23], and sleep issues[23]. To reduce the morbidity and mortality associated with diabetes and mental health conditions, non-pharmacological interventions such as critical time intervention (CTI) can be used.

CTI is an intervention program that is time-limited and designed to decrease the adverse effects associated with homelessness and other risky outcomes by providing assistance to individuals in their critical transitional time[24-26]. CTI is characterized by concentrated case management that lasts for 6 to 9 mo and is geared towards assisting mental health patients navigate the severe service system and create contact with long-term community-based links, resources, and interventions[26]. CTI may benefit adults with diabetes and mental health challenges. As a result, comorbid diabetes and mental health conditions make maintaining lifestyle changes more difficult. As a result, this group has more difficulty recognizing and discussing their health concerns, and engaging with services to manage their health[27]. Homelessness and inadequate care may also be challenges they face. Although CTI has received a lot of attention as a way of managing mental health conditions, little is known about its effectiveness in managing and treating coexistent diabetes and mental health conditions. CTI is an evidence-based practice designed to mobilize support for society's most disadvantaged individuals in times of transition[28]. This promotes greater integration into the community and ensures a continuous flow of care by allowing people to remain connected to their communities and social support networks during these difficult times. CTI is also a type of time-limited, intensive case management model of treatment, which helps maintain continuity of care for service users while they are in transition such as from a shelter to a private residence after discharge[25]. As a result of this intervention, a person's network of support within the community is strengthened [29].

In addition to reducing the risk of homelessness after institutional discharge, CTI strives to enhance the quality of life for individuals and families. It also provides time-limited direct support in terms of emotional and practical assistance during the period of transition by reinforcing the consumer's long-term ties to formal services, family, and friends[28]. Among the key features of CTI is the provision of post-discharge assistance by workers who have maintained close contact with clients before discharge[30]. Aside from providing emotional and practical assistance during critical transition periods, CTI also offers case management services to enhance the relationship between an individual and their family, friends, and services[31]. There are three stages of CTI[25]: (1) Providing direct assistance to the client and assessing the resources available to support the client; (2) evaluating and adjusting the support systems as necessary; and (3) ensuring that existing community resources are transferred to the client. A variety of groups have benefited from CTI, including veterans, individual with psychiatric disorders, those who have been incarcerated, and people with diabetes. After being discharged from hospitals, shelters, prisons, and other institutions, individuals with mental illness may become homeless. The foundation of CTI rests on elements found in other evidence-based models such as small caseloads, active community outreach, individual case management plans, psychosocial skill building, and motivational coaching are key elements[32-34].

Notwithstanding the substantial role of CTI in the management of mental health problems in patients with other health problems, there is a lacuna with respect to documented empirical evidence of the effectiveness of CTI in enhancing the mental health of diabetic patients. Therefore, conducting a scoping literature review to establish the scope and depth of empirical research on the effectiveness of CTI in improving the mental health of patients with diabetes is necessary due to the prevalence of diabetes worldwide. Taking this study into account, public health practitioners will be able to determine the extent of CTI's effectiveness in improving the mental wellbeing of diabetics. Furthermore, psychologists or therapists will find this study useful since it will expose the existing gaps regarding CTI in treating the mental health of diabetic patients.

Therefore, the major aim of this study was to establish the current significance of fostering the mental health of patients with diabetes through CTI by conducting a scoping review of the available empirical studies.

Research questions

The following questions were addressed by this review:

What are the mental health challenges associated with homeless diabetic patients?

What is the impact of CTI in enhancing the mental health of homeless individuals during the time of transition?

MATERIALS AND METHODS

Study design

Based on a scoping review of existing research studies, the current study examined the significance of fostering the mental health of diabetic patients through CTI. Due to the fact that the study relied on empirical literature analysis, no ethics approval was necessary. Scoping reviews are a valuable tool for mapping the research process on a specific topic.

Protocol development

A protocol defining the methods and defining the inclusion and exclusion criteria was developed in advance. In this review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[34].

Data sources and guidelines

The literature was searched extensively using medical and scientific databases including Google Scholar, PubMed, Scopus, PsycINFO, Reference Citation Analysis (https://www.referencecitationanalysis.com/), and Cochrane Library. Boolean operators were applied to a specific set of keywords (*i.e.* "OR," "AND") during the literature search. Search queries were used across titles, abstracts, subject-specific keywords, and topic fields in databases. The key words used in the primary search stage were: "Diabetes mellitus" OR ''type I diabetes'' OR ''type II diabetes'' AND "Mental health" "psychosocial support," "psychological," "psychiatric," "anxiety," "depression," AND "critical time interventions" and other terms relevant to the current study (see Table 1).

Following the preliminary search, which ended on September 20, 2023, the researchers added additional search terms to the list based on the results of the first search. The reference lists of the articles included in the search were further reviewed.

Eligibility criteria

This scoping review included articles that met all of the following criteria: Studies that attempted to treat participants of any age with comorbid diabetes and mental health condition; primary studies using either a retrospective or prospective design or a quantitative and/or qualitative design including clinical trials; studies in any country across the globe; full-length studies that were published in journals as peer-reviewed articles; and studies conducted in any year. There were no restrictions on variables such as culture, stage of illness, occupational class, or education. The searches were limited to the English language as the time and cost of translation were not feasible within this review's timeline.

The exclusion criteria were: Studies that dealt only with the prevalence of mental health among diabetic patients; opinion papers, pre-conference abstracts, and review studies; non-English language articles; commentaries, editorials, or case studies on transition; and studies that treated diabetes without either a mental health construct or homelessness.

Study selection and data extraction

Screening: After the database search was completed, the results were exported into Zotero and duplicates were removed. To evaluate all retrieved citations, the authors used a cloud-based systematic review management portal (rayyan.ai). Next, titles were screened to exclude irrelevant publications, opinion papers, and reviews. Then all titles and abstracts of papers were screened by two reviewers using stipulated inclusion and exclusion criteria. To extract and synthesize data, all citations eligible for full-text review were examined using the same methodology. We kept articles with uncertain eligibility status for further review during the assessment process. Finally, the abstracts were read to determine whether the study's aim met the scoping review question.

Selection: The full-text articles were read to confirm each study's eligibility according to the inclusion and exclusion criteria. A third reviewer assisted the first two reviewers in resolving potential conflicts about eligibility through discussion after all articles selected after screening were independently reviewed. Data extraction was completed after discrepancies were resolved and papers meeting standards for inclusion were selected.

Data extraction process: In the extraction phase, the data were independently extracted from articles according to the theme, purposes, and questions of the present scoping review. Relevant information from all included papers were extracted using a pre-designed data extraction form that included items on study characteristics [*e.g.*, author and year of study, location, population and year of the study, study objective, type of mental health disorder, participants' characteristics (age of participants and sex among others), method and sample, intervention description and findings]. Two reviewers participated independently in the data extraction process, and a third author reviewed all of the extracted data to ensure consistency and accuracy. All reviewers participating in data extraction discussed discrepancies and reached a consensus.

Data synthesis

Using the collective body of evidence, this scoping review produced an evidence map and identified potential gaps. A summary of the major study variables, interventions, and all comorbidity health outcomes were provided by the authors. The findings were arranged and presented in tabular form to provide an overview of the existing studies.

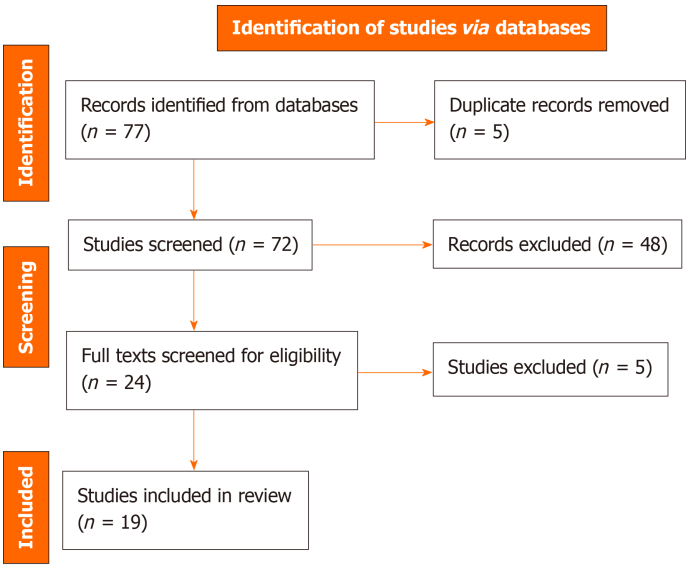
RESULTS

Selection of sources of evidence

A total of 77 articles related to the mental health of people with diabetes were found during the electronic search of the six databases. Following the removal of duplicates, 72 papers remained. Two independent researchers assessed papers based on stipulated criteria to exclude 48 papers in the first screening, which involved reading titles and abstracts. As a result, 24 papers were screened a second time by reading the full texts while still looking for the inclusion criteria, and three articles were finally selected for data extraction. After full-text assessment, more than five papers were excluded, as shown in Figure 1.

Table 1 Search strategy used in this scoping review

Search query	Search keywords applied on titles, abstracts, topics, and subject headings
1	"Diabetes mellitus" OR ''type I diabetes'' OR ''type II diabetes'' OR "diabetic patients" OR "people with diabetes" OR "diabetic conditions"
2	"Mental health" OR "psychosocial support" OR "psychological" OR "psychiatric" "anxiety," OR "depression," OR ''fear" OR ''phobia" OR "dental wellbeing" OR "dental well-being" OR "dental disorder" OR "oral health" OR "wellbeing" OR "mental disorder" OR "schizophrenia" OR "trauma"
3	"Critical time interventions" OR "case management interventions"
Final search query	1 AND 2 AND 3



DOI: 10.12998/wjcc.v11.i36.8486

Figure 1 Flow chart illustrating the screening and selection process of this scoping review.

An overview of the included studies is provided in Table 2. Findings from this scoping review revealed that the 19 articles[25,35-52] selected for data extraction were published between 2007 and 2022. The distribution of these studies reviewed across the globe showed that five studies were conducted in Canada, the United States, Japan, Britain, and the Netherlands. The study design included six survey studies, three qualitative, one retrospective evaluation, seven randomized controlled trial, and one mixed method. The minimum sample size of the included studies was five while the maximum was 6944. Of these 19 studies, 6 focused on mental health, 9 were on CTI, and 4 were on the management of diabetes among homeless individuals.

DISCUSSION

To foster the mental health of homeless diabetic patients, this study used the scoping review approach to reveal the mental health challenges of homeless diabetic patients and the impact of CTI in enhancing the mental health of homeless individuals during the time of transition. Regarding the mental health challenges associated with homeless diabetic patients, this study revealed that diabetic patients with a history of homelessness are more likely to be diagnosed with mental illness such as self-management disorder, low perception, depression, substance abuse, cognitive disability, psychotic disorder, and bipolar disorder. The comorbidity of diabetics and mental health problems of homeless patients are associated with higher hemoglobin A1c (HBA1c). However, taking medication with increased support and supervision in a shelter for patients with mental illness substantially reduces the HBA1c[46].

This review also found that social support services are impactful in the management of comorbidity of diabetes and mental health problems. Such social supports that enhances the mental health of diabetic patients are affordable house rent and rental assistance, which reduce diabetic patients' expenditure with respect to rent and increases their financial muscle to offset their diabetes-related expenses[47]. In addition, a study identified that provision of in-shelter care, peer outreach and support, diabetes specialty outreach clinics, diabetes group care specific for this population, and community-based pharmacy interventions are impactful in the management of the mental health of homeless diabetic patients[37,42]. Group medical visits to the shelter of homeless diabetic patients have been found to be impactful and

Table 2 Studies concerning the mental health challenges associated with homeless diabetic patients and impact of critical time intervention in enhancing mental health of homeless individuals during the time of transition

Authors	Location/population	Objectives	Mental health disorder/CTI/management of diabetes	Method/sample	Results
Lennox *et al* [25]	Britain, 14	CTI model was adapted to reflect the stages of transition for prisoners in England	CTI	Mixed method of qualitative and quasi-experimental	CTI intervention groups showed a lower level of anxiety regarding release and more support in terms of housing, access to services, and reintegration into the community as compared to previous imprisonment
Wiens *et al* [35]	Ontario, & Toronto, 6944	To create a population cohort of people with diabetes with a history of homelessness to understand their unique demographic and clinical characteristics and improve long-term health outcomes	Psychotic disorder, Bipolar disorder	Descriptive	Patients with a history of homelessness were more likely to be diagnosed with mental illness (49% *vs* 2%) and be admitted to a designated inpatient mental health bed (37% *vs* 1%). A suitable match was found for 5219 (75%) diabetic people with documented homelessness after the intervention. The derived matched cohort was balanced on important demographic and clinical characteristics
Davachi and Ferrari[36]	CDIRC in Canada, 524	To develop an accessible and effective diabetes management support for the homeless population especially those at risk or already diagnosed with diabetes	chronic disease self-management disorder	Survey study	There was a reduction in participants FBG and their HbA1c levels. Although the low numbers of follow-up data collected, the mean reductions in FBG of 4 mmol/L and HbA1c of 1.1% is significant for this population. Baseline results and results captured at the 3 to 12 mo follow-ups were only available for 10 patients with pre-existing diabetes
Thompson *et al*[37]	Canada, 52	Group medical visits, GMV in primary care for patients with diabetes and low socioeconomic status and low perception of life: users' perspectives and lessons for practitioners	Low perception of life	Qualitative research design	The GMV as a CTI promotes group identification and cohesion against the Diabetes mellitus disease process. The relationships made within the group were found to be supportive and therapeutic. It may also improve individuals' perception of diabetes management from problem solving, modelling, information and education, emotional support, accountability, and social competition
Campbell *et al*[38]	Canada, 28	To report the experiences of co-researchers with lived experience of homelessness and diabetes, giving voice to patients	Community-based participatory research approach	Qualitative	Many participants felt that the study provided them with intangible benefits, including feeling respected, valued, and heard; feeling accomplished and purposeful, resulting in improved self-efficacy in other areas; and building a sense of community with others who shared many of their life experiences
Campbell *et al*[39]	Canada, 96	The study documented the innovations in providing diabetes care for individuals experiencing homelessness	Management of diabetes	Survey	Among homeless individuals, this study identified five innovative and unique approaches to diabetes care. Among these approaches are the provision of in-shelter care, the provision of peer outreach, the provision of diabetes specialty outreach clinics, and the provision of diabetes group care specific to this population
Mayberry *et al*[40]	TN United States, 9	Explore acceptability of engaging family/friends in patients' T2D self-management using text messaging	Depressive symptoms	Qualitative	A majority of participants (48%) cited needing assistance and seeing the benefits of engaging others as reasons for inviting a support person, while reasons for not inviting one included being an unnecessary "burden" or being unable to text. As a result of the texts, support persons reported an increase in awareness, a creation of dialogue, and an improvement in their own health and behavior
Elder and Tubb[41]	United States, 15	Seeks to understand barriers and enablers to health for homeless people with diabetes as perceived by homeless persons and providers	Management of diabetes	Survey	Despite being regarded as peripheral to diabetes care, all social service providers considered their primary roles to be important

Kasprow and Rosenheck [42]	United States, 484	evaluate an effort to disseminate a program of CTI case management for homeless veterans with mental illness being discharged from veteran psychiatric inpatient units	CTI	Randomized controlled trial	A higher proportion of CTI clients spent more time at home and fewer days in institutional settings than those receiving typical VA services. Clients of CTI case management also reported a reduction in alcohol consumption, drug use, and psychiatric disorders
Clark *et al*[43]	United States, 230	examine two the CTI management for people with co-occurring disorders and histories of chronic homelessness and to better understand their roles in permanent supported housing	CTI	Descriptive	A significant decrease in alcohol consumption, drug use, and psychological symptoms was also observed in participants of the CTI program
Shinn *et al* [44]	United States, 200	compared effects of a FCTI to usual care for children in 200 newly homeless families in which mothers had diagnosable mental illness or substance problem	CTI	Randomized trial	In children 6-10 and in adolescents 11-16, referrals to FCTI resulted in fewer internalizing and externalizing problems, as well as self-reported school troubles
Tomita and Herman[45]	New York City, 150	Evaluated the impact of CTI in reducing rehospitalization among formerly homeless individuals with severe and persistent mental illness after discharge from inpatient psychiatric treatment	CTI	Randomized control trial	The study revealed that CTI is effective in lowering psychiatric rehospitalization and efficient in reducing the likelihood of recurrent of homelessness
Asgary *et al* [46]	New York City, 418	This study assesses diabetes control and rates and predictors of diabetes that is not well-managed among patients experiencing homelessness compared with those of domiciled patients who receive medical care at New York City's shelter-clinics	Mental illness, substance abuse	Retrospective evaluative of T2D measurement	Homeless patients were more likely to have inadequately managed diabetes than other patients. The average HBA1c of homeless individuals was greater than that of domiciled individuals. There was a significant association between diabetic patients with mental illness and a lower HBA1c, as a result of better living conditions in their shelters
Keene *et al* [47]	United States, 5	Examine transitions into rent-assisted housing as they relate to diabetes self-management behaviors	Management of diabetes	Survey	Participants were able to reduce financial stress and offset diabetes-related expenses as a result of affordable housing and rental assistance
Yamamoto *et al*[48]	Japan, 106	survey of the prevalence of diabetes and prediabetes among homeless men in Nagoya, Japan	Cognitive disability	Descriptive survey	Prevalence of prediabetes differed significantly between groups with and without a history of social support. The prevalence of prediabetes was lower in the group with social support than in others. Early intervention for preventing diabetes and social support focused on diabetes management is imperative for homeless people
Shaw *et al*[49]	Britain, 150	Establish effectiveness of CTI in improving engagement of prisoners with mental illness	CTI	Parallel group randomized controlled trial	Participants engaged more fully with CTI than their counterparts. However, the difference was not substantial. Furthermore, the intervention group demonstrated better continuity of care and improved access to services
Jarrett *et al* [50]	United Kingdom, 60	This study aimed to see whether a CTI in the 1st week's post-release effectively connects mentally ill prisoners with social, clinical, housing, and welfare services on leaving prison	CTI	Randomized Controlled	The CTI program significantly increased the number of prisoners receiving medication and being registered with their general practitioner
de Vet *et al* [51]	Dutch, 183	Examined the evidence base in Europe for effective interventions that improve the wellbeing of homeless people	CTI	Parallel-group randomized controlled trial	The CTI significantly enhanced the social support of individuals experiencing low levels of social support and psychological distress
Lako *et al*[52]	Europe, 136	To examine the effectiveness of CTI—an evidence-based intervention—for abused women transitioning from women's shelters to community living	CTI	A randomized controlled trial	There is evidence that CTI is effective in reducing post-traumatic stress symptoms and unmet care needs in a population of abused women

CDIRC: Calgary drop-in & rehab centre; CTI: Critical time intervention; FBG: Fasting blood glucose; FCTI: Family critical time intervention; GMV: Group medical visit; T2D: Type 2 diabetes; HBA1c: Hemoglobin A1c.

therapeutic[37]. This is attributed to its tendency to improve individual patient's perception of diabetes management, emotional support, accountability, and social competition. This means that medical visits give patients hope and make them feel a part of society. Therefore, social support services are an integral and impactful mechanism of managing the mental health of diabetic patients, as diabetes management with an enriched support system facilitates patient recovery from diabetes symptoms such as a reduction in fasting blood glucose and HbA1c levels.

This review reveals that CTI is impactful in enhancing the mental health of homeless patients during the transitional period from the hospital through social support and interventions to ensure that their needs are met and delivered in a timely manner as well as engagement of these homeless patients. However, the effectiveness of CTI has not been tested in homeless diabetic patients. This means that there is a lacuna in the use of CTI to enhance the mental health of patients with diabetes, especially homeless individuals transitioning from the hospital. However, the literature has shown that the effectiveness of CTI has been established in homeless individuals with mental health problems. A study revealed that CTI enhanced participants' engagement in continuity with care and improved access to service[49]. Access to service is one focus of CTI, especially for homeless patients during the transition process. CTI is a robust intervention for promoting social support in individuals experiencing psychological distress who have less social support[51]; it promotes the fulfillment of unmet needs and lessens the symptoms of post-traumatic stress symptoms among abused women[52]. Furthermore, CTI is also helpful in transitioning prisoners with mental illness because clients who receive CTI intervention are less anxious about their release and reportedly receive more support for housing, access to services, and community reintegration than their counterparts[25]. CTI also reportedly facilitates their access to medication[50], lowering psychiatric rehospitalization rates and preventing the recurrence of homelessness[45].

The reviewed studies revealed that CTI is impactful in managing individuals with a history of chronic homelessness and co-occurring disorders through a decrease in alcohol use, drugs, and psychiatric symptoms[35,46,47], possibly due to the fact that they are known to suffer from a higher frequency of diabetes-related adverse consequences. A number of factors contribute to this disparity including inadequate access to medical care, inability to pay for medications and supplies, dissatisfaction with healthcare providers, and conflicting priorities.

Moreover, one of the major contributors to the disparities in outcomes is likely related to the fact that diabetes treatments are often not tailored to the specific needs and circumstances of people who are homeless. According to the reviews, no studies have specifically examined the impact of CTI on the mental health of diabetic patients. This indicates that there is a gap in the literature concerning CTI for fostering diabetic patients' mental health. Therefore, more studies are needed to truly understand CTI's impact on the mental health of diabetic patients.

This review identified two key findings regarding CTI's effectiveness in managing the mental health of homeless patients. First, CTI improves housing outcomes and service engagement use outcomes for homeless people with diabetes-related ailments and their mental health conditions. Results like these coincide with CTI's focus of connecting individuals with community services and support to address critical transition needs. It is clear from these findings that the CTI model is practical and adaptable in that it can be successfully implemented in a variety of settings and populations[53]. This assertion was demonstrated in the study by Davachi and Ferrari[36], which used a survey research design to conduct a 12-mo intervention study to develop a diabetes management support program for homeless people, especially those at risk or already diagnosed with the disease. According to the study by Davachi and Ferrari[36], social service support, which is part of CTI, is effective for managing the mental health of people with pre-existing diabetes. A cohort study conducted by Wiens *et al*[35] between 2006 and 2019 in Ontario, Toronto in Canada further supports the above assertion. According to the study, 5219 diabetic people with documented homelessness (75%) found suitable matches. An important demographic and clinical characteristic of diabetic people was also balanced within a derived matched cohort. Second, CTI has been shown to be supportive and therapeutic in managing diabetic patients' mental health. This is substantiated by the studies of Shaw *et al*[49], de Vet *et al*[51], Kasprow and Rosenheck[42], and Shinn *et al*[44] whose findings proved that CTI is effective in enhancing the mental health of homeless individuals. CTI may improve individuals' perception of diabetes management through problem solving, modeling, information and education, emotional support, accountability, and social competition.

Implications of findings and recommendations

This study revealed that diabetic patients with a history of homelessness are more likely to be diagnosed with mental illness, and social support services are impactful for the management of comorbidity of diabetes and mental health problems. This indicates that the mental health disorder of homeless diabetic patients could be attributed to the adverse effects of their environment, which predispose them to substance abuse that increases their mental disorder. Therefore, an intervention such as CTI, which focuses on enhancing the mental health of homeless diabetic patients, is required to facilitate and manage their smooth transition and ensure that they have access to support services that facilitate their integration into society. This study supports existing research demonstrating that CTI is highly effective, supportive, and therapeutic for managing the mental health of patients, especially those who are homeless or have a history of homelessness. As a result, most homeless patients' mental health disorders are managed using either or both of these interventions and ultimately are successful in overcoming their challenges. Therefore, healthcare professionals are well positioned to identify homeless patients and work with them to reduce their individual barriers to diabetes care; however, organizations must ensure that patients are connected to the larger health care system and facilitate low barriers to accessing diabetes care. This review found limited evidence addressing how CTI achieves its positive effects. Exactly how CTI reduces the mental health conditions of diabetic patients with homelessness and other outcomes is unknown. Consequently, this lays the groundwork for future studies investigating CTI's impact on diabetic mental health. Further research is clearly needed to determine whether and how CTI's program components affect specific outcomes and to map these components onto specific mediators.

Limitations of the review

Due to the unavailability of studies that specifically dealt with the impact of CTI on homeless diabetic patients, this review revolved around the mental health challenges associated with homeless diabetic patients and the impact of CTI in enhancing the mental health of homeless individuals during the time of transition. Second, the included studies used a variety of populations and settings, resulting in a difficult comparison across them. Accordingly, we did not assess methodological quality or bias risk in accordance with the adhering guidelines. Furthermore, the study did not examine the cost of CTI or examine other kinds of case management interventions that could be used in treating diabetic patients' mental health, instead focusing solely on CTI. Therefore, future reviews should consider all kinds of case management interventions that may be used. Furthermore, we retrieved literature from leading databases to include peer-reviewed articles, while unpublished studies from unselected databases were not included. Last but not least, including only English-language articles may have resulted in a loss of evidence regarding the effectiveness of CTI for diabetic mental health.

CONCLUSION

This review has shown that homeless diabetic patients are frequently diagnosed with several mental health problems, which require an intervention program such as CTI for enhancing their mental health. The available literature reviewed for this research shows that there is no specific CTI study that focused on managing the mental health of diabetic patients. This indicates that it has not been given adequate attention by researchers. In light of this, more empirical studies should be conducted across the globe, using both participants in hospitals as well as community-based settings to determine the effectiveness of CTI in managing mental health of diabetic patients more effectively and clearly.

ARTICLE HIGHLIGHTS

Research background

Critical time intervention (CTI) is an evidence-based model of practice that is time-limited and aims to provide support for most susceptible individuals during a transition period.

Research motivation

Diabetes can cause other health problems and complications, both physically and psychologically. To reduce the morbidity and mortality associated with diabetes and mental health conditions, non-pharmacological interventions such as CTI can be used.

Research objectives

This research examined the significance of fostering the mental health of diabetes patients through CTI.

Research methods

This research employed the scoping review methodology and followed the guidelines established by the Joanna Briggs Institute. The search databases were Google Scholar, PubMed, Scopus, PsycINFO, Reference Citation Analysis (https://www.referencecitationanalysis.com/), and Cochrane Library.

Research results

Diabetic patients who had experienced homelessness are at higher risk of being diagnosed with mental illness, and social support services are impactful in the management of the comorbidity of diabetes and mental health problems. CTI is impactful in enhancing the mental health of homeless patients during the transitional period from the hospital through social support services.

Research conclusions

CTI is a promising intervention for alleviating mental health symptoms in homeless patients. Empirical studies are needed to determine how clinically effectively CTI is in managing the mental health of diabetics.

Research perspectives

It is crucial to facilitate and manage the smooth transition of homeless diabetic patients into society, as well as to ensure that they have access to supports services that facilitate their integration into society, by providing CTI that focus on enhancing their mental health.

FOOTNOTES

Author contributions: Eseadi C, Amedu AN, and Aloh HE conceived the research; conducted a review of the literature, literature

analysis, drafting, editing; All authors approved the final version of the manuscript.

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

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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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 December 26; 11(36): 8498-8506

DOI: 10.12998/wjcc.v11.i36.8498

ISSN 2307-8960 (online)

META-ANALYSIS

Impact of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on the mortality in sepsis: A meta-analysis

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Specialty type: Medicine, general and internal

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: Ghimire R, Nepal

Received: October 12, 2023
Peer-review started: October 12, 2023
First decision: November 28, 2023
Revised: November 29, 2023
Accepted: December 5, 2023
Article in press: December 5, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

The effect of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) on the mortality of patients with sepsis is not well characterized.

AIM

To elucidate the association between prior ACEI or ARB exposure and mortality in sepsis.

METHODS

The PubMed, EMBASE, Web of Science, and Cochrane Library databases were searched for all studies of premorbid ACEI or ARB use and sepsis mortality until November 30 2019. Two reviewers independently assessed, selected, and abstracted data from studies reporting ACEIs or ARBs, sepsis, and mortality. The primary extracted data consisted of premorbid ACEI or ARB exposure, mortality, and general patient data. Two reviewers independently assessed the risk of bias and quality of evidence.

RESULTS

A total of six studies comprising 281238 patients with sepsis, including 49799 cases with premorbid ACEI or ARB exposure were eligible for analysis. Premorbid ACEIs or ARBs exposure decreased the 30-d mortality in patients with sepsis. Moreover, the use of ACEIs or ARBs was associated with approximately a 6% decreased risk of 30-d mortality.

CONCLUSION

The results of this systematic review suggest that ACEI or ARB exposure prior to sepsis may be associated with reduced mortality. Further high-quality cohort studies and molecular mechanism experiments are required to confirm our results.

Key Words: Sepsis; Mortality; Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers

Core Tip: To explore the potential relationship between the effect of premorbid angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) on mortality in sepsis. We extracted data from 6 studies. The results of this systematic review suggest that ACEI or ARB exposure prior to sepsis may be associated with reduced mortality. This may have some guiding significance for the treatment of coronavirus disease 2019.

Citation: Yang DC, Xu J, Jian L, Yu Y. Impact of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on the mortality in sepsis: A meta-analysis. *World J Clin Cases* 2023; 11(36): 8498-8506
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8498.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8498

INTRODUCTION

Sepsis is a syndrome that involves physiological, pathological, and biochemical abnormalities resulting from a host response to an infection, and represents a major public health concern[1]. Sepsis is a "worldwide medical problem" that endangers human health and is associated with three main characteristics: (1) High incidence; (2) high mortality; and (3) high treatment cost. More than 19 million people suffer from sepsis every year worldwide, with a fatality rate greater than 25%[2].

As sepsis progresses after an infection, an imbalance of the pro-inflammatory and anti-inflammatory response develops[3]. The guidelines associated with development of the sepsis pathophysiology suggest: Early fluid resuscitation, antibiotic treatment, control of infection sources, use of vasoactive agents, corticosteroids, blood products, immunoglobulins, blood purification as treatment options[2]. Although the guidelines for the diagnosis and treatment of sepsis have been revised several times, the monitoring index does not fully reflect the overall situation and dynamic changes of the patients, treatment is associated with a lag period, and the mortality rate remains high[4]. Therefore, it is important to accurately identify potential patients who are at a high risk of sepsis and to take specific intervention measures to reduce the mortality of such patients. Such supplement to the previous treatment programs and may improve the prognosis of sepsis patients.

Several studies have suggested that the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) may represent a therapeutic option for patients with sepsis[5,6]. Moreover, ACEIs and ARBs have been shown to exert anti-inflammatory effects to attenuate the chronic inflammation[7]. However, the benefit of using ACE inhibitors or ARBs remains controversial[5,8]. Moreover, there are no published systematic reviews on the effects of premorbid ACEI or ARB exposure on sepsis mortality. Thus, this study sought to investigate sepsis mortality in patients with prior ACEI and ARB exposure.

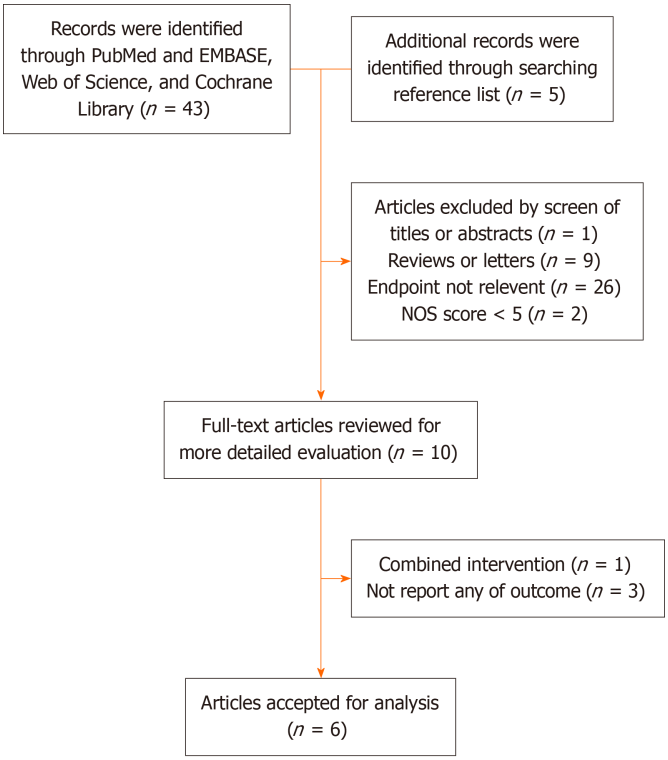
MATERIALS AND METHODS

Search strategy

This study followed the Meta-analysis Of Observational Studies in Epidemiology guidelines[9]. A literature search of relevant published studies that analyzed the association between the sepsis, mortality, and ACEIs or ABBs was conducted on 27 March 2020. We used the PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), EMBASE (http://www.embase.com/), Web of Science (http://wokinfo.com/), and Cochrane Library (http://www.thecochranelibrary.com/) databases to identify articles using the following terms: “hypotensor”; “antihypertensive”; “ACEIs”; “captopril”; “enalapril”; “sirapley”; “benazepril”; “petitopril”; “ramipril”; “ARBs”; “losartan”; “irbesartan”; “valsartan”; “telmisartan”; “sepsis”; “toxic shock”; “sepsis shock”; and “mortality”. In addition, the reference lists in each of the studies were reviewed to identify additional studies. The language of the studies was limited to English, and we did not search for unpublished literature.

Study selection criteria

A study was included in the analysis if: (1) It was a case-control or cohort study was conducted; (2) it was an original human clinical trial (independence among studies) that evaluated the association between premorbid ACEI or ARB exposure and sepsis mortality; and (3) it provided sufficient data [*e.g.*, to calculate the relative risk (RR), odds ratio (OR),



DOI: 10.12998/wjcc.v11.i36.8498

Figure 1 Search strategy and selection of studies for inclusion in the meta-analysis.

or hazard ratio (HR)]; and (4) the (Newcastle-Ottawa Scale, NOS) score value was ≥ 5. We excluded studies that contained overlapping data.

Data extraction

The data extracted from the selected articles included: the first author's name; year of publication; study population; total number of cases; RRs or ORs with 95% confidence intervals (CIs); Newcastle-Ottawa Scale (NOS); and adjustments made in the studies (Table 1). Some publications separate reported ORs for ACEI-related sepsis mortality and ARB-related sepsis mortality. In these cases, the ORs were separately extracted.

Statistical analysis

The strength of the association between premorbid ACEI or ARB exposure and susceptibility to sepsis mortality was reported using ORs and 95%CIs. ACEIs or ARBs were defined as captopril, enalapril, benazepril, fosinopril, ramipril, losartan, valsartan, and candesartan. When the data was adjusted and crude ORs were provided, the most adjusted ORs were extracted. If the article provided an HR, it was converted to an OR using the appropriate formula[10]. We used an I^2 test and *Q*-statistic to detect any possible heterogeneity between the studies, as a quantitative measure of any inconsistencies among the studies[11]. In addition, we clarified the percentage of the total variation across the studies that was due to heterogeneity rather than by chance using the I^2-statistic. Pooled ORs and 95%CIs were calculated using a random-effects model[12].

All statistical analyses for the meta-analysis were performed using STATA version 12.0 (United States, College Station, TX 77845). Statistical significance was established at a threshold of $P \leq 0.05$. All reported *P* values were obtained from two-sided statistical tests. *Egger's* and *Begger's* regression models were used to evaluate the potential publication bias[11].

RESULTS

The process used to select the studies for analysis is outlined in Figure 1. A total of 48 potentially relevant records were reviewed, of which six articles, which included 49799 cases that met the inclusion criteria were included in the meta-analysis[5,8,13-16] (Table 1). A total of 42 studies were subsequently excluded because they used a combined intervention, were duplicated reports, or were of relatively low quality. All of the six selected articles were cohort studies.

Three studies were conducted in Asia and three studies were conducted in other regions (Europe and America). Two studies presented the mortality separately for ACEIs and ARBs. The NOS was 7 and 6 in four and two studies, respectively (Table 2). The mortality data for both ACEIs and ARBs were individually extracted. The results from the six studies were inconsistent: two pool results reported that premorbid ACEI or ARB use was associated with a significant reduction in sepsis mortality, whereas the other four studies reported no association. The analysis of the six studies

Table 1 Characteristics of the studies included in the meta-analysis

Ref.	Population and country	No. of cases	Study type	Adjustment OR (95%CI)	Adjustment	NOS
Mortensen EM *et al*[15], 2007	3018; United States	547	Cohort	ARBs: 0.42 (0.24-0.76)	Age, history of myocardial infarction, heart failure, stroke, peripheral vascular disease, chronic lung disease, dementia, and moderate liver disease	6
Dial *et al*[16], 2014	21615; United Kingdom	1965	Cohort	ACEIs: 1.93 (1.56-2.40) ARBs: 0.91(0.61-1.37)	Age, gender, BMI, ever smoking, blood pressure, alcohol abuse, comorbidity, medication	7
Wiewel *et al*[17], 2017	6994; Netherlands	1483	Cohort	ACEIs/ARBs: 1.27 (0.88-1.84)	Age, gender, Acute Physiology and Chronic Health Evaluation IV score, race, weight, comorbidity and medication	7
Kim *et al*[18], 2019	4549; South Korea	673	Cohort	ACEIs/ARBs: 1.32 (1.11-1.56)	Age, gender, comorbidity (heart failure, ischemic heart disease, asthma, chronic renal disease, diabetes, cerebrovascular disease, and solid tumor)	7
Lai *et al*[19], 2019	21502; China	11918	Cohort	ACEIs/ARBs: 1.31 (1.22-1.40)	Age, gender, comorbidities, medication	7
Hsieh *et al*[20], 2020	223560; China	33213	Cohort	ACEIs: 0.93 (0.88-0.98) ARBs: 0.85 (0.81-0.90)	Age, gender, insurance premium, urbanization level and comorbidity	6

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; BMI: Body mass index; OR: Odds ratio; NOS: Newcastle-ottawa scale.

Table 2 Stratified analysis of the premorbid calcium channel blockers and mortality of sepsis according to study characteristics

Group	No. of studies	OR (95%CI)	$P_{heterogeneity}$	I^2 (%)
Geographic area				
Non-Asia	4	0.91 (0.74-1.09)	0	94.6
Asia	4	0.94 (0.91-0.98)	0	96.7
Object				
ACEIs	2	0.94 (0.89-0.99)	< 0.01	95.3
ARBs	3	0.84 (0.79-0.88)	0.006	80.7
ACEIs/ARBs	3	1.31 (1.23-1.39)	0.983	0
NOS				
6	3	0.88 (0.85-0.91)	0	88.6
7	5	1.31 (1.24-1.39)	0.013	68.4

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; OR: Odds ratio; NOS: Newcastle-ottawa scale.

yielded a combined risk estimate of (OR: 0.94; 95%CI: 0.91–0.97; P = 0.001) with a heterogeneity value (I^2) of 94.6% for 30-d mortality (Figure 2). We conducted a meta-regulation test and found that the geographical area was associated with 25.49% reduction in heterogeneity across the six studies (Figures 3 and 4). We further evaluated the role of (ACEIs, ARBs, and ACEIs/ARBs) in a meta-regulation test, which was associated with a 35.13% reduction in heterogeneity across the six studies.

Due to differences in the geographic area (Asian or non-Asian countries), NOS (7 or 6), and prior exposure (ACEIs, ARBs, and ACEIs/ARBs) between the studies, we conducted further subgroup analyses to determine the effect of these factors in our analyses (Table 2). We obtained a statistically protective effect in Asian population (OR: 0.94; 95%CI: 0.91–0.98), ACEIs (OR: 0.94, 95%CI: 0.89–0.99), ARBs (OR: 0.84, 95%CI: 0.79 – 0.88), NOS of 6 (OR: 0.88; 95%CI: 0.85–0.91), in a non-Asian population (OR: 0.91; 95%CI: 0.74–1.09), NOS of 7 (OR: 1.31; 95%CI: 1.24–1.39), and ACEIs/ARBs (OR: 1.31; 95%CI: 1.23–1.39).

Based on *Egger*'s and *Begger*'s regression models, there was no evidence of publication bias (Figures 5) regarding prior ACEI or ARB exposure and mortality in sepsis. The *Egger*'s funnel plot and *Begger* linear regression test revealed a P value > 0.05.

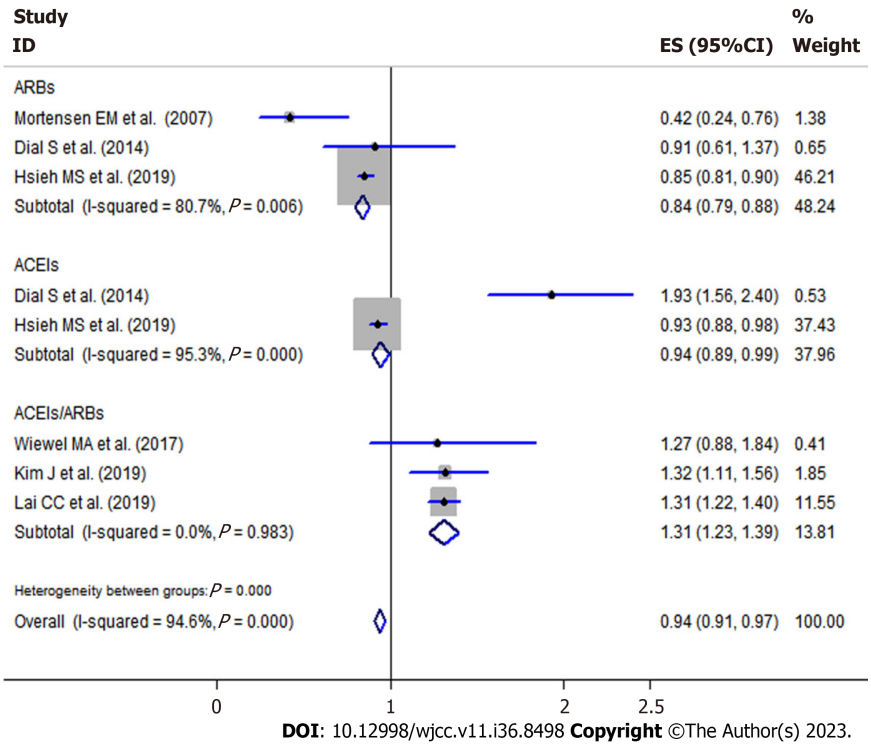


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Figure 2 Random-effects meta-analysis between premorbid angiotensin-converting enzyme inhibitors or angiotensin receptor blockers exposure, and mortality in patients with sepsis.

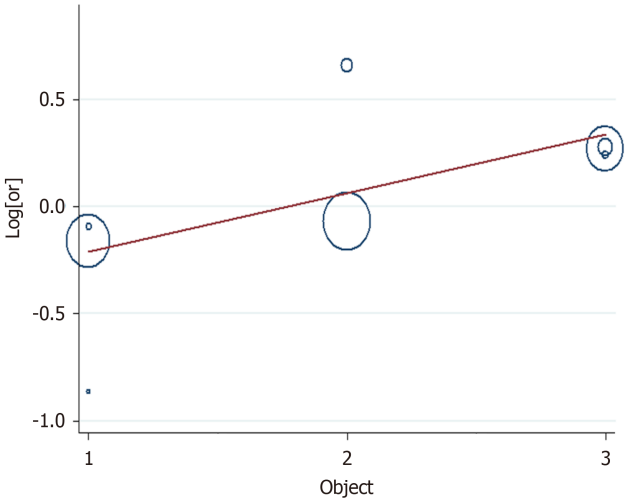

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Figure 3 Sensitivity analysis of all included studies.

DISCUSSION

This is the first systematic review examining the role of premorbid ACEI or ARB exposure on mortality outcomes in patients with sepsis. Patients receiving ACEIs or ARBs prior to developing sepsis were associated with a 6% reduction in 30-day mortality compared with those who did not receive any ACEIs or ARBs. We further conducted subgroup analyses to determine the effect of the geographic area (Asian or non-Asian countries), NOS (7 or 6), and prior exposure (ACEIs, ARBs, and ACEIs/ARBs) in our analyses (Table 2). We obtained a statistically protective effect in the Asian population (OR: 0.94; 95%CI: 0.91–0.98), ACEIs (OR: 0.94; 95%CI: 0.89–0.99), ARBs (OR: 0.84; 95%CI: 0.79–0.88), and a NOS of 6 (OR: 0.88; 95%CI: 0.85–0.91). The results of a meta-regulation test (Figures 3 and 4) revealed that the geographical area and treatment were associated with 60.62% reduction in heterogeneity across the studies.

One cause of the differences in the outcomes between population may be lifestyle and environmental factors associated with Asian and non-Asian populations[17-19]. Compared with European and American populations, Asian populations have a relatively healthy diet and a lower prevalence of chronic diseases (*e.g.*, diabetes and coronary heart disease)[20-

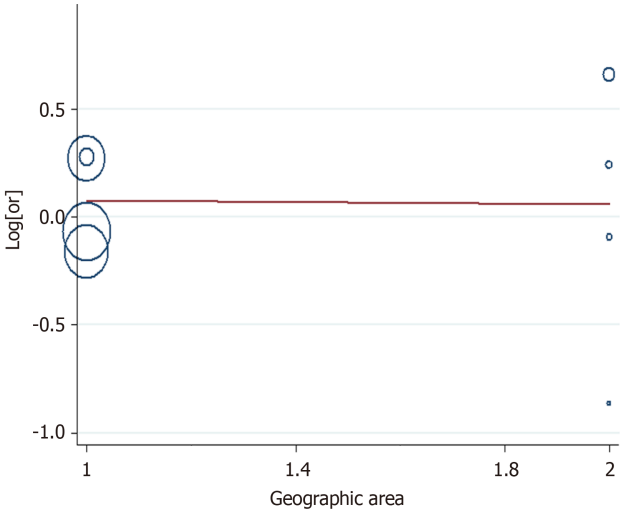

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Figure 4 Meta-regulation of premorbid angiotensin-converting enzyme inhibitors or angiotensin receptor blockers exposure and mortality in patients with sepsis.

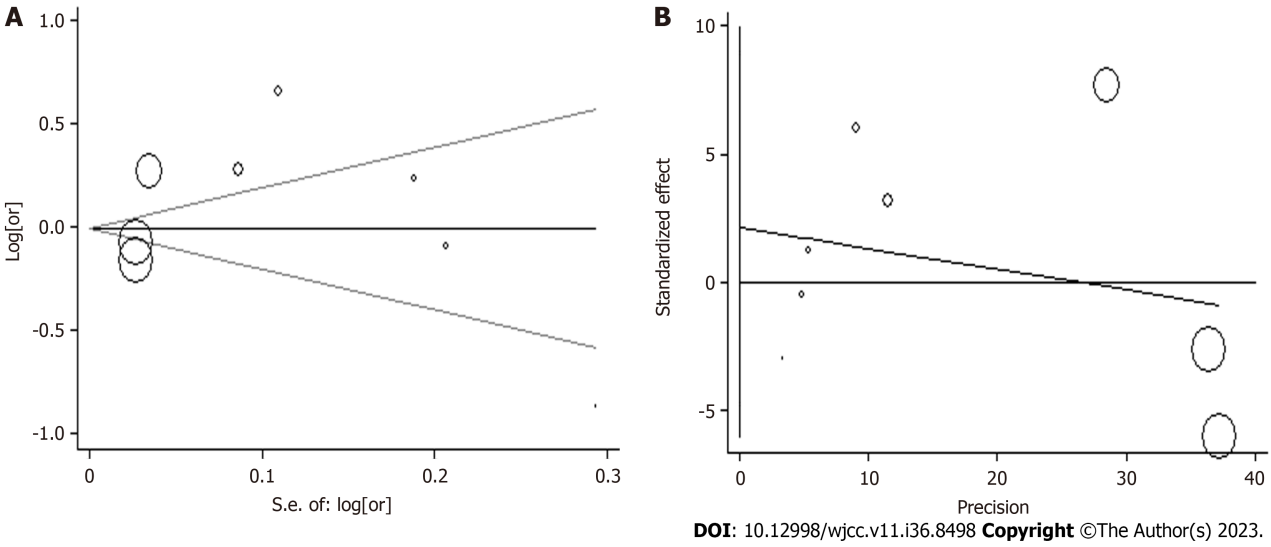

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Figure 5 Publication bias among the selected studies. A: Begg's funnel plot assessing; B: Egger's funnel plot.

22], which have a substantial impact on the prognosis of sepsis.

ACE inhibitors and ARBs reduce blood pressure by vasodilation, decreasing angiotensin II formation, and kallikrein degradation to reduce sodium and water retention[23]. These effects can also decrease the glomerular filtration rate (GFR) since angiotensin II plays a critical role in the maintenance of GFR, especially during hypovolemia or hypotension[24,25]. In the guidelines for sepsis treatment, the maintenance of a certain tissue perfusion pressure is necessary; however, the use of ACE inhibitors and ARBs appear to be contrary to the recommended treatment guidelines for sepsis. Moreover, ACE inhibitors and ARBs have not been recommended as a therapeutic drug in previous septic diagnosis and treatment guidelines. In addition to the effect of lowering blood pressure, both ACE inhibitors and ARBs also have anti-inflammatory effects, which can reduce plasma cytokine and nitric oxide concentrations[26]. In septic animal models, although ACE inhibitors have been demonstrated to reduce organ damage through the NF-kB signaling pathway[27], conflicting data exist regarding to whether an angiotensin II blockade improves survival in animal models[28,29]. Moreover, a clinical study of patients hospitalized with sepsis reported that the prior use of ARBs was associated with improved survival[8].

Our findings have potential clinical implications. Clinical medical providers should be able to identify who is at a high-risk of sepsis as early as possible and guide the course of treatment following the initial screening. Combined with our meta-analysis, the use of ACEIs or ARBs can improve the prognosis of sepsis patients, and the comparison of the effect of ACEIs and ARBs on the prognosis of sepsis is presently not supported by any data. Therefore, if patients treated with ACEIs cannot tolerate their adverse reactions, they can continue to use ARBs. It is recommended that ACEIs or ARBs be abandoned only if the adverse effects are severely intolerable[30].

This study analyzed data from six observational studies and included a larger population and range of trials compared to that previous studies, with the largest number of cases analyzed to date. We conformed to the specifications throughout the entire meta-analysis process and we also simultaneously conducted a publication bias detection. The obtained results are robust and the included analysis was free from obvious publication bias. Moreover, this meta-analysis has a high standard for the quality of the included literature, and thus meets a high quality standard.

There are a few limitations regarding this study that should be noted. First, when selecting appropriate literature, only studies written in English were included; however, a large portion of the articles that were included in our study were performed in Asia, where the official language is not English. Second, it was challenging to predict the effect of misclassification of cohort studies for the results. In addition, the systematic confounding or the risk of bias cannot easily be ruled out in observation studies. Since there was heterogeneity across the studies, we performed a regression analysis to explain the source of such heterogeneity. The observed differences may be due to the differences in the geographical area of the studies. Specifically, differences in the study geographical area and prior treatment (ACEIs, ARBs, and ACEIs/ARBs) may have contributed to the heterogeneity observed in our results (Figure 4). Besides, the practice of ACEI and ARB in the clinic are related to disease conditions like hypertension, which might also influence the prognosis of sepsis. Besides, other factors like age may also bring bias. In this analysis, the comparison between the dose and course of treatment of ACEIs or ARBs and the prognosis of sepsis were not included due to the lack of data provided in the original studies.

CONCLUSION

In summary, the findings of this systematic review suggests that exposure to ACEIs or ARBs prior to an episode of sepsis could have a role in reducing sepsis mortality; however, additional evidence is required to clarify whether premorbid ACEIs or ARBs can reduce sepsis mortality, as well as the associated mechanism. Therefore, further high-quality cohort studies and molecular mechanism experiments are required to confirm our results.

ARTICLE HIGHLIGHTS

Research background

Sepsis is a syndrome that involves physiological, pathological, and biochemical abnormalities resulting from a host response to an infection, and represents a major public health concern.

Therefore, it is important to accurately identify potential patients who are at a high risk of sepsis and to take specific intervention measures to reduce the mortality of such patients. Several studies have suggested that the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) may represent a therapeutic option for patients with sepsis.

Research motivation

The effect of ACEI or ARB on the mortality of patients with sepsis is not well characterized.

Research objectives

To elucidate the association between prior ACEI or ARB exposure and mortality in sepsis.

Research methods

This study followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. A literature search of relevant published studies that analyzed the association between the sepsis, mortality, and ACEIs or ABBs was conducted on 27 March 2020. We used the PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), EMBASE (http://www.embase.com/), Web of Science (http://wokinfo.com/), and Cochrane Library (http://www.thecochranelibrary.com/) databases to identify articles using the following terms: "hypotensor"; "antihypertensive"; "ACEIs"; "captopril"; "enalapril"; "sirapley"; "benazepril"; "petitopril"; "ramipril"; "ARBs"; "losartan"; "irbesartan"; "valsartan"; "telmisartan"; "sepsis"; "toxic shock"; "sepsis shock"; and "mortality". In addition, the reference lists in each of the studies were reviewed to identify additional studies. The language of the studies was limited to English, and we did not search for unpublished literature.

Research results

A total of 48 potentially relevant records were reviewed, of which six articles, which included 49799 cases that met the inclusion criteria were included in the meta-analysis. A total of 42 studies were subsequently excluded because they used a combined intervention, were duplicated reports, or were of relatively low quality. All of the six selected articles were cohort studies.

Research conclusions

The findings of this systematic review suggests that exposure to ACEIs or ARBs prior to an episode of sepsis could have a role in reducing sepsis mortality.

Research perspectives

However, additional evidence is required to clarify whether premorbid ACEIs or ARBs can reduce sepsis mortality, as well as the associated mechanism. Therefore, further high-quality cohort studies and molecular mechanism experiments are required to confirm our results.

FOOTNOTES

Author contributions: Jian L and Yu Y designed the study; Yang DC conducted the literature search and data analysis; Xu J drafted the manuscript; Yu Y, Xu J, and Li J revised the manuscript; All authors read and approved the final manuscript.

Supported by the Guangdong Bureau of Traditional Chinese Medicine, No. 20232049; the Guangdong Bureau of Traditional Chinese Medicine, No. 20222065; the National Natural Science Foundation of China, No. 82104989.

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

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: China

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

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World Journal of Clinical Cases

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World J Clin Cases 2023 December 26; 11(36): 8507-8511

DOI: 10.12998/wjcc.v11.i36.8507

ISSN 2307-8960 (online)

CASE REPORT

Multiple sparganosis spinal infections mainly in the thoracic region: A case report

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Specialty type: Infectious diseases

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
Grade D (Fair): D
Grade E (Poor): E

P-Reviewer: Chhabra HS, India; Viswanathan VK, United States

Received: August 20, 2023
Peer-review started: August 20, 2023
First decision: November 1, 2023
Revised: November 14, 2023
Accepted: December 12, 2023
Article in press: December 12, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Spinal infection with sparganosis is rarely seen, and multiple spinal infections with sparganosis in the thoracic spine have not been reported.

CASE SUMMARY

In this case report, a 56-year old male patient suffered from back pain for 3 mo. Computed tomography examination of the thoracic spine showed bone destruction of the T4-5 vertebral body, as well as the right pedicle and lamina of T5. Magnetic resonance imaging showed high signals on T2W1 images and fat-suppressed images in the right vertebral body of T4-5 and the right pedicle and lamina of T5, a high signal in the vertebral canal, and similar high signals in the paravertebral and subcutaneous regions of the whole spine. Puncture biopsy showed sparganosis. Following definite diagnosis, the patient was treated with debridement of T4-5 infected lesions under a microscope, bone grafting and internal fixation. Postoperatively, the patient's back pain symptoms were significantly relieved; the incision healed after one-stage treatment, and albendazole antiparasitic treatment was administered.

CONCLUSION

Puncture biopsy is the most reliable method to diagnose infection by sparganum. Removal of infected lesions under the microscope and albendazole for antiparasitic treatment are safe and effective.

Key Words: Sparganosis; Spine; Infection; Case report

Core Tip: Spinal infection with sparganosis is rarely seen, and multiple spinal infections with sparganosis in the thoracic spine have not been reported.

Citation: Wen GJ, Chen J, Zhang SF, Zhou ZS, Jiao GL. Multiple sparganosis spinal infections mainly in the thoracic region: A case report. *World J Clin Cases* 2023; 11(36): 8507-8511
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8507.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8507

INTRODUCTION

Infection due to sparganum was first reported by Cobbola[1] in 1883. Sparganum is a rare parasite, which can be found anywhere in the body, including the central nervous system. In spinal sparganosis, cervical vertebra, thoracic vertebra and lumbosacral vertebra have been reported[2-7], and sparganosis in the spinal canal, epidural, subdural and intramedullary regions have also been reported[8]. However, multiple spinal infections with sparganosis in the thoracic spine, spinal canal, vertebral body and paravertebral region have not been reported.

CASE PRESENTATION

Chief complaints

A 56-year-old male patient suffered from back pain for 3 mo.

History of present illness

No special notes.

History of past illness

No special notes.

Personal and family history

The patient had a habit of eating raw beef, raw mutton and raw snake meat in the past.

Physical examination

Physical examination showed no obvious neurological damage.

Laboratory examinations

Laboratory examination results were as follows: Leukocytes and neutrophils were not significantly increased, and no obvious abnormalities in tumor markers were found.

Imaging examinations

Computed tomography examination showed that bone of the T4-5 vertebral body was damaged; the right pedicle and lamina of T5 were also damaged (Figure 1A and B). Cervical, thoracic and lumbar magnetic resonance imaging (MRI) showed high signals on T2W1 images and fat-suppressed images in the right vertebral body of T4-5 and the right pedicle and lamina of T5, high signals in the vertebral canal, with similar high signals in the paravertebral and subcutaneous regions of the whole spine (Figure 1C-G).

FINAL DIAGNOSIS

The biopsy results showed that parasites were found in the punctured lesions, which was consistent with sparganosis (Figure 2).

TREATMENT

The patient was treated with debridement of T4-5 infected lesions, bone grafting and internal fixation. Postoperatively, the patient was treated with albendazole for 3 mo (Video).

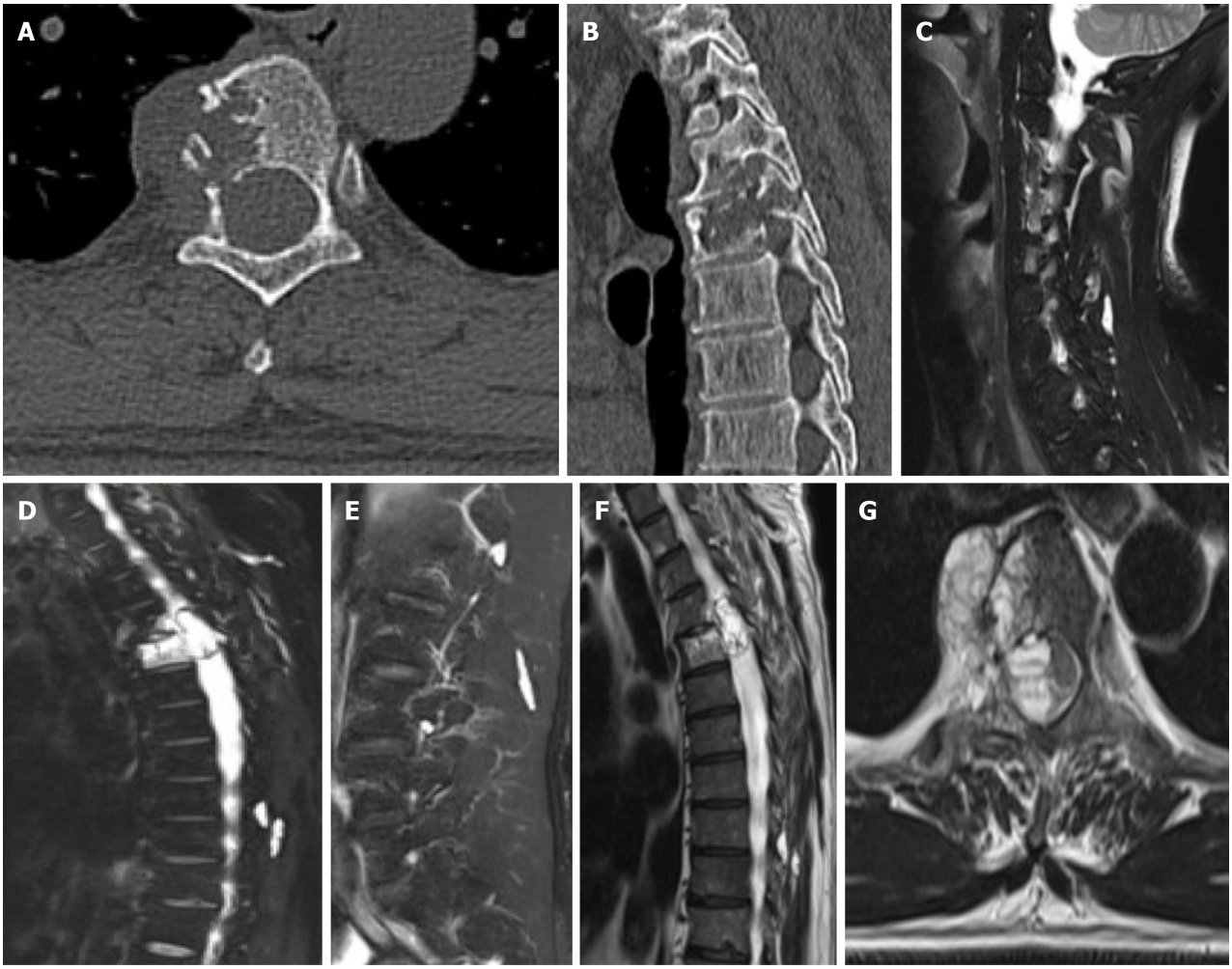

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Figure 1 Computed tomography. A and B: Computed tomography examination of the thoracic spine showed bone destruction of the T4-5 vertebral body, the right pedicle and lamina of T5; C-E: Cervical, thoracic and lumbar magnetic resonance imaging showed multiple nodules with high signals on fat-suppressed images in the paravertebral and subcutaneous regions; F and G: High signals in the right vertebral body of T4-5, the right pedicle and lamina of T5 and high signals in the vertebral canal.

OUTCOME AND FOLLOW-UP

Following surgery, the patient's back pain symptoms were significantly relieved, and there was no neurological damage. The incision healed after one-stage treatment. One week after surgery, the patient could walk normally with a brace. Nine months after surgery, the patient had no obvious back pain, MRI showed significant absorption of the lesions, and the anteroposterior and lateral radiographs suggested that local curvature and the screw positions were satisfactory (Figure 3).

DISCUSSION

Spinal sparganosis is a very rare disease. In particular, thoracic spine sparganosis with multiple infections in the spinal region has not been reported. For the diagnosis of sparganosis, anti-sparganum antibodies in serum or cerebrospinal fluid can be detected by enzyme-linked immunosorbent assay (ELISA). The sensitivity of this diagnostic technique can reach 85.7%-100%, and the specificity can reach 95.7%[9]. In 2014, Yamasaki *et al*[10] proposed a new detection technology for sparganosis, the iSpaICT kit, which is faster and easier than ELISA, with better sensitivity and specificity. Sparganosis is extremely rare, and laboratory testing is not routinely carried out in most Chinese hospitals. In the present patient, MRI of the spine showed a cystic lesion located in T4-5 compressing the spinal cord, many minor mass-like lesions were located in the paravertebral and subcutaneous regions of the spine, and the MRI features were very similar to literature reports[3, 11]. Puncture biopsy is the most effective and reliable method for diagnosing sparganosis. However, for sparganosis in the vertebral canal, subdural region, spinal cord or brain, puncture biopsy is very risky, and sometimes cannot be performed. Accordingly, these cases require to be confirmed by laboratory examinations or after focal resection. Our patient underwent a puncture biopsy on the third day after admission, and the lesion was easily visualized under

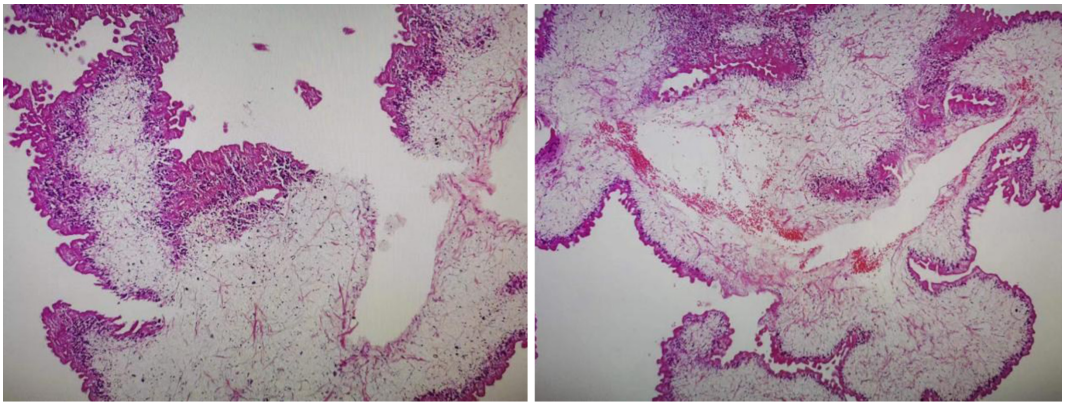

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Figure 2 High power microscopic view of the parasite. The body of the parasite has degenerated and calcareous bodies are not readily discerned, but the outer layer of the tegument was preserved.

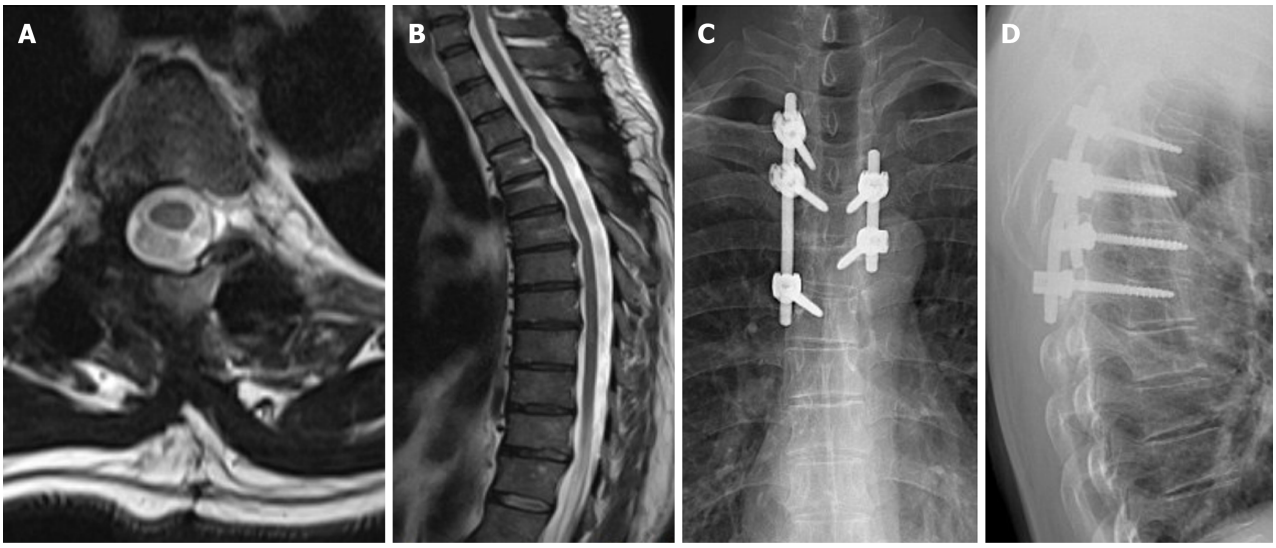

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Figure 3 Magnetic resonance imaging. A and B: At nine months after surgery, magnetic resonance imaging showed significant absorption of the lesion; C and D: Anteroposterior and lateral radiographs suggested that local curvature and the screw positions were satisfactory.

fluoroscopy. The biopsy sample was submitted for examination and culture, but no bacteria were cultured. Parasites were seen under the microscope, and a small quantity of calcareous corpuscles was seen below them, which conformed to the shape of sparganosis. Broken striated muscle tissue and dead bone tissue were also seen, in addition to an inflammatory reaction. When the pathological diagnosis was confirmed, the patient was asked about his past history. The patient had a habit of eating raw beef, raw mutton and raw snake meat.

Following the diagnosis of sparganosis, posterior thoracic 4-5 lesion removal, bone grafting and internal fixation were performed. Compared with tumor resection, the removal of sparganosis lesions is less difficult. There is no need to embolize the blood vessels before surgery, and bleeding during surgery is easily controlled. During surgery, neuroelectrophysiological monitoring was used and the infected lesion was removed under the microscope, which enhanced the safety of surgery and ensured the thoroughness of lesion removal. After thorough removal of the dead bone and the lesion in the vertebral body, bone grafting was performed using the posterior resected vertebral lamina and small articular processes as the bone graft materials. Due to instability in this region, we implanted the pedicle rod system for internal fixation. The pedicle in the right side of the T5 was damaged. The left sides of T4 and T5 were fixed, and the right sides of T3-6 were fixed.

Postoperatively, antiparasitic treatment was considered very important, and the drug of choice in the literature[3,12] for sparganosis is praziquantel. However, the patient experienced dizziness, chest tightness, nausea and vomiting after taking praziquantel, and switched to albendazole for 3 mo. Nine months after surgery, the patient had no obvious back pain, and MRI showed significant absorption of the lesions. Thus, treatment was considered safe and effective.

CONCLUSION

Spinal infection with sparganosis is a rare event. We report an uncommon case of thoracic spine sparganosis with multiple sites of infection. Puncture biopsy is the most effective and reliable method for diagnosing sparganosis. Removal of infected lesions under a microscope and albendazole antiparasitic treatment was safe and effective (Video).

FOOTNOTES

Author contributions: Wen GJ, Chen J, Zhou ZS, Zhang SF, and Jiao GL contributed equally to this work; Wen GJ wrote the manuscript; all authors have read and approved the final manuscript.

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

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Liu JH
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 December 26; 11(36): 8512-8518

DOI: 10.12998/wjcc.v11.i36.8512

ISSN 2307-8960 (online)

CASE REPORT

Iatrogenic flexor tendon rupture caused by misdiagnosing sarcoidosis-related flexor tendon contracture as tenosynovitis: A case report

Rui Yan, Zhe Zhang, Long Wu, Zhi-Peng Wu, He-De Yan

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
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bernardes A, Portugal

Received: August 26, 2023
Peer-review started: August 26, 2023
First decision: November 9, 2023
Revised: November 18, 2023
Accepted: December 7, 2023
Article in press: December 7, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Sarcoidosis is a multisystem disease characterized by granuloma formation in various organs. Sarcoidosis-related flexor tendon contractures are uncommon in clinical settings. This contracture is similar to stenosing tenosynovitis and potentially leads to misdiagnosis and mistreatment. Herein, we report a rare case of sarcoidosis-related finger flexor tendon contracture that was misdiagnosed as tenosynovitis.

CASE SUMMARY

A 44-year-old woman presented to our department with flexion contracture of the right ring and middle fingers. The patient was misdiagnosed with tenosynovitis and underwent acupotomy release of the A1 pulley of the middle finger in another hospital that resulted in iatrogenic rupture of both the superficial and profundus flexors. Radiological presentation showed multiple sarcoid involvements in the pulmonary locations and ipsilateral forearm. A diagnosis of sarcoidosis was made based on the presence of non-caseating granulomas with tubercles consisting of Langhans giant cells with lymphocyte infiltration on biopsy, and the patient underwent surgical repair for the contracture. After 2 mo, the patient experienced another spontaneous rupture of the repaired middle

finger tendon and underwent surgical re-repair. Satisfactory results were achieved at the 10 mo follow-up after reoperation.

CONCLUSION
Sarcoidosis-related finger contractures are rare; thus, caution should be exercised when dealing with such patients to avoid incorrect treatment.

Key Words: Sarcoidosis; Finger; Contracture; Iatrogenic; Misdiagnosis; Case report

Core Tip: Finger contracture due to tenosynovitis is frequently encountered in clinical settings. However, misdiagnosis can occur when rare causes such as sarcoidosis are neglected. Here, we report a case in which such a misdiagnosis led to an iatrogenic injury. The mainstream treatment method for contractures related to sarcoidosis is surgical excision of muscular lesions, with varied outcomes in several case reports. In our case, considering the contracture lesion at the flexor digitorum profundus (FDP) and the initial iatrogenic tendon rupture, cross-lengthening of the flexor digitorum superficialis and FDP was attempted to restore flexion and achieve satisfactory results.

Citation: Yan R, Zhang Z, Wu L, Wu ZP, Yan HD. Iatrogenic flexor tendon rupture caused by misdiagnosing sarcoidosis-related flexor tendon contracture as tenosynovitis: A case report. *World J Clin Cases* 2023; 11(36): 8512-8518
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8512.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8512

INTRODUCTION

Granulomatous involvement of the skeletal muscles (also known as granulomatous myopathy) is common in patients with sarcoidosis, and most cases are asymptomatic[1]. However, cases of finger flexion contractures are extremely rare. To the best of our knowledge, only a few cases of such contractures have been reported in the English literature[2-6].

Contracture of finger flexors is frequently observed in tenosynovitis (also known as trigger finger) in clinical settings [7]. Trigger finger is caused by inflammation and constriction of the retinacular sheath through which the flexor tendons run as they pass from the palm of the hand to the finger, leading to pain and movement restriction. The management of tenosynovitis is well established, ranging from conservative to surgical treatment[7-9]. Because finger contractures of other causes, such as sarcoidosis, are rare, misdiagnosis of tenosynovitis could occur, leading to empirical treatment with poor outcomes or severe complications.

Herein, we present a patient with finger contractures who was misdiagnosed with trigger finger and received acupotomy release[10,11] (similar to percutaneous release), resulting in iatrogenic rupture of both the superficial and profundus flexors of the right middle finger. We also conducted a systematic literature review of finger contractures caused by sarcoidosis.

CASE PRESENTATION

Chief complaints

A 44-year-old healthy woman presented to our hand surgery department with spontaneous flexor tendon rupture of the right middle finger and contracture of the right ring finger.

History of present illness

The patient was diagnosed with tenosynovitis of the right ring finger and middle finger at a local hospital and underwent acupotomy release of her middle finger 2 wk prior to admission. Five days after the release, a sudden complete loss of active flexion of the right middle finger was observed during routine domestic activities. Two months after the surgery, re-rupture of the repaired middle finger tendon was encountered when the patient was pulling on her pants.

History of past illness

The patient denied any past illnesses.

Personal and family history

The patient denied any personal or family history of related diseases.

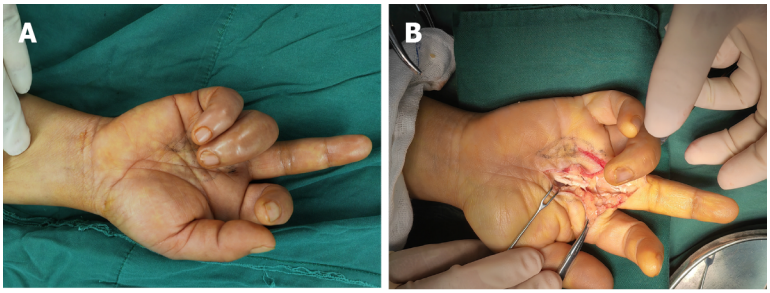

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Figure 1 Findings during the first surgery. A: The extended middle finger and flexed ring finger before exploration; B: Intraoperative view of the rupture of both flexor digitorum superficialis and flexor digitorum profundus tendon at the metacarpophalangeal joint of the middle finger.

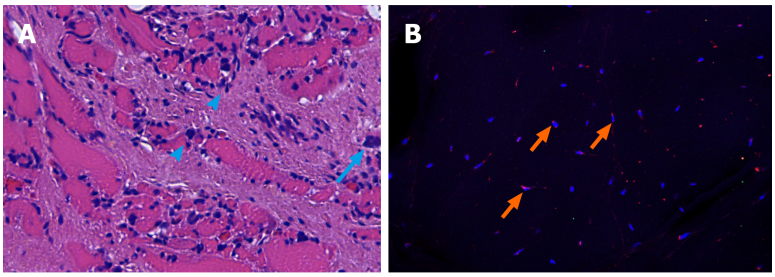

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Figure 2 Results of hematoxylin and eosin staining and immunofluorescence staining of the flexor digitorum profundus muscle. A: Interstitial diffuse infiltration of scattered lymphocytes (arrowheads) and multinucleated giant cells (arrow) in the muscle tissue; B: The cells were stained for nuclei (DAPI, blue) and CD68 (red). This highlights the giant cells that are positively immunostained for CD68 (arrows).

Physical examination

Loss of active flexion of the right middle finger and contracture of the right ring finger were observed. There was no swelling, tenderness, or numbness of the digits. No other positive findings were observed during systematic physical examination. During the operation, all lacerations of the flexor digitorum superficialis (FDS) and flexor digitorum profundus (FDP) of the right middle finger were identified in Zone II around the metacarpophalangeal (MCP) joint (Figure 1). Significantly, a high level of tension and loss of elasticity were observed at the proximal end of the FDP, whereas the proximal FDS seemed normal in tension and elasticity.

Laboratory examinations

Initial laboratory studies revealed high alkaline phosphatase (116 U/L, normal range: 35–100 U/L) and normal serum creatinine, creatine phosphokinase, and calcium levels. No further positive findings were noted in the laboratory examinations.

Histopathology revealed granulomatous involvement in the FDP muscles and tendons, showing a typical sarcoid shape with tubercles consisting of Langhans' giant cells and lymphocytes (Figure 2).

Imaging examinations

High-resolution computed tomography (CT) revealed widespread nodules in both the lungs (Figure 3).

Magnetic resonance imaging (MRI) revealed a central dark star surrounded by a peripheral high-signal area in the right forearm muscles on axial images and a three-stripe pattern on coronal and sagittal images, typical of sarcoid myopathy (Figure 4)[12-14].

FINAL DIAGNOSIS

The patient was diagnosed with sarcoidosis-related flexor tendon contractures and iatrogenic flexor tendon rupture.

TREATMENT

During the first surgical exploration, the distal FDP of the middle finger was anastomosed with the proximal end of the FDS to restore flexion. Surprisingly, the ring finger remained in contracture after complete open release of the A1 pulley,

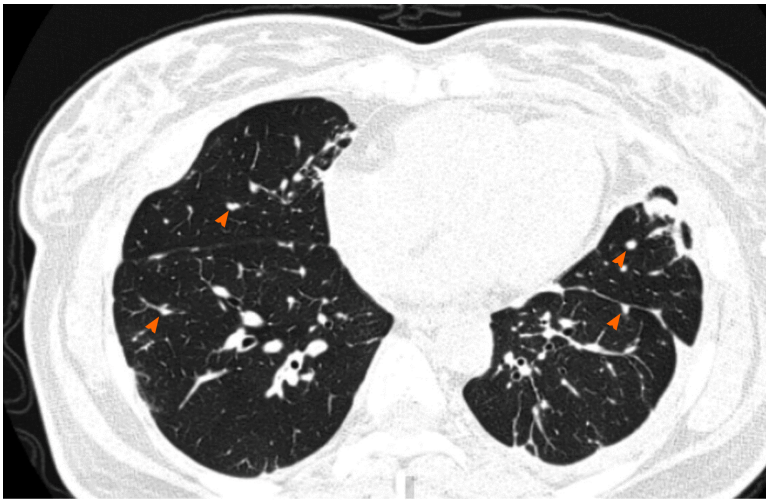

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Figure 3 High-resolution computed tomographic section showing widespread nodules (arrowheads) in both lungs.

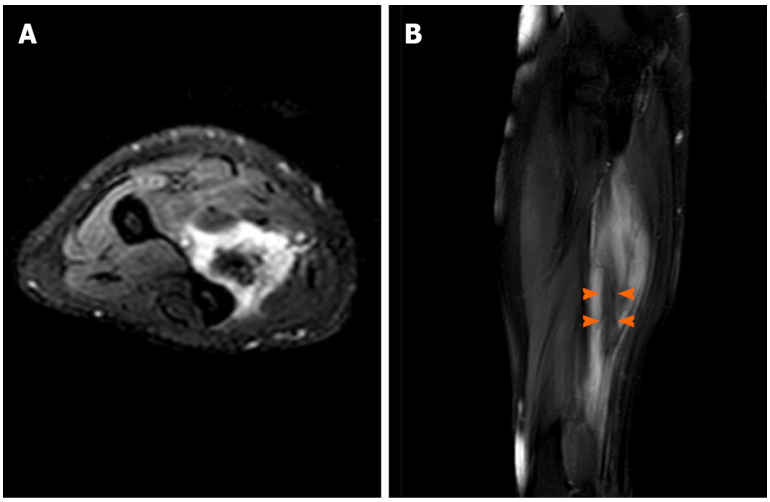

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Figure 4 Magnetic resonance imaging revealing a lesion located at the flexor digitorum profundus muscle. A: T2-weighted fat saturated axial image of the forearm shows a nodule of increased signal intensity, while the center structure shows decreased signal intensity; B: T2-weighted fat saturated sagittal image of the forearm shows an inner stripe of decreased signal intensity (arrowheads) and outer stripes of increased signal intensity.

indicating that the contracture was not due to tenosynovitis. No further intraoperative intervention was performed after discussion with the patient. Routine postoperative management was performed, including splinting for 4 wk and corresponding rehabilitation.

Unfortunately, 2 mo after the operation, re-rupture of the repaired tendon was encountered when the patient was pulling on her pants (Figure 5A). Repeat operations were performed on the right middle and ring fingers. Anastomoses of the proximal FDS to the distal FDP using tendon grafting were performed for the middle finger and direct repair was performed for the ring finger (Figure 5B).

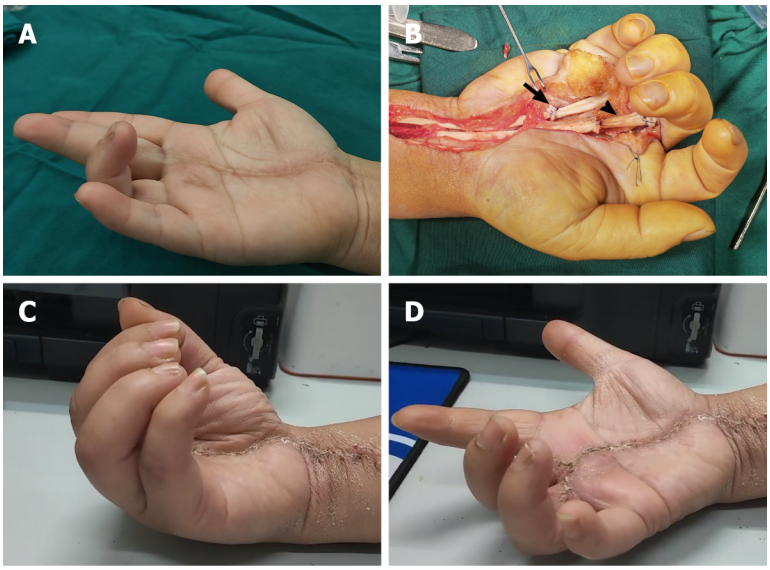
OUTCOME AND FOLLOW-UP

The patient partially regained the motion of her middle finger, while contracture of her right ring finger persisted after the first surgical attempt. After reoperation, the patient could use the hand without discomfort despite persistent mild stiffness at the 10 mo follow-up (Figure 5C and D).

Table 1 Literature review of published cases of flexor contractures associated with sarcoidosis

Ref.	Sex	Age	Affected hands	Affected fingers	Treatment	Outcomes of contractures
Warburg[20]	F	56	L and R	All fingers	None	NA
Simmonds and Hoffbrand[19]	F	58	L and R	3rd fingers	Prednisolone and dapsone	Worsened
	M	65	R	4th finger	Steroids, and Azathioprine	Cured after duration of 6 yr
Ikeda *et al*[2] and Tada *et al*[4]	F	63	R	2-4th fingers	Granulomatous lesion excision	Worsened two years postoperatively
Motomiya *et al*[5]	F	61	L and R	5th fingers	Granulomatous lesion excision	NA
Bowers *et al*[3]	M	14	L	3-5th fingers	Occupational therapy	Improved
Ueba and Obara[18]	F	58	L and R	4, 5th fingers	Granulomatous lesion excision	Cured at a follow-up of 2.5 yr
Walter *et al*[21]	M	36	L and R	3-5th fingers	Low-dose thalidomide therapy	Markedly improved

F: Female; M: Male; L: Left hand; R: Right hand; NA: Not available.



DOI: 10.12998/wjcc.v11.i36.8512

Figure 5 The second surgery and follow-up. A: The extended middle finger and flexed ring finger before reexploration; B: Intraoperative view of the repaired tendons of the middle and ring fingers. Arrow: The repaired site of the ring finger with suturing the distal end of the flexor digitorum profundus to the proximal end of the flexor digitorum superficialis. Arrowhead: The repaired site of the middle finger with tendon grafting; C and D: Range of active motion of the affected fingers 10 mo after reoperation.

DISCUSSION

In the present case, surgery was performed when the patient presented with an iatrogenic rupture. Sarcoidosis was not considered until the second surgical attempt and was confirmed after MRI and chest CT. After the re-rupture, a comprehensive medical history revealed an additional experience of mild discomfort with tenderness on physical examination around the forearm flexor muscles, indicating a muscular lesion. Furthermore, tenosynovitis should have been ruled out because the patient denied experiencing pain or triggering around the MCP joint or had a history of aggravation after housework.

Although contractures due to sarcoidosis are extremely rare, neglecting these distinct symptoms and the absence of a systematic examination resulted in misdiagnosis and subsequent mistreatment.

The diagnosis of sarcoidosis is not well established, but is recommended according to three major aspects: A compatible clinical and/or radiological presentation, histological evidence of non-necrotizing granulomatous inflammation in one or more tissues, and exclusion of alternative causes of granulomatous disease[15].

Chest radiography has been the cornerstone of sarcoidosis diagnosis since 1961, when Scadding[16] proposed a standardized staging system. Chest CT is currently the reference standard for the assessment of pulmonary findings and mediastinal lymph nodes[17]. In our case, MRI and biopsy revealed lesions in the forearm muscles, whereas a clear diagnosis of sarcoidosis was made only after CT imaging.

The treatment of sarcoidosis-related contractures has been reported in several case reports with varied results[2-5,18-21] (Table 1).

Acute sarcoid myopathy improves with systemic treatment in most patients, while patients with chronic sarcoid myopathy commonly experience severe disability such as flexor contractures and seldom recover after corticosteroid, immunosuppressive, or anti-tumor necrosis factor-α treatment[22,23]. Surgical intervention has been attempted in such chronic cases of finger contractures[2,4,5,18]. In 1996, Ikeda *et al*[2] reported that contractures due to sarcoidosis could be successfully treated by surgical excision of the lesion. However, in 2009, they reported that even with complete excision of the granulomatous lesion, a new lesion may appear in a previously healthy area; therefore, radical cure by surgery alone is difficult[4]. Conservative treatments have also been reported. Walter *et al*[21] reported a case in which the contractures improved after 9 mo of treatment with low-dose thalidomide. Bowers reported a 14-year-old patient who improved with occupational therapy[3]. Notably, while in previous cases, biopsy tests focused on forearm muscles, our biopsy results revealed a lesion at the tendon as well.

Coincidentally, Motomiya *et al*[5] also reported a patient with sarcoidosis-related flexor contracture who was initially misdiagnosed with trigger finger and underwent open surgery. Fortunately, the tendon was fully exposed during the operation, and the misdiagnosis of tenosynovitis was realized. In our case, the patient was misdiagnosed with tenosynovitis and treated by acupotomy (a type of blind release) during the first visit to a local hospital. The operation did not provide further information about the contracture, inevitably resulting in iatrogenic flexor rupture when pursuing complete finger flexion. Therefore, the treatment of tenosynovitis using acupotomy should be performed with great caution in preoperative diagnosis.

In our case, because of the initial iatrogenic flexor tendon rupture, tendon grafting was performed to repair the FDP tendon by connecting the proximal end of the FDS to the distal FDP. Notably, open surgery of the digit revealed normal tension at the FDS, and the FDS muscle was later proven to be free of lesions based on biopsy results; thus, this surgery was able to partially restore flexion to the affected fingers. In conclusion, this method was adapted because of the initial attempt to repair the tendon rupture and achieved satisfactory results in alleviating the contractures at the 10 mo follow-up.

CONCLUSIONS

Sarcoid involvement of the musculoskeletal system that causes finger contractures is rare and can lead to misdiagnosis if clinicians are not aware. Our case shows that finger contracture release by connecting the normal proximal end of the FDS to the distal FDP may be an option for such cases, although the management of sarcoidosis-related flexor contractures remains controversial, with varied outcomes based on a literature review.

ACKNOWLEDGEMENTS

We thank Dr. Mazhar Ali Raza for the editing assistance.

FOOTNOTES

Author contributions: Yan R and Zhang Z prepared the initial draft of this manuscript and made subsequent revisions; Wu L and Wu ZP performed the data collection and manuscript review and editing; Yan HD performed the conceptualization and validation of the study and acquired funding of the report; all authors have reviewed and approved the final manuscript.

Supported by Zhejiang Provincial Natural Science Foundation of China, No. LY23H090009; Clinical Research Foundation of the Second Affiliated Hospital Wenzhou Medical University, No. SAHoWMU-CR2018-08-417.

Informed consent statement: The study participant provided written informed consent before study enrollment.

Conflict-of-interest statement: The authors have no conflicts of interest related to this manuscript.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

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S-Editor: Lin C
L-Editor: Wang TQ
P-Editor: Lin C

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World Journal of Clinical Cases

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World J Clin Cases 2023 December 26; 11(36): 8519-8526

DOI: 10.12998/wjcc.v11.i36.8519

ISSN 2307-8960 (online)

CASE REPORT

Cholecystoenteric fistula in a patient with advanced gallbladder cancer: A case report and review of literature

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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, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kai K, Japan; Shariati MBH, Iran; Wani I, India

Received: August 29, 2023
Peer-review started: August 29, 2023
First decision: September 28, 2023
Revised: October 12, 2023
Accepted: December 7, 2023
Article in press: December 7, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Cholecystoenteric fistula (CEF) involves the formation of a spontaneous anomalous tract between the gallbladder and the adjacent gastrointestinal tract. Chronic gallbladder inflammation can lead to tissue necrosis, perforation, and fistulogenesis. The most prevalent cause of CEF is chronic cholelithiasis, which rarely results from malignancy. Because the symptoms and laboratory findings associated with CEF are nonspecific, the condition is often misdiagnosed, presenting a challenge to the surgeon when detected intraoperatively. Therefore, a preoperative diagnosis of CEF is crucial.

CASE SUMMARY

We present the case of a 57-year-old male with advanced gallbladder cancer (GBC) who arrived at the emergency room with persistent vomiting, abdominal pain, and diarrhea. An abdominopelvic computed tomography scan revealed a contracted gallbladder with bubbles in the fundus connected to the second portion of the duodenum and transverse colon. We suspected that GBC had invaded the adjacent gastrointestinal tract through a cholecystoduodenal fistula (CDF) or a cholecystocolonic fistula (CCF). He underwent multiple examinations, including esophagogastroduodenoscopy, an upper gastrointestinal series, colo-noscopy, and magnetic resonance cholangiopancreatography; the results of these tests confirmed a diagnosis of synchronous CDF and CCF. The patient underwent a Roux-

en-Y gastrojejunostomy and loop ileostomy to address the severe adhesions that were previously observed to cover the second portion of the duodenum and hepatic flexure of the colon. His symptoms improved with supportive treatment while hospitalized. He initiated oral targeted therapy with lenvatinib for further anticancer treatment.

CONCLUSION
The combination of imaging and surgery can enhance preoperative diagnosis and alleviate symptoms in patients with GBC complicated by CEF.

Key Words: Cholecystoenteric fistula; Biliary enteric fistula; Cholecystoduodenal fistula; Cholecystocolonic fistula; Gallbladder neoplasms; Case report

Core Tip: Cholecystoenteric fistulas are rarely associated with malignancy, and synchronous cholecystoduodenal and cholecystocolonic fistulas are even rarer. We present the case of a 57-year-old male with advanced gallbladder cancer complicated by synchronous cholecystoduodenal and cholecystocolonic fistulas. He presented with persistent vomiting, abdominal pain, and diarrhea. We also review 30 cases of gallbladder cancer-related cholecystoenteric fistulas published between 1973 and 2023. We performed a statistical analysis of clinical symptoms, imaging findings, and management. Our aim is to share our experience with diagnosis and surgical treatment of this condition and offer our insights to guide future clinical decision-making.

Citation: Wang CY, Chiu SH, Chang WC, Ho MH, Chang PY. Cholecystoenteric fistula in a patient with advanced gallbladder cancer: A case report and review of literature. *World J Clin Cases* 2023; 11(36): 8519-8526
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8519.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8519

INTRODUCTION

Gallbladder cancer (GBC) is a lethal disease typically diagnosed at an advanced stage, leading to a grim prognosis[1]. Cholecystoenteric fistula (CEF) is an uncommon complication of biliary disease that results from an abnormal connection between the gallbladder and the adjacent gastrointestinal tract. CEF occurs in only 3%-5% of patients with cholelithiasis and 0.15%-4.8% of those undergoing biliary surgery[2]. The most prevalent type of CEF is the cholecystoduodenal fistula (CDF), accounting for 70% of cases, followed by the cholecystocolonic fistula (CCF) at 20%[2,3]. CEF can be attributed to various factors, including cholelithiasis, peptic ulcer disease, and malignant neoplasms[2,4]. However, malignancy is associated with CEF in only 3%-14% of cases[5-8]. The coexistence of CDF and CCF is exceedingly rare, with reported incidences ranging from 1.5% to 5%[5,9-11].

We present the case of a 57-year-old male with advanced GBC complicated by synchronous CDF and CCF, who presented with persistent vomiting, abdominal pain, and watery diarrhea.

CASE PRESENTATION

Chief complaints

A 57-year-old Taiwanese male presented to our emergency department in November 2022 with a 3-d history of vomiting, abdominal pain, and watery diarrhea.

History of present illness

The patient reported experiencing postprandial vomiting, epigastric abdominal pain, and watery diarrhea more than 10 times daily for 3 d.

History of past illness

His past medical history was significant for gallstones, for which he received conservative treatment. In April 2022, he was diagnosed with poorly differentiated gallbladder adenocarcinoma, cT3N1M1, stage IVB, with liver metastases. He underwent 3 mo of palliative chemotherapy with cisplatin and gemcitabine. While the primary tumor exhibited a partial response, the hepatic tumor progressed. He subsequently underwent 3 mo of treatment with gemcitabine, high-dose 5-fluorouracil, and leucovorin.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

A physical examination revealed generalized abdominal tenderness but no Murphy's sign or rebound abdominal tenderness. His body temperature was 36.0 ℃, blood pressure 130/90 mmHg, heart rate 103 beats per minute, and respiratory rate 18 breaths per minute.

Laboratory examinations

Laboratory blood tests revealed a white blood cell count of 10990/L (normal range: 4500-11000), hemoglobin level of 8.0 g/dL (normal range: 13.5-18.0), platelet count of 466 x 10^3/μL (normal range: 150-400 × 10^3), creatinine level of 1.1 mg/dL (normal range: 0.7-1.2), aspartate aminotransferase 10 U/L (normal range: < 40), alanine aminotransferase 5 U/L (normal range: < 40), C-reactive protein 18.09 mg/dL (normal range: < 0.8), and lipase < 3 U/L (normal range: 11-82).

Imaging examinations

Abdominopelvic computed tomography (CT) displayed a gallstone in the gallbladder and a contracted gallbladder with bubbles in the fundus connected to the second portion of the duodenum and transverse colon (Figure 1). We suspected GBC invasion of the adjacent gastrointestinal tract through a CDF or a CCF. A subsequent esophagogastroduodenoscopy (EGD) and upper gastrointestinal (UGI) series identified a CDF in the second portion of the duodenum (Figure 2). A colonoscopy revealed a fistula-like lesion in the transverse colon near the hepatic flexure region. Magnetic resonance cholangiopancreatography (MRCP) confirmed the diagnoses of CDF and CCF.

FINAL DIAGNOSIS

Considering the patient's medical history, we arrived at a final diagnosis of advanced GBC complicating synchronous CDF with CCF.

TREATMENT

The patient was administered empiric antibiotic treatment for his intra-abdominal infection and parenteral nutrition. Nevertheless, the postprandial vomiting and watery diarrhea persisted, leading us to consider that his symptoms were the result of the synchronous CDF and CCF. We referred the patient to a general surgeon for palliative surgery to improve his quality of life. During the exploratory laparotomy, we identified GBC with invasion of the duodenum and transverse colon, resulting in CDF and CCF. Furthermore, severe adhesions over the second portion of the duodenum and hepatic flexure of the colon posed challenges for fistulectomy, fistula closure, and stent placement. As a result, we performed a Roux-en-Y gastrojejunostomy and loop ileostomy.

OUTCOME AND FOLLOW-UP

Following surgery, his symptoms improved, and he resumed oral intake. On day 50, he was discharged and commenced oral targeted therapy with lenvatinib for ongoing anticancer treatment.

DISCUSSION

While most CEFs arise as late complications of gallstone disease, they can also develop when GBC invades the adjacent gastrointestinal tract, as reported in several studies (Table 1). Adenocarcinoma is the predominant cancer type (68.7%). The incidence of CCF is similar to CDF, with rates of 45.2% and 38.7%, respectively. Synchronous CCF and CDF occur in 12.9% of all patients, typically within the hepatic flexure (72.2%) and transverse colon (28.8%). Gallstones and recurrent gallbladder inflammation preceding GBC invasion may contribute to CEF development[12]. Direct GBC invasion into the duodenal and colonic walls likely contributed to our case's fistula formation.

The primary clinical manifestations of CEF include abdominal pain (typically in the right upper quadrant), nausea, vomiting, weight loss, and diarrhea[2,5]. Our review of the literature found that the most common symptoms of GBC-related CDF are abdominal pain (68.8%), nausea or vomiting (62.5%), and weight loss (25%). These symptoms resemble GBC-related CCF (abdominal pain: 88.9%, nausea or vomiting: 33.3%, and weight loss: 33.3%). Only 16.7% of patients with GBC-related CCF experience diarrhea. Due to its nonspecific symptoms, signs, and laboratory investigations, preoperative diagnosis of CEF can be challenging (reported rates of 31%-58.6% in recent research)[2,5,9]. Furthermore, distinguishing GBC-related CEF from GBC alone can be difficult due to their overlapping symptoms[1]. Failing to diagnose CEF before surgery can complicate surgery, potentially necessitating a more complex procedure and leading to additional complications. Various diagnostic imaging techniques, including abdominal ultrasound, barium studies, EGD, colo-

Table 1 Summary data of gallbladder cancer related cholecystoenteric fistula

Ref.	Sex/age(yr)	Clinical symptoms	Image modalities and findings	Type of GBC	Type of CEF	Management
[4]	M/68	Abdomen pain, anorexia, weight loss	CT, colonoscopy: GBC, HF colon fistula	Adenocarcinoma	CCF	Diverting loop ileostomy
[15]	F/64	Right abdomen pain, weight loss, fever, jaundice	CT: GBC, HF colon fistula	Carcinoma	CCF	Palliative treatment
[16]	F/78	Nausea, vomiting	EGD, CT: GBC, duodenal fistula	Adenocarcinoma	CDF	Cholecystectomy, left hepatic lobectomy, antrectomy, resection of first portion of duodenum, reconstruction with a Roux-en-Y gastrojejunostomy
[17]	F/81	Right upper abdomen pain, anorexia, fever	EGD, CT, MRI, gastrografin: GBC, duodenal fistula, HF colon fistula	SqCC	CDF, CCF	EGD and colonoscopy with endoscopic fistula closure
[18]	F/59	Nausea, vomiting	CT, ERCP: GBC, duodenal fistula	Adenocarcinoma	CDF	Endobiliary RFA with stents placement
[19]	F/80	Right upper abdomen pain	CT: Transverse colon fistula	SqCC	CCF	Cholecystectomy, partial colectomy
[20]	M/68	Right upper abdomen pain, weight loss	CT: Duodenal fistula	SqCC	CDF	Palliative chemotherapy, targeted therapy, and radiotherapy
[21]	M/68	None	PET CT, MRI, EGD: porcelain gallbladder, suspected GBC, duodenal fistula	Adenocarcinoma	CDF	Subtotal stomach-preserving pancreatoduodenectomy, radical cholecystectomy
[22]	M/59	Abdomen pain, vomiting	CT: HF colon fistula, a gallstone in the left colon	Carcinoma	CCF	Colostomy
[23]	M/74	Right upper abdomen pain, weight loss	CT: Duodenal fistula	Adenocarcinoma	CDF	Unknown
[24]	F/67	Upper abdomen pain, nausea, diarrhea, weight loss	CT: GBC	SGCC	CCF	Cholecystectomy, bisegmentectomy IVb-V, right hemicolectomy
[25]	M/87	Abdomen pain	CT: Transverse colon fistula	Carcinosarcoma	CCF	Cholecystectomy with partial transverse colectomy
[6]	F/62	None	CT: Gallstone, suspected HF colon cancer	Adenocarcinoma	CCF	Cholecystectomy, right hemicolectomy
[26]	F/81	Upper abdomen pain, fever	PTC: GBC, transverse colon fistula	Papillomatosis	CCF	Cholecystectomy, fistula closure, choledocholithotomy with T-tube drainage
[27]	M/66	Right upper abdomen pain, nausea, vomiting	CT, EGD: Duodenal fistula	SqCC	CDF	Palliative treatment
[28]	F/48	Right upper abdomen pain, jaundice, melena	US, CT: GBC, HF colon fistula	Adenocarcinoma	CCF	Chemotherapy, radiotherapy
[29]	F/81	Upper abdomen pain,	CT: Duodenal fistula	Adenocarcinoma	CDF	Cholecystectomy, fistula closure, gastrojejunostomy, choledochojejunostomy

		vomiting				
[30]	F/75	Abdomen pain, vomiting, diarrhea	CT: Air-filled thickened-walled gallbladder	Adenocarcinoma	Unknow	Laparotomy with stone extraction, palliative treatment
[31]	F/80	Anorexia	EGD: Duodenal fistula	Adenocarcinoma	CDF	Cholecystectomy, fistula closure, choledocholithotomy with T-tube drainage
[32]	F/46	Right upper abdomen pain, weight loss	US, CT: GBC, gallstone	Adenocarcinoma	CCF	Cholecystectomy with partial hepatic segments resection (IV and V), fistulectomy, right hemicolectomy
[33]	F/76	Right upper abdomen pain, vomiting	CT: Air-filled thickened-walled gallbladder, duodenal fistula	Carcinoma	CDF	Enterotomy with stone extraction
[34]	M/84	Coffee ground emesis	EGD, CT: Gallstone, duodenal fistula	Adenocarcinoma	CDF	Cholecystectomy, duodenum repair
[35]	F/60	Right upper abdomen pain, fever, nausea, vomiting	US, PTC, MRI: GBC, gallstone, HF colon fistula	Adenocarcinoma	CCF	Laparotomy, right hemicolectomy, primary anastomosis
[36]	F/67	Right upper abdomen pain, anorexia	CT, gastrografin: Gastric fistula	Adenocarcinoma	CGF	Cholecystectomy, liver wedge resection, and gastric antrectomy including the fistula, gastroduodenal anastomosis
[37]	F/70	Abdomen pain, nausea, vomiting, weight loss	US, gastrografin: HF colon fistula	SqCC	CCF	Extended right hemicolectomy, subtotal excision of the gallbladder
[38]	F/72	Upper abdomen pain, nausea, vomiting	Gastrografin, EGD: Gallstone in duodenum	Metastatic breast carcinoma	CDF	Laparotomy with stone extraction
[39]	F/75	Abdomen pain, nausea, diarrhea, weight loss	US, gastrografin, EGD: Gallstone, gastric outlet obstruction	Adenocarcinoma	CDF	Enterostomy with stone extraction, cholecystectomy with fistula excision
[40]	M/55	Right upper abdomen pain, diarrhea, weight loss	Gastrografin, colonoscopy, EGD: duodenal fistula, transverse colon fistula	Adenocarcinoma	CDF, CCF	Radical cholecystectomy, partial gastrectomy, vagotomy, duodenectomy, proximal pancreatectomy, right hemicolectomy, resection of the proximal jejunum, anticolic antiperistaltic gastrojejunostomy (Polya), end-to-side choledochojejunostomy, ileotransverse colostomy
[41]	F/51	Right upper abdomen pain, fever, vomiting	Gastrografin: Leakage from the duodenum	Adenocarcinoma	CDF, CCF	Diagnostic laparotomy, palliative treatment
[41]	M/63	Right upper abdomen pain, melena	None	Adenocarcinoma	CCF	Palliative treatment
Our case	M/57	Abdomen pain, vomiting, diarrhea	CT, EGD, colonoscopy, gastrografin, MRCP: GBC, gallstone, duodenal fistula, transverse colon fistula	Adenocarcinoma	CDF, CCF	Roux-en-Y gastrojejunostomy, loop ileostomy

M: Male; F: Female; GBC: Gallbladder cancer; CEF: Cholecystoenteric fistula; CT: Computed tomography; HF: Hepatic flexure; CCF: Cholecystocolonic fistula; EGD: Esophagogastroduodenoscopy; CDF: Cholecystoduodenal fistula; MRI: Magnetic resonance imaging; SqCC: Squamous cell carcinoma; ERCP: Endoscopic retrograde cholangiopancreatography; RFA: Radiofrequency ablation; PET: Positron emission tomography; SGCC: Spindle and giant cell type undifferentiated carcinoma; PTC: Percutaneous transhepatic cholangiography; US: Ultrasonography; CGF: Cholecystogastric fistula; MRCP: Magnetic resonance cholangiopancreatography.

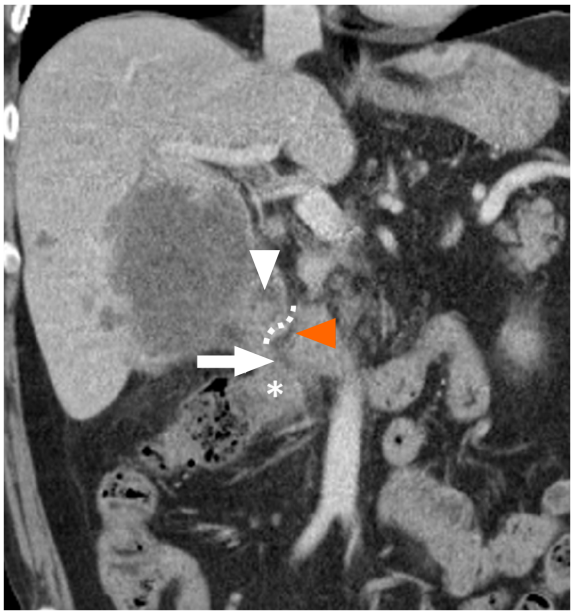

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Figure 1 Abdominopelvic computed tomography. Coronal contrast-enhanced abdominal computed tomography reveals a contracted gallbladder (white arrowhead) in close contact with the second portion of the duodenum (orange arrowhead), with a compromised fat plane between these two structures (white dotted line). A soft-tissue density (white arrow) connects the contracted gallbladder and transverse colon (asterisk).

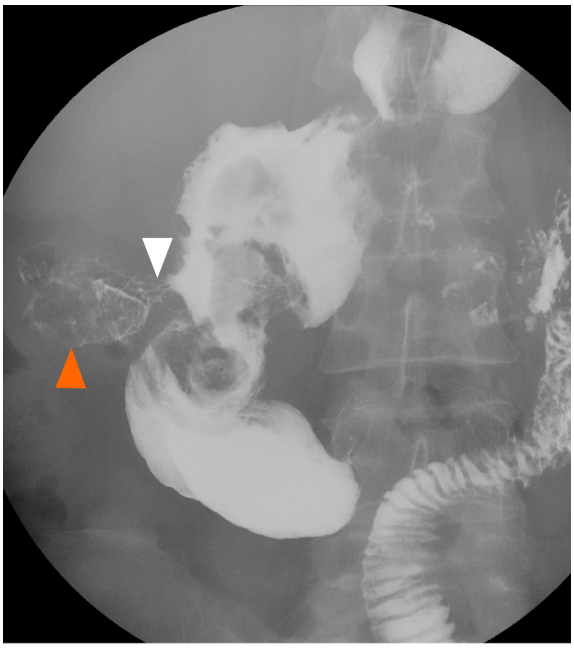

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Figure 2 Barium upper gastrointestinal series. The examination reveals a contrast-filling sac-like structure in the right lower quadrant of the abdomen (orange arrowhead) connected to the second portion of the duodenum (white arrowhead).

noscopy, abdominopelvic CT, MRCP, and endoscopic retrograde cholangiopancreatography, have been used to diagnose CEF[2,4,9]. In most cases, the fistulous tract lesion was detectable in imaging studies (75%; Table 1). In our case, abdominopelvic CT suggested the presence of CCF; however, a colonoscopy could not confirm it. CDF was suspected *via* EGD and confirmed by the UGI series and MRCP. The diagnosis of synchronous CDF and CCF was ultimately esta-blished during laparotomy. Advances in imaging technology have improved our ability to detect CEF, and combining various imaging techniques can improve the likelihood of an accurate preoperative diagnosis.

Conventional surgery for CEF involves cholecystectomy and fistula closure, performed as an open or laparoscopic procedure based on the surgeon's experience and the patient's condition[2,5,9,11,13]. However, few cases are suitable for resection, and palliative chemotherapy with gemcitabine and cisplatin is the current standard of care for patients with advanced-stage GBC[1,14]. Therefore, surgical closure of fistulas, stent placement therapy, and bypass surgery may be

considered. Our patient underwent an exploratory laparotomy for palliative purposes. Further palliative treatment, such as chemotherapy, radiation therapy, or targeted therapy, is indicated. Due to the failure of previous standard chemotherapy and malnutrition, our patient received lenvatinib as an oral targeted therapy.

CONCLUSION

Clinicians should consider CEF in patients with GBC who present with persistent vomiting or diarrhea. Use of multiple imaging modalities can increase the likelihood of detecting CEF before surgery. Despite its grim prognosis and 5-year survival rate of < 5%, surgery remains a viable option for alleviating GBC symptoms and enhancing quality of life.

FOOTNOTES

Author contributions: Wang CY contributed to manuscript writing, editing, and data collection; Chiu SH and Chang WC prepared the figures; Ho MH completed the surgery; Chang PY were responsible for manuscript modification; 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: 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: Taiwan

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S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

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World Journal of Clinical Cases

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World J Clin Cases 2023 December 26; 11(36): 8527-8534

DOI: 10.12998/wjcc.v11.i36.8527

ISSN 2307-8960 (online)

CASE REPORT

Intraperitoneal hyaline vascular Castleman disease: Three case reports

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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): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Khalil G

Received: September 1, 2023
Peer-review started: September 1, 2023
First decision: November 16, 2023
Revised: November 27, 2023
Accepted: December 13, 2023
Article in press: December 13, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Castleman disease (CD) was first reported in 1954. It is a rare non-malignant lymphoproliferative disease with unclear etiology. As the clinical manifestations of CD are different, there are difficulties in its diagnosis and treatment. Therefore, for patients with CD, it is important to establish the diagnosis in order to choose the appropriate treatment.

CASE SUMMARY

In this report, three patients with intraperitoneal CD treated at our center from January 2018 to June 2023 were reviewed, and the clinical and paraclinical examinations, diagnosis, and treatment were analyzed, and all three patients were diagnosed with CD by routine histopathological and immunohistochemical examinations.

CONCLUSION

CD is a complex and rare disease. Because there are no special clinical symptoms and laboratory abnormalities, the diagnosis often depends on routine pathological and immunohistochemical findings.

Key Words: Castleman disease; Intraperitoneal mass; Lymph node; Case report

Core Tip: Castleman disease (CD) is a rare and complex disease. As the clinical signs and laboratory results are not specific, clinical diagnosis is difficult, which often depends on imaging and pathology examinations. This report summarizes the diagnosis and treatment of three cases of CD and reviews the related literature to explore the diagnosis and treatment of CD in order to improve the clinical management of this disease.

Citation: Gao JW, Shi ZY, Zhu ZB, Xu XR, Chen W. Intraperitoneal hyaline vascular Castleman disease: Three case reports. *World J Clin Cases* 2023; 11(36): 8527-8534
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8527.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8527

INTRODUCTION

Castleman disease (CD) is a group of rare disorders with characteristic histopathological features. Monocentric CD is a benign localized lymphoproliferative disease, which was first reported in 1954 and described as mediastinal localized lymphoproliferative disease[1]. The clinical subtypes of CD include monocentric type and multicentric type, and histological subtypes include hyaline vascular, plasma cell, and mixed types[2,3]. Overall, monocentric CD has a good prognosis, requiring only local surgical resection and no additional treatment. Patients usually survive without recurrence following treatment. However, at present, there is still no standard treatment for multicentric CD due to its potential invasiveness. Multicentric CD has a poor prognosis, and some lesions may develop into malignant tumors[4]. Comprehensive treatment includes monoclonal antibody immunotherapy, and combination of radiotherapy and chemotherapy. Due to its rich blood supply, anti-angiogenic drugs also play an important role in treatment.

CASE PRESENTATION

Chief complaints

Case 1: A 37-year-old man was admitted to hospital due to "a mass in the pancreas found 1 wk ago".

Case 2: A 38-year-old woman was admitted to hospital due to "an abdominal mass found for 1 mo".

Case 3: A 71-year-old woman was admitted to hospital due to "a gallbladder mass found 2 mo ago".

History of present illness

During the course of the disease, all patients had no paroxysmal palpitations, headache, or other positive symptoms.

History of past illness

Case 1 and Case 2: The patients had no previous history of hypertension or other chronic diseases, and had no obvious abnormal tumor markers after admission.

Case 3: Blood pressure control was satisfactory, and the patient had a history of hypertension for > 3 years.

Personal and family history

None of the three patients had personal or family history of the disease.

Physical examination

Cardiopulmonary and abdominal examinations of all three patients showed no abnormalities and no positive signs.

Laboratory examinations

Case 1: Endocrine tests showed the following: The adrenocorticotropin-cortisol rhythm was normal, the renin-angiotensin II-aldosterone test in the recumbent position and 24-h urinary aldosterone were normal. Blood 3-methoxynorepinephrine, blood 3-methoxyepinephrine, and 24-h urine catecholamine and vanillymandelic acid were normal, and there was no evidence of cor pulmonale, primary aldosteronism, or pheochromocytoma. The human immunodeficiency virus (HIV) test was negative.

Case 2: There were no obvious abnormalities in hemoglobin (77 g/L), routine biochemical and urine testing, blood coagulation function, tumor markers, and HIV testing.

Case 3: Laboratory examinations showed that there were no obvious abnormalities in routine biochemical, blood, and urine tests, and tumor markers were normal. Endocrine tests showed the following: The adrenocorticotropin-cortisol rhythm was normal, the renin-angiotensin II-aldosterone test in the decubitus position showed no abnormalities, and HIV testing was negative.

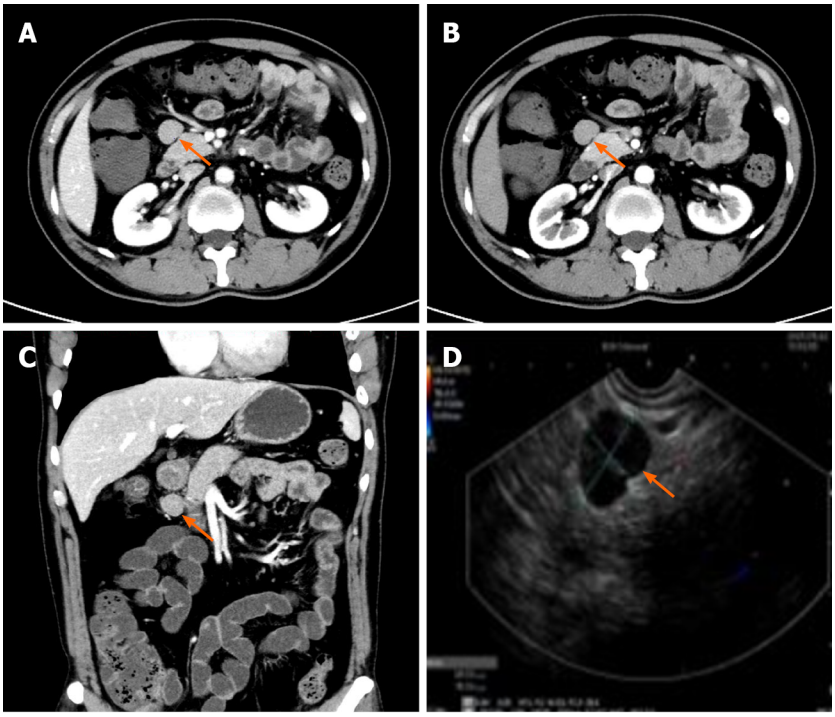

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Figure 1 Abdominal computed tomography showed a soft tissue occupying focus in front of the pancreas in Case 1. The lesion had a quasi-round soft tissue density, the edge was smooth, and the enhanced scan showed obvious uniform and continuous enhancement. A: Venous phase; B: Arterial phase; C: Coronal imaging; D: Ultrasonic gastroscopic image.

Imaging examinations

Case 1: A contrast-enhanced computed tomography (CT) scan showed a soft tissue lesion in front of the pancreas with a quasi-circular density, and a diameter of approximately 22 mm, smooth edges, and obvious uniform and continuous enhancement. Similar nodules were seen at the edge of the mass, and there were also several small abdominal lymph nodes with an average diameter of 5 mm. Giant lymph node hyperplasia/ectopic pancreas was considered. In order to further confirm the diagnosis, a painless ultrasonic gastroscopic biopsy was performed. A linear 7.5 MHz ultrasonic gastroscope was used to explore the gastric cavity and duodenum. During the procedure, enlarged lymph nodes above the head of the pancreas were seen, showing a triangular shape, hilar structure could be seen inside, and no obvious blood flow signal was seen in the periphery of the lymph nodes. One cross-section was approximately 20 mm × 15 mm, the lymphatic edge was sharp, showing uniform hypoechoic changes, and 3 Lymph nodes were punctured (Figure 1).

Case 2: Before admission, a head and chest plain CT scan revealed a low density focus in the left lobe of the liver, and the patient was admitted to the hospital for further examination. Enhanced CT suggested multiple masses in the abdominal and pelvic cavities, the largest mass was found in the pelvic cavity which had a clear boundary and irregular shape, and a small nodular calcification was seen around the focus. Moderate enhancement was seen, the enhancement pattern of other abnormal soft tissue nodules was similar, and the possibility of stromal tumor was considered (Figure 2).

Case 3: The patient underwent B-ultrasound examination more than 2 mo previously, which indicated gallbladder enlargement and thickening of the gallbladder wall. Enhanced magnetic resonance imaging of the upper abdomen was performed, which indicated an abnormal signal focus in the lower part of the pancreas that was circular, approximately 25 mm × 24 mm in size, the edge was smooth and the boundary was clear, and the possibility of giant lymph node hyperplasia was considered. Cholecystitis and thickening of the gallbladder wall did not exclude the possibility of malignancy. The patient was then admitted to hospital to complete the preoperative examination. Enhanced CT indicated a round soft-tissue density focus below the pancreas, with obvious enhancement in the arterial phase and slightly decreased enhancement in the venous phase and delayed phase, with a length of approximately 25 mm. The possibility of giant lymph node hyperplasia was considered and as the gallbladder wall was not uniformly thickened, the possibility of local malignancy was also considered (Figure 3).

FINAL DIAGNOSIS

Case 1: Routine postoperative pathology showed that a large number of small round cells were stretched and lymphoproliferative lesions were considered. Immunohistochemical diagnosis showed hyaline vascular CD due to the presence of AE1/AE3 (-), CD10 (-), CD20 (+), CD3 (+), CD45R0 (+), CD79 α (+), LCA (+), Ki-67 (+, 15%), CD5 (+), and Bc1-2 (+)

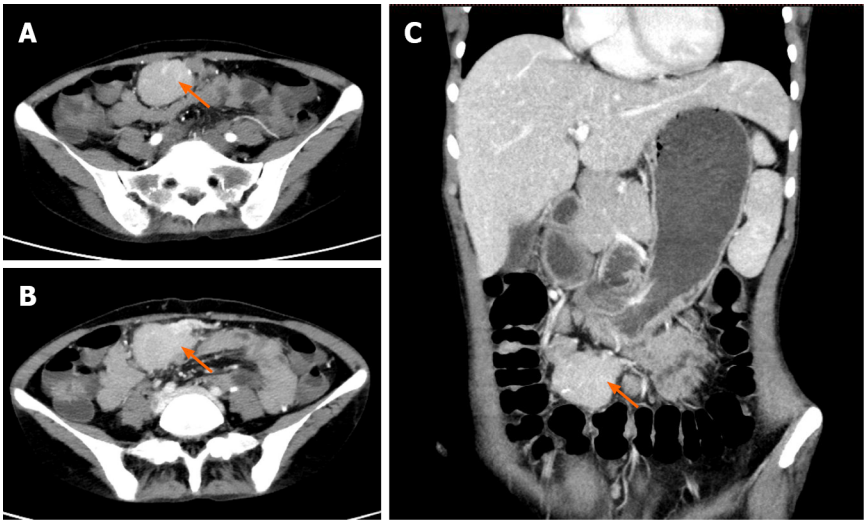

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Figure 2 A mass of approximately 50 mm × 38 mm × 36 mm can be seen in the pelvic cavity in Case 2. The boundary is clear and the shape is irregular. Small nodular calcification can be seen around the focus, and moderate enhancement was seen on the enhanced scan. A: Arterial phase; B: Venous phase; C: Coronal imaging.

(Figure 4).

Case 2: Following excision of the mass, rapid pathology suggested lymphoproliferative lesions. A postoperative pathological diagnosis of hyaline vascular CD was made due to the presence of CD20 (+), CD3 (+), CD21 (follicular dendritic +), CD23 (follicular dendritic +), CD5 (+), CyclinD1 (-), Bcl-2 (germinal center -), Bcl-6 (germinal center +), Ki67 (+, about 40%), CD10 (-), MuM1(-), Pax-5 (+), CD30 (-), ALK (-), and CD4 (+) (Figure 5).

Case 3: Following excision of the mass, rapid pathology indicated lymphoproliferative lesions. Postoperative pathology showed hyaline vascular CD. Immunohistochemical results were as follows: CK20 (+), Pax5 (+), CD3 (+), CD5 (+), CD21 (germinal center +), CD15 (-), CD30 (-), EMA (-), CD10 (germinal center +), Bcl-6 (germinal center +), MuM1 (-), EBER-ISH (-), and Bcl-2 (-) (Figure 6).

TREATMENT

Case 1

Conservative treatment was provided following communication with the patient.

Case 2

Exploratory laparotomy was performed after preoperative preparation, and a mass in the greater omentum on the greater curvature of the stomach was found, which was approximately 5 cm × 4 cm in size.

Case 3

Radical resection of gallbladder cancer and excision of the abdominal lesion were performed. During the operation, a mass of approximately 3 cm in size was found in the lower part of the pancreas, which was closely adhered to the lower margin of the pancreas. The anatomical mass was completely separated using an ultrasonic knife.

OUTCOME AND FOLLOW-UP

Case 1

The patient's condition was stable and there was no obvious disease progression during the 2-year follow-up.

Case 2

The patient's condition was stable and there was no obvious disease progression during the 2-year follow-up.

Case 3

After the operation, anti-inflammatory, stomach protection, and other symptomatic support was provided, and the patient recovered well and was subsequently discharged. CT reexamination 2 mo after surgery showed no signs of

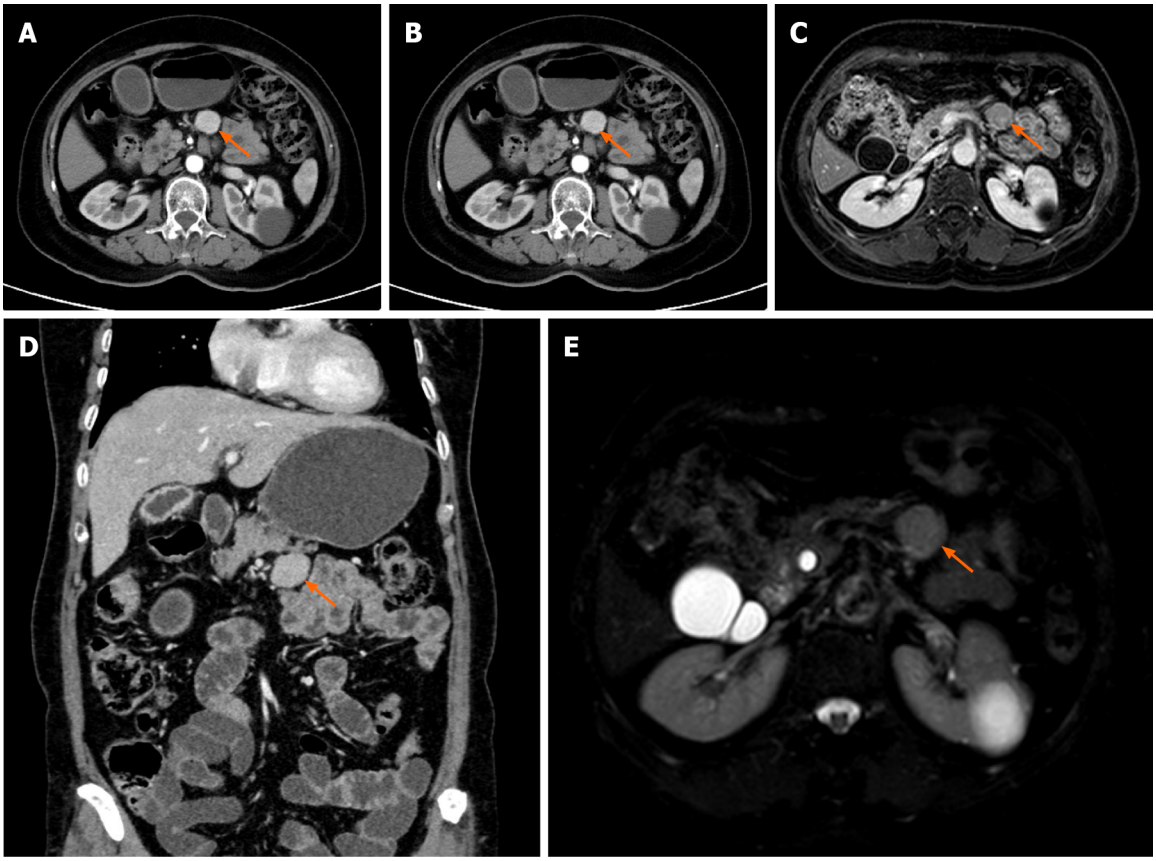

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Figure 3 The density focus of quasi-circular soft tissue below the body of the pancreas in Case 3. The lesion shows obvious enhancement in the arterial phase and a slight decrease in the venous phase and delayed phase, with a diameter of approximately 25 mm, smooth edge, and clear boundary. A: Arterial phase; B: Venous phase; C: Delayed phase; D: Coronal imaging; E: T2W imaging.

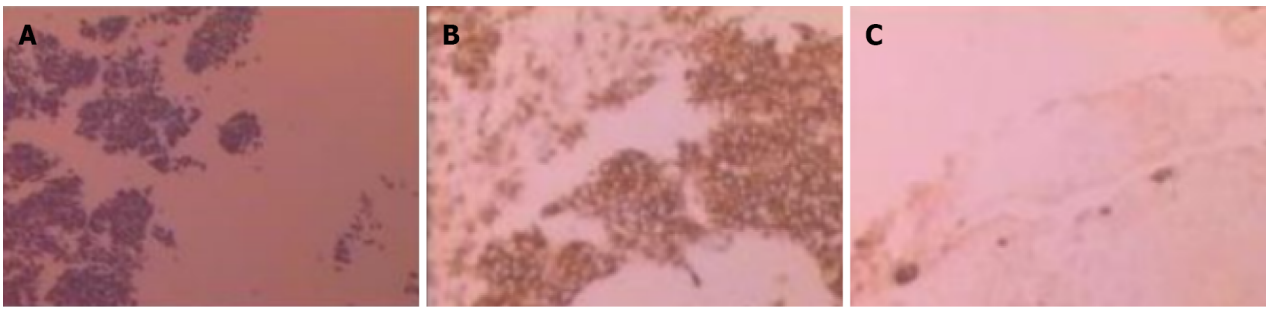

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Figure 4 Immunohistochemical diagnosis of hyaline vascular Castleman disease in Case 1. The results were as follows: AE1/AE3 (-), CD10 (-), CD20 (+), CD3 (+), CD45R0 (+), CD79 α (+), LCA (+), Ki-67 (+ 15%), CD5 (+), and Bc1-2 (+). A: HE staining; B: Immunohistochemical staining for CD20; C: Immunohistochemical staining for CD10.

recurrence.

DISCUSSION

CD is a rare lymphoproliferative disease characterized by the proliferation and enlargement of lymphoid tissue[5]. The most common site of CD is the mediastinum, accounting for approximately 70% of all CD patients, while the occurrence of CD in the abdomen is uncommon, and only a few cases have been reported[6]. The exact cause of the disease is unknown, but some studies have suggested that it is related to HIV and human herpes virus-8.

CD can be divided into monocentric and multicentric subtypes, and the different types of CD are characterized by significant lymphatic architecture changes in all lymph node septa. Monocentric type includes hyaline vascular type and

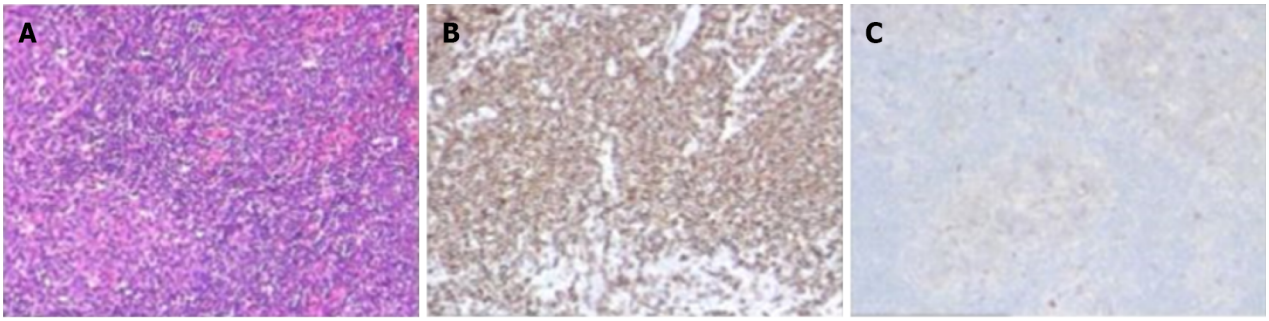

Figure 5 Pathological diagnosis was hyaline vascular Castleman disease in Case 2. Immunohistochemical results showed CD20 (+), CD3 (+), CD21 (follicular dendritic +), CD23 (follicular dendritic +), CD5 (+), CyclinD1(-), Bcl-2 (germinal center -), Bcl-6 (germinal center +), Ki67 (+, about 40%), CD10 (-), Mul1 (-), Pax-5 (+), CD30 (-), ALK (-), and CD4 (+). A: HE staining; B: Immunohistochemical staining for CD20; C: Immunohistochemical staining for CD10.

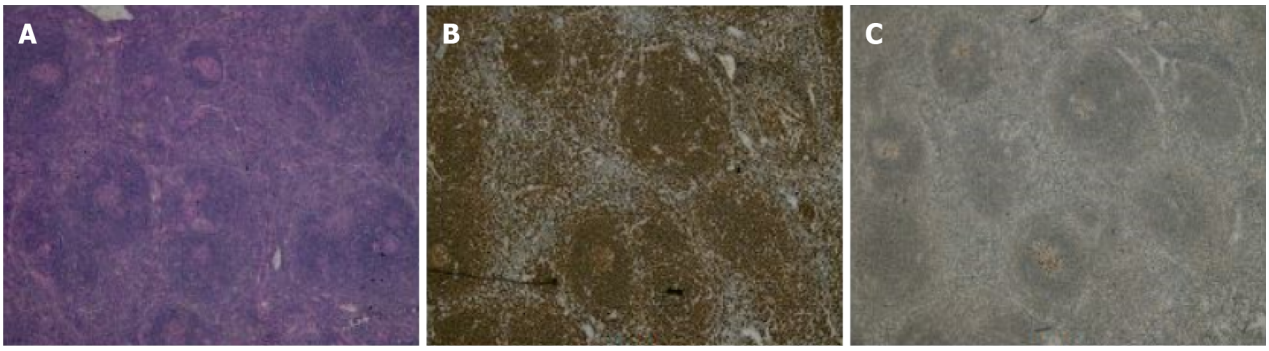

Figure 6 Pathology suggested hyaline vascular Castleman disease in Case 3. The immunohistochemical results were CK20 (+), Pax5 (+), CD3 (+), CD5 (+), CD21 (germinal center +), CD15 (-), CD30 (-), EMA (-), CD10 (germinal center +), Bcl-6 (germinal center +), MuM1 (-), EBER-ISH (-), and Bcl-2 (-). A: HE staining; B: Immunohistochemical staining for CD20; C: Immunohistochemical staining for Bcl-6.

plasma cell type. Multicentric CD is mainly characterized by plasma cell variants, with a few cases showing mixed type. In this report, all three patients underwent routine pathological and immunohistochemical examinations, and all showed hyaline vascular type CD. Hyaline vascular CD presents as an affected lymphoid follicle with an enlarged outer layer of concentric rings of small lymphocytes that surround a small germinal center of atrophy or degenerative transformation. Germinal centers usually have penetrating transparent small blood vessels and protruding follicular dendritic cells that may be dilated, destroyed, or have multiple tight connections[7].

In contrast, the germinal center of plasma cell CD is proliferative rather than degenerative, and the interfollicular region of the lymph nodes is vascularized and contains plasma cell sheets with polyclonal characteristics. However, these histopathological findings are not specific to CD and diseases that may cause similar changes in proliferative reactive lymph nodes, such as rheumatoid arthritis and viral lymphadenitis, need to be ruled out[8].

The diagnosis of CD mainly depends on histological examination by excision or puncture of the swollen lymph nodes, and radiological examination, the most common of which is whole-body CT or CT-18F-fluorodeoxyglucose positron emission tomography examination. Currently, monocentric CD is considered a soft tissue mass with clear and regular edges, uniform density, and speckle calcification, or accompanied by bleeding and necrosis on CT[9]. On an enhanced scan, the mass shows enhancement in the arterial phase, with continued enhancement in the venous phase and delayed phase. On CT, multicentric CD usually presents as multiple round and low-density masses of similar size, most of which have uniform enhancement, and partial irregular enhancement may occur if the lesion is large[10]. However, the imaging features of CD are difficult to distinguish from other diseases such as neuroendocrine tumors or lymphomas, such as neurogenic tumors, lymph node metastases, and gastrointestinal stromal tumors. In many cases, the preoperative imaging diagnosis is inconsistent with the postoperative histopathological diagnosis. In the current report, it was found that there were indeed difficulties in preoperative diagnosis. A patient was considered to have a stromal tumor after completing preoperative examination. The diagnosis could only be made after the mass was removed intraoperatively and rapid pathology was obtained, and corresponding surgical methods were selected to avoid unreasonable extensive resection. Surgical removal of monocentric CD is currently the gold standard of treatment, and we report two surgical patients with no signs of recurrence. In other reports, long-term follow-up of patients also showed that monocentric CD was cured after surgical resection, and there was no recurrence during the follow-up period of up to 20 years[11]. Recurrence after complete resection was rare, and paraneoplastic complications, such as AA amyloidosis, were usually gradually relieved after complete resection. In unresectable monocentric CD, if no adjacent structures are threatened by

compression, the patient can be followed up regularly without intervention, as lesion growth may be very slow. If symptoms develop, rituximab with or without steroids may be considered to reduce the size of the lesion. For patients with a reduced mass after treatment, surgical resection is recommended if complete resection is feasible. For patients who cannot undergo complete surgical resection of the lesion after medication, radiotherapy or arterial embolization can be considered[12]. Multicentric CD is rare and has a poor prognosis. It is usually treated with glucocorticoids combined with chemoradiotherapy. At present, there are no clear guidelines for the treatment of CD. Many drugs have been tried, such as monoclonal immunotherapy against IL-6[13], antiviral drugs used in relation to HIV infection[14], and related chemotherapeutic drugs (such as doxorubicin, vincristine, cyclophosphamide, melphalan, and chloramphenicol)[15,16], and even some new targeted drugs have achieved satisfying results in some clinical applications due to their anti-angiogenic effects[17]. However, there is limited clinical practice experience, comprehensive treatment should be given to suitable patients, and it is necessary to closely observe patients after medication.

CONCLUSION

CD is a complex and rare disease, and a standard treatment is still lacking. For clinicians, it is difficult to make a clear diagnosis before surgery due to the lack of specific radiological markers. Therefore, when the diagnosis is unclear, histopathological examination is important to guide treatment. Complete resection is the gold standard for the treatment of monocentric CD, while multicentric CD requires comprehensive treatment depending on the patient's condition, but the overall prognosis is poor.

FOOTNOTES

Co-first authors: Jia-Wei Gao and Zhe-Yi Shi.

Co-corresponding authors: Xiang-Rong Xu and Wei Chen.

Author contributions: Gao JW and Shi ZY conceived, designed, and refined the study protocol; Gao JW, Shi ZY, Zhu ZB, and Xu XR were involved in the data collection; Gao JW and Shi ZY analyzed the data; Gao JW, Shi ZY, Xu XR, and Chen W drafted the manuscript; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Gao JW and Shi ZY contributed equally to this work as co-first authors. Xu XR and Chen W contributed equally to this work as co-corresponding authors. The reasons for designating Gao JW and Shi ZY as co-first authors, and Xu XR and Chen W as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-first authorship and co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-first authors and co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Gao JW and Shi ZY, and Xu XR and Chen W contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors or co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Gao JW and Shi ZY as co-first authors, and Xu XR and Chen W as co-corresponding authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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

Conflict-of-interest statement: The authors declare that they have no conflicts of interest or competing interests 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: China

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S-Editor: Lin C
L-Editor: Wang TQ
P-Editor: Lin C

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World Journal of Clinical Cases

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

World J Clin Cases 2023 December 26; 11(36): 8535-8541

DOI: 10.12998/wjcc.v11.i36.8535

ISSN 2307-8960 (online)

CASE REPORT

Iris metastasis from clear cell renal cell carcinoma: 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): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mubarak M, Pakistan

Received: September 6, 2023
Peer-review started: September 6, 2023
First decision: November 1, 2023
Revised: November 14, 2023
Accepted: December 12, 2023
Article in press: December 12, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Clear cell renal cell carcinoma (ccRCC) is a common type of tumor that can metastasize to any organs and sites. However, it is extremely rare for ccRCC to metastasize to the iris. Here, we describe a rare case of iris metastasis from ccRCC with a history of left nephrectomy in 2010.

CASE SUMMARY

A 62-year-old male was admitted to the hospital due to blurred vision and red eyes, and a mass was found on the iris in the right eye. B-scan ultrasonography revealed a well-bounded high-density lesion at the corner of the anterior chamber at the 3-4 o'clock position. Phacoemulsification with simultaneous intraocular lens implantation and iridocyclectomy was performed in the right eye. The lesion was confirmed to be metastatic ccRCC by histological and immunohistochemical analyses. The patient was still alive at 9 mo after surgical treatment. Ocular metastasis can be an initial sign with a poor prognosis. Timely detection and treatment may improve survival. Clinicians should pay attention to similar metastatic diseases to prevent misdiagnosis leading to missed treatment opportunities.

CONCLUSION

This report of the characteristics and successful management of a rare case of iris metastasis from ccRCC highlights the importance of a comprehensive medical history, histopathology, immunohistochemistry, and clinical manifestation for successful disease diagnosis.

Key Words: Iris metastasis; Clear cell renal cell carcinoma; Diagnosis; Prognosis; Literature review; Case report

Core Tip: Here, we report a rare case of iris metastasis from clear cell renal cell carcinoma. We found that a complete medical history, histopathology, and immunohistochemistry combined with clinical manifestations are crucial for the successful diagnosis of this disease. In addition, a total of 11 cases of iris metastasis from renal tumors were identified in the literature and are reviewed in this report.

Citation: Wang TT, Chen XY, Min QY, Han YZ, Zhao HF. Iris metastasis from clear cell renal cell carcinoma: A case report. *World J Clin Cases* 2023; 11(36): 8535-8541
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8535.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8535

INTRODUCTION

Renal cell carcinoma (RCC) is the most common type of renal tumor (approximately 90%), and clear cell RCC (ccRCC) is the most common subtype of RCC, accounting for approximately 75% of cases. More than 50% of patients with ccRCC are asymptomatic and rely on computed tomography (CT) for diagnosis[1]. While up to half of ccRCCs are confined to the kidney at presentation, approximately 30% develop metastases[2]. CcRCC can metastasize to any organs and sites including the eyes, but the most common sites of metastases are lung (50%) and bone (33%)[3]. It is very unusual for ccRCC to metastasize to the iris.

The iris is a rare location for cancer to metastasize and spread, and most instances occur with breast and lung cancers [4]. Iris metastasis is usually unilateral and unifocal; bilateral and multifocal involvement are considerably less common. Due to its rarity, iris metastasis is often misdiagnosed. In patients with iris lesions and a history of RCC, the possibility of kidney cancer metastasis should be considered. The clinician should perform an iridocyclectomy promptly and confirm the diagnosis by pathology.

In this article, we report a 62-year-old male who was diagnosed with iris metastasis from ccRCC. We hope this case will raise awareness of this rare disease, as clinical suspicion of this condition will lead to early diagnosis and treatment.

CASE PRESENTATION

Chief complaints

A 62-year-old male was admitted to the hospital due to the discovery of a mass in his right eye 1 mo prior with no history of eye disease.

History of present illness

The patient had a medical history of blurred vision and red eyes.

History of past illness

A previous left nephrectomy with the diagnosis of ccRCC [World Health Organisation/International Society of Urological Pathology (WHO/ISUP) nuclear grading was not mentioned].

Personal and family history

The patient denied any family medical history.

Physical examination

The visual acuity of the left eye was 0.6 and that of the right eye was 0.4. The conjunctiva of the right eye was slightly congested, and the vessels of the nasal conjunctiva were tortuous and dilated. The cornea was clear. A keratic precipitate was visible behind the cornea and a red mass with a diameter of approximately 5 mm was visible at 2-5 o'clock in the front of the cornea. The depth of the anterior chamber was moderate. The iris texture was not clear and was partially posterior synechiae. The pupil was round, but slow to light reflex. Pigment was seen in the precrystalline capsule. There was no obvious abnormality in the left eye except the phacoscotasmus. The intraocular pressure was 14 mmHg in the left eye and 21 mmHg in the right eye.

Laboratory examinations

Complete blood counts, aspartate aminotransferase, alkaline phosphatase, bilirubin, serum electrolytes, creatinine, and urea were all within normal ranges.

Imaging examinations

B-scan ultrasonography revealed that the central depth of the anterior chamber was approximately 3.14 mm and a well-bounded high-density lesion could be seen at the corner of the anterior chamber at 3-4 o'clock (Figure 1). Chest CT showed a lobulated uneven enhanced mass at the anterior basal segment of the lower lobe of the right lung, with clear boundaries and small streaks at the margin, indicating the high possibility of malignancy. Abdominal CT showed that the left kidney was absent and there was no obvious mass in the right kidney.

Pathological examination

The mass was received in several small pieces with a total diameter of 1 cm. Histologically, normal iris tissue could be seen around the tumor (Figure 2A). There was no fibrous envelope separation between the tumor and iris tissue. The tumor cells were large, cube-shaped, and in a solid nest-like arrangement. The cytoplasm was clear because it contained a lot of glycogen and lipids. The nuclei were round or ovate, and the nucleoli were visible (hematoxylin and eosin staining, 400 ×) (Figure 2B). There were abundant capillaries in the mesenchyme. Tumor cells were immunoreactive for cytokeratin pan (Figure 2C), vimentin, paired box gene 8 (Figure 2D), cluster of differentiation 10 (CD10) (Figure 2E), and carbonic anhydrase IX, but were negative for cytokeratin 7, CD117, CK20, and thyroid transcription factor-1. The Ki-67 proliferation index was 10%.

FINAL DIAGNOSIS

The lesion was confirmed to be metastatic ccRCC (WHO/ISUP nuclear grade 2).

TREATMENT

To restore the patient's vision and make a clear diagnosis, phacoemulsification with simultaneous intraocular lens implantation and iridocyclectomy was performed after the clinician assessed the patient's condition in the right eye. During the operation, a lesion about the size of a peanut could be clearly seen on the surface of the iris. The lesion was confirmed to be metastatic ccRCC. After the diagnosis was confirmed, the patient refused targeted drug therapy and transbronchial lung biopsy (TBLB) and discharged himself from the hospital against the advice of doctors.

OUTCOME AND FOLLOW-UP

The patient was still alive, with no recurrence noted at 9 mo post-surgery.

DISCUSSION

RCC includes many subtypes, with the predominant ones being ccRCC, papillary renal tumors, and chromophobe renal tumors[5]. Of these three subtypes, ccRCC is the most common and has the worst prognosis because it is usually found at an advanced stage[4]. CcRCC may have no specific symptoms in the early stage, whereas symptoms such as hematuresis may appear in the advanced stage. However, a diagnosis cannot be made only by urine examination and should be assisted by imaging examination. More than 90% of kidney tumors can be detected by CT and such imaging can distinguish between benign or malignant tumors, as well as their relationship to surrounding tissue[1].

The preferred treatment for any nonmetastatic, solid, or Bosniak III or IV complex cystic kidney mass is surgical excision, preferably using a minimally invasive approach[1]. After local nephrectomy, tumors often recur near the surgical scar, and approximately 30% of nonmetastatic kidney tumors will metastasize to other organs after surgery[6]. Metastasis of RCC is hematogenous and lymphatic. The lung is the most common location of distant metastasis, followed by the bone and liver. Ocular metastasis is rare, and iris metastasis has only been recorded in a few cases[3,4,6-8]. Both primary and metastatic renal tumors have von Hippel-Lindau (VHL) mutations, while primary tumors also have the telomerase reverse transcriptase (TERT) promoter C228T mutation, but abnormal deletion of TERT appears in metastatic tumors[2]. The absence of TERT abnormality in metastasis supports the notion that an aberrant VHL protein is sufficient to confer metastatic capacity in ccRCC, as proposed in tumors with low-grade histology. Metastasis of ccRCC to the iris may originate from low-grade clones in high-grade primary tumors[2].

Iris metastasis is extremely rare. In previous reports, the most common site of uveal metastases is the choroid, followed by the iris and ciliary body. This may be due to the posterior ciliary artery supplying a large amount of blood to the posterior choroid. Iris metastasis accounts for 7.8% of uveal metastasis[8]. The most common primary tumors with iris metastasis are breast cancer in women and lung cancer in men[3]. In addition, iris metastasis can also occur with esophageal squamous cell carcinoma[9], prostate carcinoma[10], kidney cancer[1-4,6,7], gastrointestinal malignancies[9], sarcoma and melanoma[11]. Nephrogenic iris metastasis accounts for < 1% of ocular metastasis and < 5% of iris metastasis[12]. After diagnosis of uveal metastatic cancer, more than half of patients have associated systemic metastasis, with the lungs being the most common site, followed by bones, liver, and central nervous system[2]. Our patient had

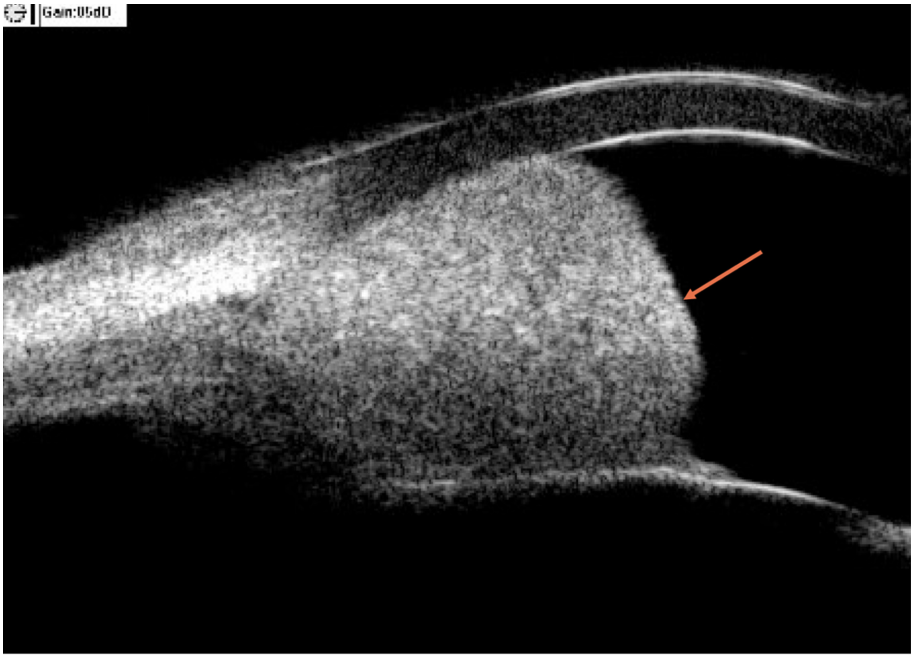

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Figure 1 Eye ultrasound image. A well-bounded, high-density lesion was observed at the corner of the anterior chamber at the 3 o'clock position.

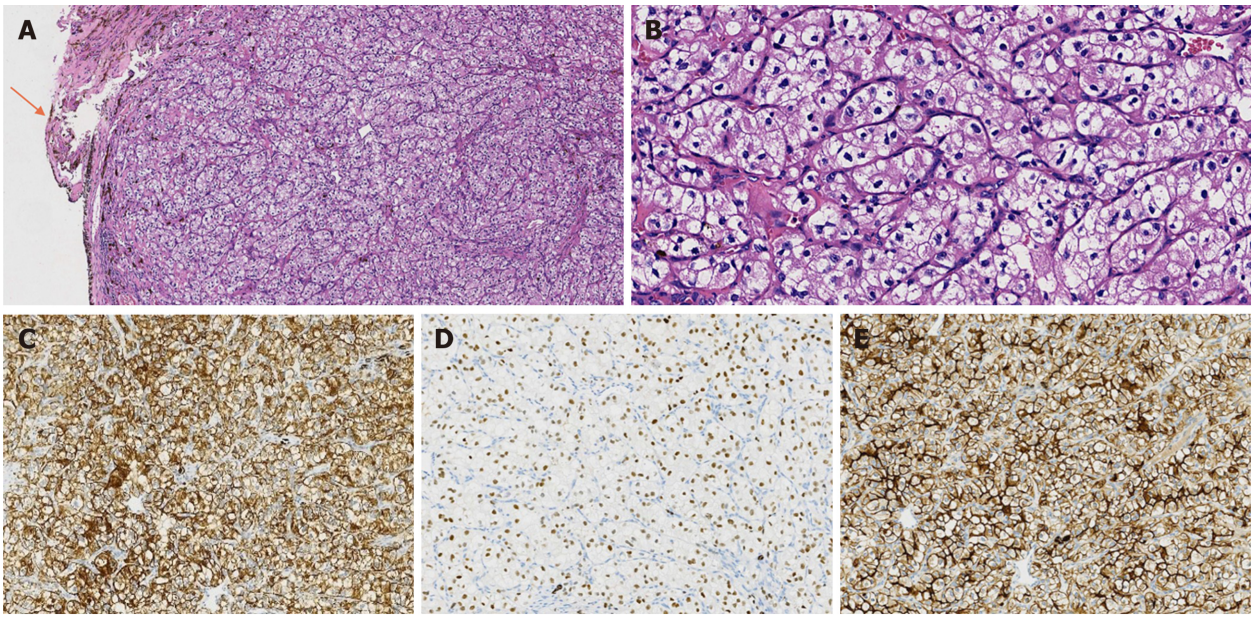

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Figure 2 Hematoxylin and eosin staining and immunohistochemical staining of the Iris mass. A: Normal iris tissue was observed around the tumor (100 ×); B: The tumor cells were large, cube-shaped, and in a solid nest-like arrangement and the nuclei were round or ovate with visible nucleoli (400 ×); C-E: The tumor cells were immunoreactive for cytokeratin pan (200 ×) (C), paired box gene 8 (200 ×) (D), and cluster of differentiation 10 (200 ×) (E).

suspected lung metastasis, but the patient refused TBLB, and we were unable to make a definitive diagnosis.

In the domestic and international literature, we found only 12 cases of iris metastasis from renal tumors, including our report (Table 1). This further confirms the rarity of nephrogenic iris metastases. The 12 patients were all male, aged between 54-years-old and 70-years-old. There were eight cases of blurred vision and decreased vision. The iris masses were 2-10 mm in size. Among them, 8 cases had ccRCC as the primary tumor and 1 case had renal adenocarcinoma. The time from diagnosis of RCC, ccRCC, or renal adenocarcinoma to metastasis to the iris ranged from 1 mo to 13 years, and 4 cases were detected by iris metastasis as the first manifestation. There were 4 cases of ipsilateral metastasis and five cases of contralateral metastasis, and only one case of bilateral iris metastasis. There were 3 cases that only metastasized to the iris, compared with 5 cases that simultaneously metastasized to the iris and lungs and 7 cases with metastasis to other organs. Four patients died between 2 and 9 mo after the diagnosis of iris metastasis due to multiple site metastasis or cerebral infarction. Only 5 patients remained alive during the follow-up (6-18 mo).

Table 1 Metastasis to the iris from renal cell carcinoma: Summarized data

Ref.	Sex	Age in year	Presenting symptoms	Tumor size	Type of RCC	Time to detection of iris metastasis after diagnosis of primary RCC	Simultaneous lung metastasis	Other metastatic sites	Systemic outcome
Lopes Abath Neto *et al* [2]	Male	56	Painless blurred vision in right eye	3.5 mm × 2.2 mm	ccRCC (right)	Iris metastasis is the first manifestation	NA	Nothing	Alive
Ware *et al* [3]	Male	70	Iris mass in left eye	3 mm × 2 mm	RCC (left)	Iris metastasis is the first manifestation	NA	Conjunctiva	NA
Shome *et al* [4]	Male	67	Progressive painless vision loss in left eye for 3 mo	2.8 mm × 1.5 mm	ccRCC (right)	14 mo	Yes	Bone, lymph node	Alive
Ikeda *et al* [7]	Male	55	Decreased vision in the right eye	8 mm × 4 mm	ccRCC (right)	21 mo	Yes	Brain, liver, bone, lymph nodes	Deceased
Marie-Louise *et al* [12]	Male	NA	Ocular tumor, ocular hypertension	NA	ccRCC	NA	NA	Cerebellar	Alive
Wyzinski *et al*[13]	Male	60	Sudden and painless loss of vision in right eye (bilateral mass)	2.8 mm	RCC (left)	Iris metastasis is the first manifestation	NA	Nothing	Deceased
Mello *et al* [14]	Male	61	Blurred vision and iris lesion in right eye	7 mm × 4 mm	Renal adenocarcinoma	5 yr	Yes	Cerebrum, liver	Alive
Ramskold *et al*[15]	Male	63	Pain in right eye, photophobia	8.1 mm × 5.7 mm × 4.6 mm	RCC (left)	2 yr	Yes	Mediastinum, paratracheal lymph nodes	NA
Lou and Zhang[16]	Male	54	Foreign body sensation in left eye	Mung bean size	ccRCC (left)	1 mo	Yes	Nothing	NA
Xing[17]	Male	59	Blurred vision in left eye; pain and exophthalmia in right eye	4 mm × 4 mm	ccRCC (right)	2 mo	NA	Brain, skin, rib	Deceased
Lu *et al*[18]	Male	59	Left eye secretions, foreign body sensation, red eye, swelling pain, vision loss, ipsilomatous headache, nausea, vomiting	4.5 mm × 3 mm × 1.5 mm	ccRCC (right)	Iris metastasis is the first manifestation	NA	Nothing	Deceased
This study	Male	62	Blurred vision, red eyes, mass on iris in right eye	10 mm	ccRCC (left)	13 yr	NA	Nothing	Alive

Data in the table are based on the availability of data in the original articles. ccRCC: Clear cell renal cell carcinoma; NA: Details of case not available; RCC: Renal cell carcinoma.

The main clinical manifestations of iris metastasis are blurred vision, ocular pain, redness, photophobia[8], diplopia, exophthalmos, and periorbital swelling[9]. Visual acuity is usually poor when patients develop ipsilateral choroidal metastasis associated with retinal detachment, or with severe anterior chamber tumor implantation with secondary glaucoma[7]. When tumor cells spread to the anterior chamber, secondary glaucoma can occur owing to the spread of inflammation. Metastatic tumors may manifest as stromal nodules or ill-defined iris thickening. Only 10% of the iris mass is visible, with the mass being 1-12 mm in size and isolated, fragile, yellowish-white, pink, or red[8]. The pink or red color may be due to the abundance of capillaries in the tumor.

When a patient is known to have a primary tumor and a significant iris mass, the possibility of iris metastasis from the primary tumor should be considered and a timely biopsy should be performed to make a definitive diagnosis. However, when a patient has no exact primary tumor and there is no obvious iris mass, it is easy to miss the diagnosis of iris metastasis. Slit lamp examination, fluorescein angiography, and ocular ultrasound are highly warranted. In addition, early systemic examination is crucial to determine whether there are tumors in other organs. At this time, attention should be paid to the identification of other diseases of the eyes. Differential diagnoses of nonpigmented iris masses

include iris choristoma, acquired iris cysts, unpigmented melanoma, sphincter-leiomyomas, granulomatous iridocyclitis, and xanthogranulomas[13].

When an ophthalmologist is unable to make an immediate diagnosis, slit lamp examination, fluorescein angiography, and ocular ultrasound should be performed first, even if these tests do not provide additional assistance in diagnosis. Positron emission tomography/CT can help identify benign or malignant lesions and indicate potential primary sites[9]. Ultimately, diagnostic tests for an iris mass include fine-needle aspiration biopsy and mass excision biopsy. When tumor cells are seen under the microscope, the corresponding immunohistochemistry is performed in combination with the patient's clinical symptoms, medical history, and imaging examination to obtain a final diagnosis and determine the primary tumor site.

Treatments for an iris mass include radiotherapy, laser therapy, chemotherapy, anti-vascular endothelial growth factor (VEGF), and ophthalmectomy. The current recommended treatment option is external beam radiation, which can damage the DNA of rapidly growing tumor cells and is effective in reducing the size of the lesion and improving or stabilizing visual acuity. Laser treatment-including transpupillary thermotherapy, laser photocoagulation with the use of argon or krypton, and photodynamic therapy-has significant curative effect. Chemotherapy, which uses different cytotoxic agents depending on the type of cancer, can lead to tumor shrinkage and sometimes even complete regression. VEGF-targeted treatment, such as bevacizumab, has been shown to be beneficial in patients with different types of cancers and has been used in clinical practice with significant efficacy[11]. In addition, systemic interferon therapy is effective for nephrogenic iris metastases, with a report showing that a tumor began to resolve after 3 wk of treatment and had completely resolved at 16 wk[7]. Therefore, conservative interferon therapy may be considered when a patient does not have visual loss, secondary glaucoma, or multiple organ metastasis.

CONCLUSION

Ocular metastasis is extremely rare and can be an initial sign with a poor prognosis of primary tumor. The prognosis of ocular mass is good after treatment, but systemic prognosis remains poor. The overall mean survival of iris metastasis is 20 mo and the median survival is 13 mo[8]. Timely detection and treatment may improve survival.

FOOTNOTES

Author contributions: Wang TT, Min QY, and Han YZ collected the clinical data and wrote the first draft; Chen XY and Zhao HF revised the draft; and all authors approved the final version, and agree to be accountable for the work and publish the final manuscript in this journal.

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

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

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S-Editor: Wang JJ
L-Editor: Filipodia
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 December 26; 11(36): 8542-8550

DOI: 10.12998/wjcc.v11.i36.8542

ISSN 2307-8960 (online)

CASE REPORT

Spinal cord infarction attributed to SARS-CoV-2, with post-acute sequelae of COVID-19: 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): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Masyeni S, Indonesia

Received: September 8, 2023
Peer-review started: September 8, 2023
First decision: November 9, 2023
Revised: November 29, 2023
Accepted: December 12, 2023
Article in press: December 12, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

While stroke and lower extremity venous thromboemboli have been commonly reported following acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spinal cord infarction or ischemia has been extremely rare. Findings of long coronavirus disease (COVID) in this select population have not been studied.

CASE SUMMARY

We present the case of a 70-year-old female with sudden onset of trunk and lower extremity sensorimotor loss due to spinal cord infarction, attributed to acute infection with SARS-CoV-2. Diagnostic work up confirmed a T3 complete (ASIA impairment Scale A) paraplegia resulting from a thrombotic infarct. Her reported myalgias, neuropathic pain, spasticity, bladder spasms, and urinary tract infections exceeded the frequency and severity of many spinal cord injury (SCI) individuals of similar age and degree of neurologic impairment. In her first year after contracting COVID-19, she underwent 2 separate inpatient rehabilitation courses, but also required acute hospitalization 6 additional times for subsequent infections or uncontrolled pain. Yet other complications of complete non-traumatic SCI (NTSCI), including neurogenic bowel and temperature hypersensitivity, were mild, and pressure injuries were absent. She has now transitioned from the acute to chronic phase of spinal cord injury care, with subsequent development of post-acute sequelae of SARS-CoV-2 infection (PASC).

CONCLUSION

This individual experienced significant challenges with the combined effects of acute T3 NTSCI and acute COVID-19, with subsequent progression to PASC.

Key Words: Spinal cord infarction; Paraplegia; COVID-19; SARS-CoV-2; Post-acute

sequelae of SARS-CoV-2 infection; Long COVID; Case report

Core Tip: Although stroke and venous thromboembolism have been frequently observed with acute coronavirus disease 2019 (COVID-19), spinal cord infarction leading to paraplegia has rarely been seen. We report a case of spinal cord infarction shortly following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Consequently, this individual has experienced severe neurologic disability, with subsequent development of long COVID. Symptoms such as myalgias, neuropathic pain, muscle spasms, and frequent bacterial infections are present in post-acute sequelae of SARS-CoV-2 infection (PASC), independent of spinal cord injury (SCI). Over the past 3 years, the dual presence of PASC and recent SCI may have led to increased severity of symptoms shared by both conditions.

Citation: Oleson CV, Olsen AC, Shermon S. Spinal cord infarction attributed to SARS-CoV-2, with post-acute sequelae of COVID-19: A case report. *World J Clin Cases* 2023; 11(36): 8542-8550
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8542.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8542

INTRODUCTION

Among vascular events, spinal cord infarction is relatively rare, accounting for only 0.3%-1% of all strokes[1] and 5%-8% of acute myelopathies[2]. One cause of spinal cord infarction arises from a thrombotic event in vulnerable areas of the thoracic cord, particularly between T8-12, which is supplied by the artery of Adamkiewicz. While deep vein thrombosis, pulmonary embolism, and stroke are commonly observed complications of coronavirus disease 2019 (COVID-19), spinal cord infarction is comparatively infrequent[3-6]. The cytokine release following acute infection, which peaks 7 d after contracting the virus, may be responsible for the increase in thrombotic events associated with acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[7,8].

This case discussed in this report differs from other published accounts describing spinal cord infarcts attributed to acute SARS-CoV-2, because we have followed this individual for nearly 3 years after contracting COVID-19, covering her difficulties with "long COVID," which has now officially named post-acute sequelae of SARS-CoV-2 infection (PASC) by the World Health Organization[9]. The term PASC may be assigned to "individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 mo from the onset of COVID-19 with symptoms that last for at least 2 mo and cannot be explained by an alternative diagnosis". The definition further states that PASC generally impacts everyday functioning and that symptoms may be of new onset, follow initial recovery from an acute COVID-19 episode, or persist from the initial illness. Moreover, symptoms may also fluctuate or relapse over time[9].

Common complaints of PASC include fatigue, cough shortness of breath, cognitive deficits or "brain fog". Reported features of PASC may also involve headache, heart palpitations, exercise intolerance, joint pain or swelling, myalgias, vertigo, peripheral neuropathy, altered taste or smell, disordered sleep, anxiety, depression, and thromboembolic events [10-13]. While a number of the above symptoms may occur subsequent to SCI, many would be unusual, such as persistent cough, fatigue months after SCI, changes in taste or smell, continued exercise intolerance, new onset cognitive deficits or "brain fog", unrelated to any sedating medications or concomitant brain injury.

Our patient became symptomatic prior to COVID-19 vaccine availability and has given written consent to share her story for educational publication. This project was approved by the Institutional Review Board of the MetroHealth System.

CASE PRESENTATION

Chief complaints

A 71-year-old female with a past medical history of undifferentiated connective tissue disease (UCTD) presented to an acute care hospital in December, 2020 after experiencing sudden onset of lower extremity weakness over 8-10 min, sensory loss from the lower trunk down, urinary retention, and worsening hypotension.

History of present illness

This individual had recently been exposed to COVID-19 through a household member and subsequently tested positive, with COVID cycle thresholds suggestive of recent infection. She demonstrated cough and fever before hospitalization, but did not require supplemental oxygen beyond the first few hospital days. She was issued 5 d of IV methylprednisolone and remdesivir, followed by an oral prednisone taper of 5 additional days. Neurological exam in acute care found incomplete sensory deficits T3-8 but complete absence of sensation from T9 and below.

History of past illness

During inpatient rehabilitation, we did acquire some key historical information about her UCTD, which to date had never progressed to a defined connective tissue disorder such as mixed connective tissue disease (MCTD). This condition is characterized by the presence of certain antibodies, particularly presence of the U1 small nuclear ribonucleoprotein particles (snRNP). Notes received indicate a negative titer for U1snRNP in 2020 when she had acute COVID-19, similar to her level when last tested in 2016. No lab quantification of U1-anti RNP titer was listed among lab results, other than a note stating it was not present. She had no clinical features of MCTD other than presence of sclerodactyly and stated history of Raynaud's, which was not active during rehabilitation. She had myalgias but no evidence of synovitis or myositis that would prompt us to request a muscle biopsy. At the time of her admission to rehabilitation, this individual's discomfort and spasms, as well as pain were in the middle and upper trunk and mid-back. However, during past UCTD exacerbations, she had endured aching and often sharp pain specifically in the posterior cervical spine and shoulders and during more significant attacks, pain and swelling in her fingers. Except during practice with wheelchair transfers, she reported no shoulder, arm, or hand pain with physical or occupational therapies.

Personal and family history

The possibility exists that some of the pain and spasms she was feeling was a different manifestation of her usual UCTD flare. In the past, such instances had always affected more proximal areas of the body, specifically neck, shoulders and hands. In her 2.5 years since discharge from her second inpatient rehabilitation stay, she has only experienced two significant UCTD exacerbations, both during an acute hospital admission for secondary complications of her NTSCI. The first occurred in the summer of 2022 when septic from a severe UTI. Her antibiotics for that condition included first intravenous cephalosporins and then ciprofloxacin. Both agents may have impaired absorption of hydroxychloroquine prescribed daily for chronic UCTD. In addition, several doses of this long-term medication were missed due to acute illness. During this hospitalization, she became weaker and had increased joint pain, neck pain, and hand swelling. However, the only serology that was abnormal among rheumatologic indices was an elevated ESR of 3 points beyond the upper limit of normal, which could have been outside the normal range simply due to the UTI. During this admission, the same labs as appeared in Table 1 were performed and no findings revealed a change in her degree of UCTD.

Physical examination

Upon arriving to rehabilitation, her exam demonstrated a C7 left, T3 right ASIA Impairment Scale A, with a zone of sensory preservation to T8 bilaterally and complete absence of sensory and motor function from T9-S5. Her first month of rehabilitation was marked by expected neurogenic bowel and bladder, moderate thoracic non-radiating back pain, and mild spasticity below T9. She also had a band-like tightness in the T4-5 dermatomes in the absence of imaging findings there. The pain continued to intensify during subsequent weeks in rehabilitation, progressively taking on more neuropathic features with relentless mid-back and chest tightness.

She was discharged home after 8 wk but continued to experience unrelenting truncal pain between the T3-T8 dermatomes, above and at the level of the infarct, estimated to be located at T8. Several additional acute care and rehabilitation admissions for pain and urinary tract infections ensued during the subsequent two months. Her exam in this time now showed T3 complete SCI with partial preservation to T8.

Laboratory examinations

Table 2 gives additional studies undertaken in the diagnostic workup, including the presence of viruses other than SARS-CoV-2 (enterovirus, Varicella zoster, Herpes simplex, and West Nile), and markers of inflammatory, autoimmune, and neoplastic disorders. Specifically, there was no evidence of Neuromyelitis Optica, based on absent aquaporin-4, and no evidence of myelin oligodendrocyte glycoprotein antibody, which is characterized by immune mediated demyelination of the spinal cord and other regions of the central nervous system. Moreover, immunoglobulin G synthesis of the cerebral spinal fluid (CSF) index was also negative, suggesting other inflammatory processes were not present. No oligoclonal bands were detected in CSF, a finding commonly seen in multiple sclerosis (MS) and in neoplastic processes such as multiple myeloma. Myelin basic protein was elevated but is a nonspecific finding, present in autoimmune disorders such as MS and ischemic conditions. including stroke[14]. Lumbar puncture on presentation had serum and cerebrospinal fluid studies that were entirely unremarkable.

Her managing team at the acute care hospital did not have access to her outpatient records about her rheumatologic condition from her community physicians. They did perform a comprehensive serologic workup during her acute COVID admission, but the specimens were sent to an outside lab. Her results were not finalized prior to acute hospital discharge and thus were never added to her inpatient record, nor subsequently forwarded to the rehabilitation team.

Several weeks into her first inpatient rehabilitation stay, partial rheumatologic history and the labs drawn while admitted for COVID-19 were eventually obtained from her outpatient physician's office. This individual's initial diagnosis of UCTD occurred in 1993, prior to acute COVID-19, and was classified as non-antinuclear antibody UCTD. Her condition was based on the presence of CREST syndrome, the pneumonic of which represents calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, and telangiectasias[15]. This information was from her first available outpatient record dating back to 2004, nearly 20 years preceding this publication. In 1993, her predominant features were Raynaud's affecting fingers and sclerodactyly. She began on disease-modifying medication hydroxychloroquine and a plan was made to arrange for oral prednisone as needed for any exacerbations. Outpatient records from 2004-2020 indicate patient reported feeling well, with a "stable UCTD presentation", without changes in lab indices, recorded hospitalizations, or flares. Documents did note an exacerbation of symptoms of neck and shoulder pain in 2016 that was managed as an outpatient with a combination of hydroxychloroquine and nifedipine, a calcium-channel blocker. At that

Table 1 Laboratory indices of rheumatologic disorders

Specific test	Individual result (normal range)	Test results in context of undifferentiated connective tissue disease[16]
Anti-Smith antibody	< 0.2 AI (≤ 0.9)	Highly sensitive for SLE
Anti-DS DNA	< 12 IU/mL (< 30)	Specific to SLE
SSA Ab (anti-Ro AB)	< 0.2 AI (≤ 0.9)	Seen as elevated in 90% of those with Sjogren's and in 40%-50% of those with SLE
SSB AB (anti-La Ab) anti	< 0.2 AI (≤ 0.9)	
Scleroderma Ab IgG	< 0.2 AI (≤ 0.9)	Specific to scleroderma but can be found as positive in combined rheumatologic disorders
Jo-Ab	< 0.2 AI (≤ 0.9)	Positive in dermatomyositis and polymyositis and in other CTD
Ribosomal RNP	< 0.2 AI (≤ 0.9)	Nonspecific index seen in SLE and other rheumatologic disorders
Scleroderma AB IgG	< 0.2 AI (≤ 0.9)	Specific to scleroderma

Artificial intelligence risk calculations were used to indicate likelihood of positivity. Tests were done using multiplex flow immunoassay. More specific units were not given by the reference lab but individual result findings represent a value under 20% of the upper limit of normal. The above laboratory tests were performed 2 d prior to transfer to rehabilitation in December 2020 during her acute episode of COVID-19. Most indices were performed with each subsequent flare of her condition and were not found outside the normal range except as noted in the text. AI: Artificial intelligence; anti-DS: Anti-double stranded; CTD: Connective tissue disease; RNP: Ribonucleoprotein; SSA and SSB: Sjogren syndrome antigens A and B; SLE: Systemic lupus erythematosus.

Table 2 Investigative studies of alternative diagnoses

Lab	Result
SARS-CoV-2	Positive
CSF enterovirus	Negative
CSF VZV	Not detected
CSF WNV	Not detected
CSF HSV	Not detected
AQP4	Not detected
Myelin basic protein	Elevated
MOG ab, IgG	Negative
Oligoclonal bands	Not detected
IgG synthesis CSF and serum	WNL

These studies of infectious or inflammatory disorders were performed to eliminate other etiologies of her symptoms. As findings were either nonspecific or negative, this individual's diagnosis remained as spinal cord infarct. CSF: Cerebrospinal fluid; WNL: Within normal limits; VZV: Varicella zoster virus; WNV: West Nile virus; HSV: Herpes simplex virus; AQP4: Aquaporin-4; MOG: Myeline oligodendrocyte glycoprotein; ab: Antibody; IgG: Immunoglobulin G.

time a core panel of rheumatologic markers was drawn, identical to the panel drawn in December 2020 given in Table 1. No specific rheumatologic markers were concerning, with the exception of an elevated erythrocyte sedimentation rate that resolved using the above medications. Between 2016-2020, she continued with annual visits to rheumatology without a documented flare or change in medications. Although normal values vary from one lab to another, the purpose of each test and the ratio of positive to negative values is similar between institutions[16]. The labs were selected by the referring facility where the acute care team made the decisions in diagnostic workup.

Imaging examinations

Initial workup included magnetic resonance imaging (MRI) of the cervical, thoracic, and lumbar spine, which showed acute cord ischemia T9 to the conus medullaris. Thoracic cord expansion and increased intramedullary signal extending many vertebral segments were compatible with a spinal cord infarct, particularly in light of the CSF findings and her

acute onset of weakness. The above helped to differentiate an infarct from transverse myelitis. The brain MRI was negative for optic neuritis or lesions suggestive of MS, features needed to diagnose those conditions.

Figure 1 demonstrates a lengthy region of T2 hyperintensity from T9 to the conus, yet absent imaging findings above T9, despite observed sensory abnormalities for many segments rostral to T9. She was diagnosed with a T8 spinal cord thrombotic stroke. Her infarct occurred approximately 7 d after acute infection with COVID-19, consistent with the timing reported by Zhang *et al*[7] in relation to COVID cytokine storm.

FINAL DIAGNOSIS

Our final diagnosis is new-onset spinal cord infarction attributed to acute infection with SARS-CoV-2. Table 3 lists common symptoms of PASC and which of these were present in our patient[12,13]. Among the traditional symptoms of SCI, neuropathic pain, muscle spasms, and neurogenic bladder were severe. Other common conditions seen in complete SCI such as temperature dysregulation, pressure injuries, significant problem with neurogenic bowel, were noticeably absent or very well controlled with non-pharmacologic measures of positioning, diet, and environmental adaptations.

TREATMENT

Although her pain had been manageable in the first month after contracting COVID-19, the next 16 mo were marked by both bony and neuropathic pain of an unremitting nature along with common symptoms of PASC, including fatigue, headache, mental exhaustion ("brain fog"), and myalgias. Her neuropathic pain was largely unresponsive to anticonvulsant medications (gabapentin, pregabalin); serotonin-based agents (duloxetine); opiate medications; a thoracic paravertebral selective nerve root block; a spinal cord stimulator trial, and most recently, an intrathecal pain pump that is set at very low rates to minimize hypotension. She did not tolerate baclofen orally so no intrathecal administration of that agent was attempted. Muscle spasms in the region of T3-8 were similarly intense, limiting the number of hours she could sit and forcing her to lie supine due to painful muscle cramping. Yet no spasms occurred below the area of the infarct.

Detrusor areflexia was managed through frequent intermittent catheterization, yet still resulted in monthly UTIs. She experienced 8 urinary tract infections over a period of 9 mo, but the causative organism differed from month to month (*EColi, Klebsiella pneumonia, and Enterobacter*). Transition to a suprapubic tube only marginally improved the infection rate. More recent months have been characterized by continued fatigue, decreased appetite, and self-recognized depression.

OUTCOME AND FOLLOW-UP

Regarding flares of this individual's UCTD, her second exacerbation came in April 2023 when she was hospitalized for severe constipation and a suspected small bowel obstruction. This situation arose following an increase in the morphine dose of her intrathecal pain pump. She again reported severe shoulder and neck pain but no discomfort in the regions of her back, pelvis or legs. She was unable to process any oral medications. Despite being given intravenous methylprednisolone as a replacement for hydroxychloroquine, her symptoms remained severe. During each of the aggravations of her UCTD that transpired while in the stage of PASC, pain and swelling remained localized to the same areas as prior to COVID-19 and did not affect the areas of her body impacted by PASC. From both this episode and her earlier exacerbation, it is apparent that neurogenic bowel and bladder complications, including UTIs, may precipitate a flare of UCTD. Because these are among the most common complications of any patient with SCI, increased clinical oversight and management of such patients is warranted from physicians in both rehabilitation and rheumatology.

Symptoms of PASC reported by this patient varied as her condition progressed. Although her spasms did improve after implantation of the morphine pump, she continued to endorse fatigue, post-exertional malaise, altered taste with poor appetite, and widespread muscle aches and pains. This patient's complaints of myalgias and neuropathic pain above and below the neurologic level of injury are atypical of an SCI condition, in which such symptoms are traditionally at or below the infarct level. Unlike many with spinal infarcts, she regained no dorsal column function. There can be some inflammation surrounding the original infarct that makes the sensory examination altered in dermatomes rostral to the lesion. We believe this temporary finding could have occurred in this case. The best assessment of localized edema after an infarct would be MRI, and specifically the diffusion-weighted imaging (DWI) sequences. However in her case, DWI sequences were not performed[17]. One year after original diagnosis with COVID-19, a follow up examination demonstrated the neurologic level of injury was T6, rather than T3 complete SCI. There were present but impaired findings at dermatomes T7 and 8, with no sensory of motor function from T9 to the sacrum.

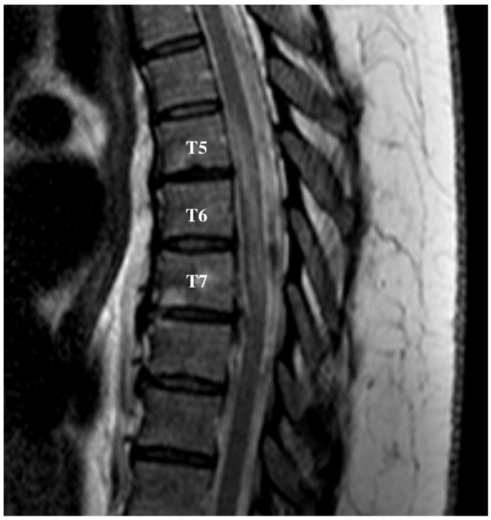
DISCUSSION

The case described in this narrative is characterized by some unusual features in her diagnosis and by the unpredictability of the clinical course. The patient's sensory function was impaired but not completely absent between T3-8, yet it was in this region and not below T8, where the lancinating neuropathic pain and muscle spasms arose. Neurology and

Table 3 Common symptoms of post-acute sequelae of COVID-19

Symptoms	Sneller *et al*[12]	Davis *et al*[13]	Present in case described
Fatigue	26%	98.3%	Yes
Cough	5%	66.2%	Yes
Concentration Deficit	12%	85.1%	Yes
Dyspnea	19%	77.4%	Yes
Anosmia/parosmia	14%	35.9%	No
Headache	12%	77%	Yes
Insomnia	9%	60%	No
Chest pain/discomfort	8%	53.1%	No
Anxiety	6%	57.9%	Yes
Myalgia	6%	69.1%	Yes
Tinnitus	6%	26.2%	No
Palpitations	5%	67.4%	No
Arthralgia	3%	52.2%	Yes
Taste disorder	5%	33.7%	Yes
Depression	3%	47.3%	Yes
Alopecia	4%	N/A	No
Dizziness	4%	67.3%	No
Paresthesias	1%	35.4%	Yes
Visual Impairment	1%	10.4%	No

Symptoms of two large coronavirus disease studies compared with the same symptoms in our case presentation, occurring at any point beyond 90 d of diagnosis.



DOI: 10.12998/wjcc.v11.i36.8542

Figure 1 Sagittal view of T2 weighted magnetic resonance imaging obtained approximately 20 h after the onset of symptoms.

infectious disease researchers at the referring institution attributed the sensory loss in T3-T8 to a COVID-induced direct viral neurotoxicity, in a similar manner to HIV-1[18,19]. We suspect the infarct, which is clinically apparent at T9, occurred from a thrombus in the artery of Adamkiewicz, yet no sensory function was preserved. Similar cases of arterial involvement of this vessel would result in an anterior cord syndrome, sparing dorsal column function. However, this individual had no dorsal column function of proprioception, position sense or vibration. Despite clean intermittent catheterization technique, her monthly infections in the bladder far exceeded the average number of 2.6 infections per

year found in those SCI individuals choosing clean technique intermittent catheterization[20].

This case is also notable for the heroic measures that have been undertaken subsequent to acute COVID infection to manage both neuropathic pain and intense back spasms localized to the mid-thoracic region. Patients with PASC frequently report myalgias, "pins and needles"[21,22] and spasms[22,23]. These struggles are similarly echoed by many of those with PASC who endure daily challenges that severely impact their quality of life and participation in the community[24]. In the case of our patient, an exacerbation of any aspect of her bowel or bladder function may lead to interventions that trigger a UCTD flare, further creating challenges for the patient and the physicians who manage her complex care.

In this case report of a NTSCI directly attributed to COVID-19, the most persistent complaints were myalgia, neuropathic pain, muscle spasms, and bladder dysfunction in the forms of bladder hyperreflexia and urinary tract infections[25]. While myalgias and neuropathic pain are commonly reported[11,13], the urinary symptoms of PASC, apart from renal impairment, have only recently been recognized. Lamb and colleagues have published a study on COVID-19 associated cystitis among those with PASC[26]. Their group has also linked COVID-19 inflammation to an increase in urine cytokines and to bladder hyperreflexia, nocturia, and urge incontinence[27]. In a person with SCI, such factors could certainly contribute to frequent urinary tract infections.

The severity and persistence of her clinical complaints represent a combination of severe SCI sequelae and those of PASC, the sum of which has greatly diminished her quality of life and participation in her community.

CONCLUSION

For the individual discussed in this report, the neurological sequelae of COVID-19 may be contributing to the secondary effects of NTSCI. In the chronic care setting, physicians may have difficulty separating which symptoms are due to a NTSCI and which are a direct consequence of PASC. Regardless, appropriate rehabilitation interventions for each condition encountered must be developed regardless of the cause. In the case of this particular patient, the plan must also encompass measures to minimize exacerbations of a chronic CTD. Only through such a comprehensive approach can we hope to optimize an individual's quality of life. Over the next decade, many of those living with SCI could face a new disability. It will be our role to provide life-long care for their COVID-19 concerns, as well as their chronic spinal cord injury needs.

ACKNOWLEDGEMENTS

The authors acknowledge efforts of Samuel Onusko DO in creating a secure database for entry of demographic and clinical data.

FOOTNOTES

Author contributions: Oleson CV was responsible for concept design, for the great majority of the writing of this manuscript, and for creation of Table 1 and 3; Oleson CV was also responsible for portions of data extraction; Olsen AC was responsible for background information and literature review, consent of the participant, and portions of the written manuscript. He was also responsible for image extraction and translation to jpg format and for Table 2; Shermon S was responsible for background information, a literature review and formatting of the manuscript including footnotes, tables and references.

Informed consent statement: Written consent using IRB approved forms for publication of case reports were obtained from the participant.

Conflict-of-interest statement: The authors have no conflict of interests that would be relevant for this publication to report.

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: Fan JR

L-Editor: A
P-Editor: Zhang XD

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World Journal of Clinical Cases

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

World J Clin Cases 2023 December 26; 11(36): 8551-8556

DOI: 10.12998/wjcc.v11.i36.8551

ISSN 2307-8960 (online)

CASE REPORT

Spontaneous gastric hematoma as a rare cause of acute abdomen: 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): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Qi XS, China; Shiryajev YN, Russia

Received: September 23, 2023
Peer-review started: September 23, 2023
First decision: November 17, 2023
Revised: December 2, 2023
Accepted: December 8, 2023
Article in press: December 8, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Spontaneous gastric hematoma is an exceedingly rare condition characterized by the accumulation of blood within the gastric wall without any apparent iatrogenic or traumatic cause. Coagulopathies are the most frequent cause of gastric hematomas. However, other causes include amyloidosis, pancreatitis, visceral vascular aneurysms, endoscopy complications and others. The pathophysiology of spontaneous gastric hematoma is not completely understood. However, it is postulated that it is caused by disruption of submucosal vessels that leads to dissection of the muscularis layer and formation of false lumen. The rarity of this condition increases the challenge of diagnosis, and there is no standard treatment protocol.

CASE SUMMARY

We present the case of a spontaneous gastric hematoma in a 22-year-old male. He presented to our emergency department complaining of pain in the left flank area lasting for 2 wk. There was no history of trauma, anticoagulant medications or endoscopy procedures. His hemoglobin and hematocrit levels were slightly lower than normal. Multi-slice computed tomography, ultrasound and endoscopy confirmed a gastric intramural hematoma. We recommended conservative treatment because there was no hemodynamic instability nor significant bleeding. The patient responded well, and there were no unexpected events. At the 3-mo follow-up, the ultrasound examination revealed complete regression of the hematoma.

CONCLUSION
After reviewing the literature and our experience, we recommend that more of these cases should be treated conservatively. The tendency to treat these cases with potentially burdensome procedures such as total or subtotal gastrectomy should be significantly reduced.

Key Words: Spontaneous; Intramural hematoma; Stomach; Acute abdomen; Conservative treatment; Case report

Core Tip: It is our intention to emphasize spontaneous gastric intramural hematoma as one of possible causes of acute abdomen. Also we would like to underline the option for conservative treatment of this condition. With our experience and by reviewing the literature we are under impression that majority of these cases could have been treated conservatively and number of surgical procedures could be reduced to some extent.

Citation: Budimir I, Žulec M, Eljuga K, Židak M, Lisek V. Spontaneous gastric hematoma as a rare cause of acute abdomen: A case report. *World J Clin Cases* 2023; 11(36): 8551-8556
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8551.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8551

INTRODUCTION

Intramural hematomas of the gastrointestinal tract are uncommon lesions. They most commonly occur in the esophagus and duodenum[1]. Spontaneous gastric hematoma is a rare clinical entity characterized by the accumulation of blood within the gastric wall in the absence of trauma or an underlying gastrointestinal pathology. Coagulopathies are the most frequent cause of gastric hematomas. However, other causes include amyloidosis, pancreatitis, visceral vascular aneurysms, acute lymphoblastic leukemia, endoscopy complications and others[2-4]. The rarity of this entity increases the challenge of diagnosis. This case highlighted the importance of considering spontaneous gastric hematoma as a differential diagnosis in patients with abdominal pain.

CASE PRESENTATION

Chief complaints

A 22-year-old male presented to our emergency department with a complaint of persistent blunt abdominal pain in the left flank that first occurred 2 wk prior.

History of present illness

The patient stated that he vomited and had diarrhea a few days prior to the onset of pain. These symptoms were interpreted as gastroenteritis and resolved spontaneously. The patient denied a history of trauma or recent endoscopic procedures and was not taking anticoagulant medications. It is known that some patients, especially younger ones, do not mention abdominal trauma because they do not recognize it as a trauma or because they want to hide illicit or inappropriate behavior[5,6]. However, we ruled out these possibilities for this patient.

History of past illness

Chronic illnesses and bleeding disorders were absent. There was no history of trauma nor endoscopy procedures.

Personal and family history

There was no family history of blood disorders, vascular diseases nor gastrointestinal diseases.

Physical examination

Physical examination revealed tenderness in the left flank and epigastric region but with no signs of peritoneal irritation. There was a palpable mass below the left costal arch. It was 10 cm in diameter, spheric, soft and mildly painful on palpation. There were no signs of any type of trauma such as bruises or excoriations. The vital parameters (blood pressure, respiration and pulse) were all within normal ranges. Digital rectal examination did not show any abnormalities.

Laboratory examinations

Initial blood count showed slightly lower hemoglobin (123 g/L; normal range: 138-175 g/L) and hematocrit (0.367 L/L; normal range: 0.415-0.530 L/L). All other laboratory findings, including coagulation profile, were within normal ranges.

Imaging examinations

An abdominal ultrasound demonstrated a thickened and hypoechoic gastric wall. The radiologist determined the findings to be inconclusive but indicated a suspicion of an intramural hematoma. An abdominal contrast-enhanced multislice computed tomography examination confirmed a heterogenous intramural mass within the gastric wall, measuring approximately 15 cm × 11 cm × 9 cm (Figure 1A-C). There were no signs of calcifications specific to malignant lesions nor gastrointestinal stromal tumor (GIST)-specific cystic masses. The described mass had the density of a hematoma[7].

Endoscopy procedures

Endoscopic evaluation was performed to assess the source of bleeding and to rule out any underlying pathology. Esophagogastroduodenoscopy revealed a large, submucosal mass occupying the greater curvature of the stomach (Figure 1D). There were no signs of active bleeding, ulcers nor mucosal lesions. Neither endophytic growth nor lumen obstruction were present, providing additional support against the suspicion of GIST[8].

FINAL DIAGNOSIS

Spontaneous gastric intramural hematoma (GIH).

TREATMENT

We opted to not perform ultrasound-guided biopsy. The patient was hospitalized and conservative treatment was chosen because of the absence of active bleeding and the presence of hemodynamic stability. The patient received pantoprazole, a proton pump inhibitor (PPI) (40 mg every morning, by mouth). Metamizole (500 mg) was administered for analgesia as needed, by mouth. The patient only received metamizole for the 1st 2 d, as his pain decreased significantly. Serial abdominal examinations and hemoglobin monitoring were performed to assess any signs of hematoma expansion or severe bleeding.

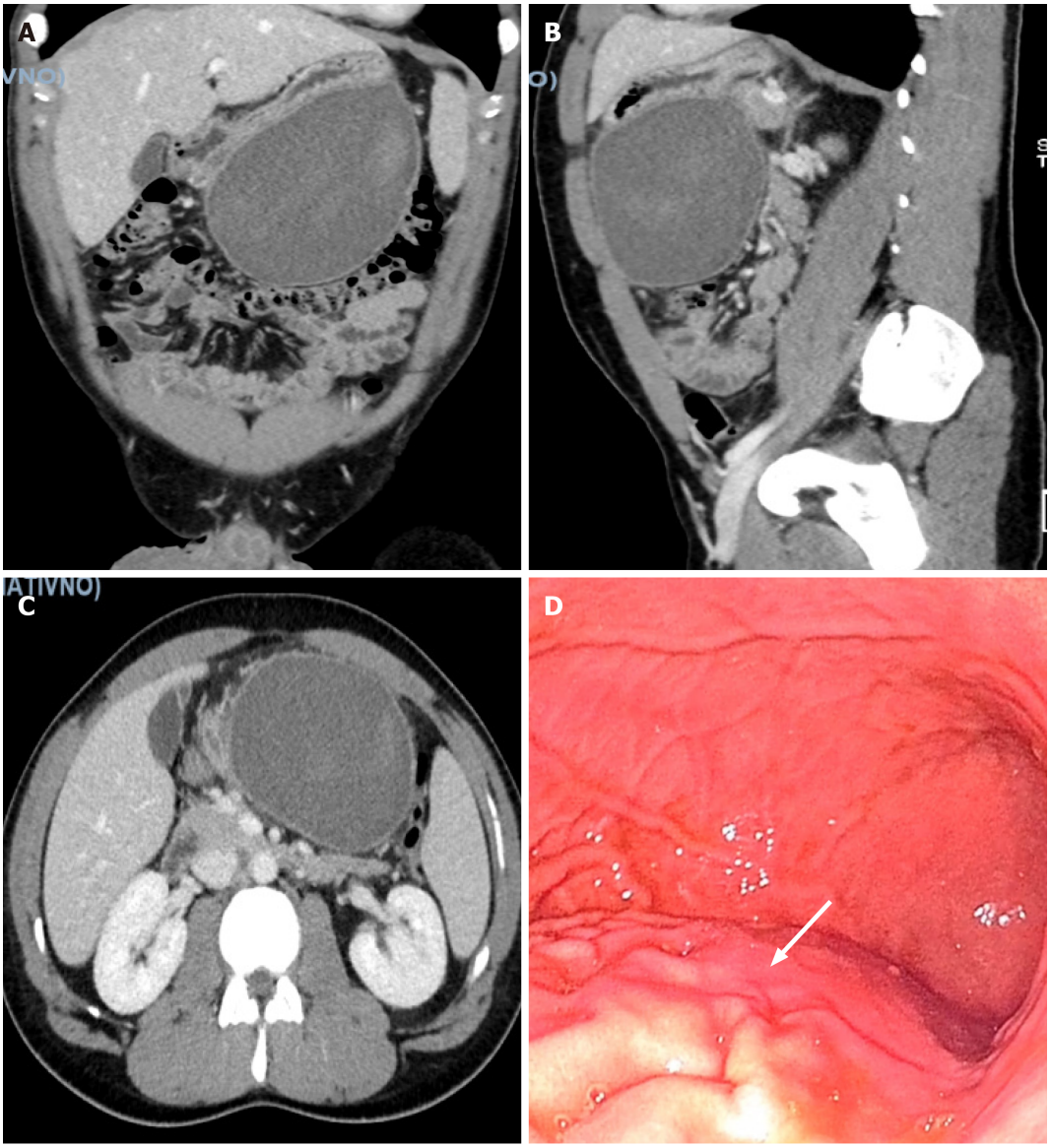
Over the course of several days, the patient's symptoms were significantly relieved. Repeated abdominal ultrasound showed a gradual decrease of the hematoma, and the hemoglobin level remained the same. The patient was discharged after 4 d with instructions for a soft diet and continued pantoprazole therapy as during the hospitalization.

OUTCOME AND FOLLOW-UP

The first follow-up examination was completed 2 wk after discharge. Laboratory findings were within normal limits. The patient stated that he did not experience any pain, did not use any analgesics and was following the diet and medication instructions. Ultrasound also showed a significant decrease in the mass. The patient was instructed to discontinue pantoprazole. A soft diet was unnecessary because he was not at risk for mechanical erosions of the mucosa and subsequent hematoma evacuation. At the 3-mo follow-up, abdominal ultrasound and physical examination showed complete regression of the gastric hematoma. The patient reported no abdominal pain and denied the use of analgesics and PPIs during the period.

DISCUSSION

Spontaneous GIH is a rare clinical entity that presents unique challenges for diagnosis and management. GIH was first described by MacLauchlan in 1838 and described as a pseudoaneurysmal tumor of the duodenum[9]. However, almost 200 years later, the pathophysiology is still not completely understood. When GIST is the working diagnosis, postoperative pathologic examination reveals signs of chronic inflammation but no biochemical GIST markers[7]. It is widely believed that GIH is caused by disruption of submucosal vessels that leads to dissection of the muscularis layer and formation of false lumen[3,10].



DOI: 10.12998/wjcc.v11.i36.8551

Figure 1 Imaging and endoscopic examination of gastric intramural hematoma. A: Contrast enhanced multi-slice computed tomography (MSCT) coronary view of the gastric intramural hematoma (GIH); B: MSCT sagittal view of GIH; C: MSCT transversal view of GIH; D: Endoscopic view of GIH (white arrow indicates the bulging of the greater curvature mucosa).

GIH is mostly caused by coagulopathy, peptic ulcers, fishbone ingestion and endoscopy procedures. In these types of cases, the patient has a higher chance of being appropriately diagnosed and managed, which is often not the case with idiopathic GIH.

Several studies have shown that the majority of GIH cases are treated conservatively. However, in idiopathic cases, surgery has been the treatment of choice in more than half of the patients[2,3]. Conservative treatment regimens include blood and coagulation factor replacement for cases of intrinsic coagulopathy[11]. When warfarin overdose is the cause, patients are treated with coagulopathy reversal[4,11]. The discontinuation of aspirin prior to an endoscopic or other invasive procedure, such as percutaneous gastrostomy, can prevent the development of GIH[12]. After reviewing the literature, it was apparent that no standard treatment protocol exists. Treatment was personalized according to the supposed cause of GIH and the individual patient's symptoms[4,7,11-13].

Tabbikha *et al*[2] conducted a literature review of spontaneous GIH cases published in English. Their case report was the seventh published case. They found that 5 of 7 patients were treated surgically with total or subtotal gastrectomy or wedge gastric resection[2]. We found in our literature search that most GIH cases were misdiagnosed as visceral artery aneurysms, GIST, tuberculosis, or Dieulafoy's lesion[2,7,11]. Spontaneous GIH was rarely the initial diagnosis[10,14-16] and was confirmed in most cases after surgical intervention. If the diagnosis of GIH is confirmed earlier, then gastrectomies and other surgical procedures could be decreased. We found that conservative treatment was successful in the cases initially diagnosed with spontaneous GIH[17].

Even though we did not complete a biopsy of the specimen, the absence of cystic masses and calcifications on multislice computed tomography assisted in excluding carcinomas and GIST[7,8]. Ultrasound findings were inconclusive but

suggested GIH. The lack of the biopsy is one of the limitations in the management of this case because we did not confirm GIH pathohistologically. However, the patient was young and there were no indications of malignancy. Therefore, we determined that the risks of a biopsy outweighed the benefits.

Our patient was hemodynamically stable and responded well to analgesics. Therefore, conservative treatment was recommended. Interestingly, no publications on GIH cases mentioned that the patients were hemodynamically instable. Even though patients in the other published reports were initially diagnosed with superior mesenteric artery branch aneurysm, severely bleeding GIST or peptic ulcers, they were hemodynamically stable[3,7,13]. Some studies reported tachycardia and decreased hemoglobin levels, but the patients were normotensive[2,3,7,13,17].

Due to the scarcity of cases, we are aware that we do not have enough data nor experience to strongly recommend a conservative treatment protocol for all spontaneous GIH cases. However, we postulate that presentations similar to our patient are likely seen more frequently in emergency departments and are not widely reported. Therefore, it is important to recognize that a conservative treatment approach would be beneficial for such patients[2,7,13]. It is also our impression that the majority of spontaneous GIH cases could be treated conservatively, and potentially risky and burdensome procedures such as total or subtotal gastrectomy could be significantly reduced.

CONCLUSION

Spontaneous gastric hematoma is a rare condition that can mimic other gastrointestinal emergencies. Clinicians must maintain a high level of suspicion when evaluating patients with acute abdominal pain, especially in the absence of trauma or known bleeding disorders. Early diagnosis through imaging and endoscopy along with tailored management strategies can lead to successful outcomes for patients with this rare and unusual condition. Further research is warranted to expand our understanding of the pathophysiology of GIH with the purpose of finding the most appropriate treatment.

FOOTNOTES

Author contributions: Budimir I contributed to data collection, conceptualization, writing and editing; Žulec M and Eljuga K contributed to data collection and data analysis; Židak M and Lisek V contributed to conceptualization; Lisek V contributed to supervision and editing; all authors 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: 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: Croatia

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

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World J Clin Cases 2023 December 26; 11(36): 8557-8562

DOI: 10.12998/wjcc.v11.i36.8557

ISSN 2307-8960 (online)

CASE REPORT

LiNA OperaScope™ for microwave endometrial ablation for endometrial polyps with heavy menstrual bleeding: 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): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Zhang S, China

Received: October 3, 2023
Peer-review started: October 3, 2023
First decision: November 22, 2023
Revised: November 28, 2023
Accepted: December 11, 2023
Article in press: December 11, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

The procedure for microwave endometrial ablation (MEA) follows established MEA practice guidelines but requires hysteroscopic observation of the uterine lumen before and after MEA. When a luminal uterine lesion is recognized, its removal requires preoperative dilation of the cervix because the outer diameter of a conventional rigid hysteroscope is 8.7 mm. Recently, a fully disposable rigid hysteroscope (LiNA OperaScope™) with a narrow diameter (4.4 mm) and forceps capable of extracting endometrial lesions has become available.

CASE SUMMARY

Here, we report a case of heavy menstrual bleeding (HMB) complicated by endometrial polyps where MEA was performed after removing endometrial polyps using the LiNA OperaScope™ device. A 48-year-old woman with three prior pregnancies and three deliveries was referred to our hospital for further examination and treatment after being diagnosed with HMB 2 years earlier. The patient underwent MEA following endometrial polypectomy using LiNA OperaScope™. After MEA, endometrial cauterization was again examined using the LiNA OperaScope™, and the procedure was completed. No preoperative cervical dilation was performed. The patient's clinical course was favorable, and she was discharged 3 h after surgery. One month after surgery, menstruation resumed, and both HMB and dysmenorrhea improved markedly from 10 preoperatively to 1 postoperatively, as assessed subjectively using the visual analog scale. The patient's postoperative course was uneventful with no complications.

CONCLUSION

LiNA OperaScope™ can be a minimally invasive treatment for MEA of HMB with

uterine lumen lesions.

Key Words: Heavy menstrual bleeding; Microwave endometrial ablation; Endometrial polyp; Hysteroscopy; Minimally invasive surgery; Dysmenorrhea; Case report

Core Tip: LiNA OperaScope™ is a fully disposable rigid hysteroscope with an outer diameter of 4.4 mm, narrower than conventional hysteroscopes, and equipped with forceps capable of excising endometrial lesions. We report a case of heavy menstrual bleeding (HMB) with endometrial polyps where microwave endometrial ablation (MEA) was performed after endometrial polyp removal using LiNA OperaScope™. This case suggests that MEA using the LiNA OperaScope™ can remove luminal lesions without preoperative cervical dilation and can be a less invasive treatment option than conventional techniques for patients with HMB presenting with endometrial polyps.

Citation: Kakinuma K, Kakinuma T, Ueyama K, Shinohara T, Okamoto R, Yanagida K, Takeshima N, Ohwada M. LiNA OperaScope™ for microwave endometrial ablation for endometrial polyps with heavy menstrual bleeding: A case report. *World J Clin Cases* 2023; 11(36): 8557-8562
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8557.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8557

INTRODUCTION

Heavy menstrual bleeding (HMB) is defined as heavy menstrual blood loss, severe anemia, and difficulty in daily living. It limits social activities due to the decrease in a woman's quality of life. Although pharmacological treatment with hemostatic agents and hormones is often the first choice for HMB, hysterectomy is a curative treatment for patients who are unresponsive to conservative treatment and have no desire for a baby. However, many patients desire less invasive treatments due to preexisting conditions, complications, or social background.

Microwave endometrial ablation (MEA) is an ultrasound-guided method of endometrial ablation using microwave irradiation at 2.45 GHz. MEA is a treatment method that destroys the endometrium, including its basal layer, using a protein coagulator that uses dielectric heating produced by microwave irradiation of the tissue, thereby reducing its function. It aims to achieve a decrease in menstrual blood volume or transition to amenorrhea. MEA has gained popularity as a minimally invasive alternative to conventional hysterectomy, and its usefulness has been reported at our institution and others[1-3]. The procedure is performed following the MEA[4] guidelines and requires hysteroscopic observation of the uterine lumen before and after MEA. If there is an elevated lesion in the uterine lumen, it should be removed. When excising a bulging lesion under hysteroscopy, the cervix must be dilated preoperatively because the outer diameter of a conventional rigid hysteroscope is 8.7 mm. In recent years, a fully disposable rigid hysteroscope (LiNA OperaScope™) with an outer diameter of 4.4 mm, narrower than conventional hysteroscopes, and equipped with forceps capable of excising endometrial lesions, has been introduced.

Here, we report a case of HMB with endometrial polyps in which MEA was performed after endometrial polyp removal using LiNA OperaScope™.

CASE PRESENTATION

Chief complaints

The patient, a 48-year-old woman with three prior pregnancies and three vaginal deliveries, presented with HMB.

History of present illness

The patient had been experiencing HMB for 2 years. She visited her local doctor and was found to be anemic (hemoglobin level: 7.9 mg/dL). Subsequently, she was referred to our hospital for further examination and treatment.

History of past illness

First menstruation at age 11 years; 28-d cycle; duration, 6 d; regular, characterized by heavy menstrual blood with clots and severe dysmenorrhea.

Personal and family history

There was no pertinent history.

Physical examination

On admission, she was 160.0 cm tall, weighed 55.0 kg, and had a body surface area of 21.5 kg/m^2. She was fully conscious. Her blood pressure was 123/78 mmHg, pulse rate was 99/min, and SpO_2 was 99% (supine position, room air).

Laboratory examinations

Cytological examination of cervical specimens was negative for intraepithelial lesions or malignancy. Cytological examination of the endometrial samples was also negative.

Imaging examinations

Ultrasonography in the follicular phase revealed irregular thickening of the endometrium, and endometrial polyps were suspected.

Hysteroscopic examination revealed a pale-red, elevated lesion in the lower part of the uterine body (Figure 1).

FINAL DIAGNOSIS

Based on these findings, abnormal uterine bleeding with polyps was diagnosed according to the International Federation of Gynecology and Obstetrics Abnormal Uterine Bleeding System.

TREATMENT

Surgery was initiated with the patient in the lithotripsy position under general anesthesia. After observing the uterine lumen using the LiNA OperaScope™ device (Terumo Corporation, Tokyo, Japan) (Figure 2), endometrial polyps were excised using basket forceps (Figure 3). MEA was performed under transabdominal ultrasound guidance after endometrial polypectomy using a Microtase AFM-712 device (Alfresa Pharma Corporation, Osaka, Japan) and a sounding applicator, CSA-40CBL-1006200C (Alfresa Pharma Corporation), to cauterize the endometrium with a microtase output of 70 W and a coagulation energization time of 50 S per cycle. After MEA, the uterine cavity was again observed with the LiNA OperaScope™ to confirm that the endometrium was coagulated and necrotic, cauterization did not extend into the endometrial or cervical mucosa, and no necrotic tissue was retained by the endometrial cautery (Figure 4). Preoperative cervical dilation was unnecessary. The operative time was 33 min, and blood loss was minimal.

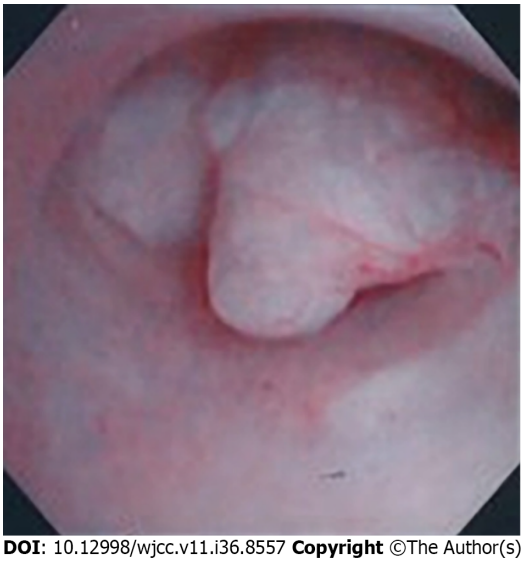
OUTCOME AND FOLLOW-UP

The patient's progress was favorable; she was discharged 3 h after surgery and followed up as an outpatient. Histopathological examination of the excised specimen revealed the presence of an endometrial polyp. The patient resumed menstruating 1 mo postoperatively, and both HMB and dysmenorrhea improved markedly (from 10 to 1 on subjective evaluation using the visual analog scale). No complications occurred during the patient's clinical course, and the postoperative course was favorable. As of postoperative month 6, there was no HMB recurrence.

DISCUSSION

MEA is a treatment for functional or organic hypermenorrhea in which the endometrium is destroyed using microwave ablation. MEA is considered less invasive than hysterectomy; therefore, its effectiveness as an alternative treatment to hysterectomy has been reported in cases where the perioperative risk is considered high due to medical complications, obesity, or previous abdominal surgery. This procedure is also gaining widespread use as a treatment characterized by high patient satisfaction[1-3].

For the implementation of MEA, we followed the Guidelines for the Implementation of Microwave Endometrial Ablation (2012 revision), published in Japan, that describes the details of the MEA procedure with safety assurances[4]. These guidelines state that MEA should be performed under ultrasound guidance and that the endometrium should be observed with a hysteroscope before and after MEA, especially to ensure no uncauterized endometrium at the end of the cautery. The presence of an uncauterized portion of the endometrium is also an important risk factor for HMB recurrence after MEA. Complications of MEA include thermal injury to the pelvic organs, cervical stenosis, retained uterine fluid due to endometrial cauterization, retained uterine hematochezia, pelvic inflammation such as endometritis from an ascending infection, and retained uterine pyometra[5]. Therefore, if the cauterization is extended to the endometrial or cervical mucosa, the cervix must be dilated postoperatively to prevent cervical stenosis and adhesions. In the present case, intrauterine infection was observed postoperatively[3]. Thus, we took precautionary steps to excise as much necrotic tissue as possible that remained due to endometrial ablation when checking the status of endometrial ablation using hysteroscopy immediately after MEA. Observation of the uterine lumen *via* hysteroscopy after MEA is also important to avoid complications.



DOI: 10.12998/wjcc.v11.i36.8557

Figure 1 Hysteroscopic findings. A pale-red, elevated lesion is observed in the lower portion of the uterine body.

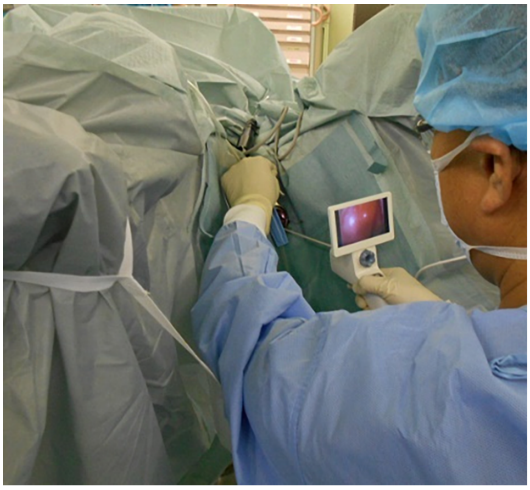


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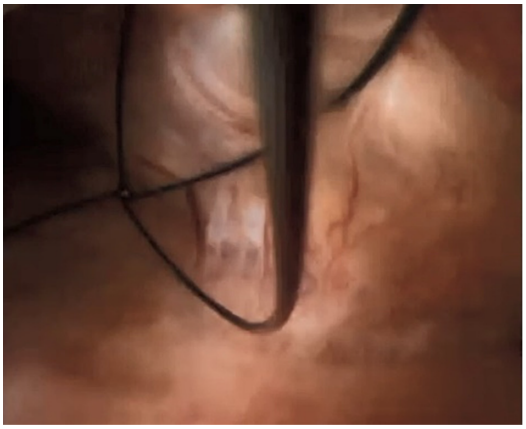
Figure 2 Surgical procedure. The uterine lumen is observed using a LiNA OperaScope™ device.

A microwave surgical instrument and microwave applicator are required to perform MEA. A sounding applicator manufactured by Alfresa Pharma was used[6]. Because its diameter is as thin as 4 mm, cervical dilation is not necessary if only the observation of the uterine lumen is required.

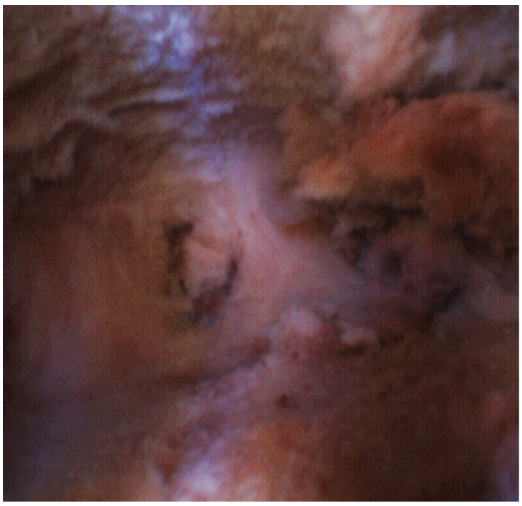
As explained in the MEA guidelines, no endometrial lesions suggestive of malignancy should be confirmed before MEA. If a luminal uterine lesion is present, as in the present case, removal is required for histopathological evaluation. It is important to exclude malignant lesions from the uterus lumen before MEA. However, in a report from our institution, despite the preoperative exclusion of malignant endometrial lesions *via* endometrial cytology and histology, malignant endometrial lesions were found during endometrial histology during MEA[7]. In addition, atypical polypoid adenomyoma (APAM) is a mixed epithelial-stromal tumor that develops in a polypoid shape in the uterine lumen. Although APAM is classified as a benign tumor, it is associated with endometrial hyperplasia and endometrial adenocarcinoma and has a high risk of recurrence and progression to endometrial cancer[8]. Hysteroscopy is also useful for observing the degree of protrusion and coloration of the lesion and abnormal vascular images on the lesion surface. In recent years, the usefulness of transcervical resection has been highlighted in cases where it is difficult to evaluate benign or malignant lesions *via* preoperative histological examination; it can be used for luminal uterine lesions that are difficult to evaluate using magnetic resonance imaging or ultrasound tomography[9-11].

Using a conventional rigid hysteroscope (diameter, 8.7 mm) for this procedure would require cervical dilation prior to MEA. The smaller 4.4 mm outer diameter of the LiNA OperaScope™ used in the present case allowed us to remove the lesion in the uterine lumen without preoperative cervix dilation. The lack of preoperative dilation of the cervix may enable a more minimally invasive procedure for MEA in HMB with luminal uterine lesions. In the present case, the patient was discharged within 3 h after surgery. If this procedure can be performed under local anesthesia, such as a paracervical block, it may be possible to perform it as an outpatient procedure without requiring hospitalization.



DOI: 10.12998/wjcc.v11.i36.8557

Figure 3 Performance of endometrial polypectomy. Endometrial polyps are removed using basket forceps while under LiNA OperaScope™ endoscopy.



DOI: 10.12998/wjcc.v11.i36.8557

Figure 4 Post-microwave endometrial ablation hysteroscopic findings. The absence of uncauterized areas of the endometrium and necrotic tissue following endometrial cauterization is confirmed.

In addition, because this hysteroscopic instrument has a liquid crystal display, a light source with a built-in light-emitting diode, and a power supply with built-in dry batteries, and all parts are integrated into one unit, this one instrument alone is sufficient to observe the uterine cavity and remove lesions. Therefore, unlike conventional rigid hysteroscopic surgical systems, this does not incur high initial investment costs. Furthermore, as this device is a disposable, single-use product, it reduces the risk of infection and reduces the labor required by medical personnel to clean and sterilize surgical instruments.

The forceps that can be used with this device are limited to biopsies, scissors, and basket-type forceps. However, it is not equipped with a device with a hemostatic function using a high-frequency current generator or other heat source. It is not indicated for masses that protrude into the uterine lumen at a low rate or for lesions that bleed easily and are difficult to control.

The LiNA OperaScope™ has been on the market for only a short time. Therefore, it is necessary to conduct clinical verification from various perspectives, such as histopathological examination of the extracted material, postoperative complications, HMB recurrence rate, time until recurrence, selection of cases prone to recurrence in MEA for HMB with uterine lumen lesions using this device, and detailed studies on the indications for this procedure prior to its widespread use.

CONCLUSION

MEA using the LiNA OperaScope™ can remove luminal lesions without requiring preoperative cervical dilation and can be a less invasive treatment option than conventional techniques for patients with HMB presenting with endometrial polyps.

FOOTNOTES

Author contributions: Kakinuma T contributed to conceptualization, methodology, software, validation, original draft preparation, manuscript review and editing, visualization, supervision, and project administration; All authors contributed to formal analysis, investigation, resources, and data curation, and have read and agreed to the published version of 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: 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: Lin C
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 December 26; 11(36): 8563-8567

DOI: 10.12998/wjcc.v11.i36.8563

ISSN 2307-8960 (online)

CASE REPORT

Colonoscopy-induced acute appendicitis: A case report

Xiao-Ling Song, Jin-You Ma, Zhi-Gao Zhang

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
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Day AS, New Zealand

Received: October 16, 2023
Peer-review started: October 16, 2023
First decision: November 1, 2023
Revised: November 11, 2023
Accepted: December 12, 2023
Article in press: December 12, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Colonoscopy is widely used for examination, diagnosis, and treatment because of its low incidence of associated complications. Post-colonoscopy appendicitis (PCA) is very rare and is easily misdiagnosed as electrocoagulation syndrome or colon perforation. Therefore, clinicians should pay close attention to this complication.

CASE SUMMARY

A 47-year-old female patient underwent a colonoscopy for a systematic physical examination, and the procedure was uneventful with normal endoscopic and histologic findings. However, the bowel preparation was suboptimal (Boston 2-3-2). After the examination, the patient experienced pain in the lower abdomen, which progressively worsened. Computed tomography of the lower abdomen and pelvis revealed appendiceal calcular obstruction and appendicitis. As the patient refused surgery, she was managed with antibiotics and recovered well.

CONCLUSION

In the current literature, the definition of PCA remains unclear. However, abdominal pain after colonoscopy should be differentiated from acute appendicitis.

Key Words: Colonoscopy; Complications; Appendicitis; Differential diagnosis; Case report

Core Tip: Abdominal pain is a common symptom after colonoscopy and is generally considered to be caused by perforation or electrocoagulation syndrome. Acute appendicitis is often ignored as a differential diagnosis. This case report aims to improve clinicians' awareness of possible appendicitis after colonoscopy. The causal relationship between colonoscopy and acute appendicitis remains unclear. However, regardless of whether it is defined as a complication, it should be differentiated from colonoscopy-associated abdominal pain, particularly in the right lower abdomen.

Citation: Song XL, Ma JY, Zhang ZG. Colonoscopy-induced acute appendicitis: A case report. *World J Clin Cases* 2023; 11(36): 8563-8567
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8563.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8563

INTRODUCTION

Colonoscopy is a common clinical examination, involving an endoscopic analysis of the entire colon, which aids in diagnosis and treatment. Colonoscopy is widely used because of its safety. However, although rare, serious complications, such as pain, bleeding, inflammation, perforation, cardiopulmonary complications, and death, can occur after colonoscopy.

Abdominal pain is a common symptom of colonoscopy. Mild abdominal pain is considered normal, and acute appendicitis, a relatively rare condition, is often ignored as a possible cause. Indeed, a previous study reported that the incidence of acute appendicitis after colonoscopy was approximately 0.038%[1]. However, considering that non-specific abdominal pain symptoms and minor appendicitis are easily overlooked, the recorded incidence of acute appendicitis may have been underestimated.

The number of patients undergoing colonoscopy have recently been increasing, and more cases of appendicitis after colonoscopy have consequently been reported. Since the first reported case in 1988, over 50 cases have been reported in the literature[2,3]. Many cases of perforation or gangrene, for which surgery is the primary treatment, have been reported [4-7]. Herein, we report the case of a woman who developed non-perforated appendicitis 10 h after colonoscopy and was treated with antibiotics immediately after a definitive diagnosis. This treatment yielded satisfactory results. This article aims to attract clinical attention to appendicitis after colonoscopy. Early identification and timely treatment are of paramount importance to avoid serious consequences and improve prognosis.

CASE PRESENTATION

Chief complaints

The patient complained of abdominal pain after undergoing colonoscopy. Appendicitis was diagnosed 10 h later.

History of present illness

The patient underwent a colonoscopy for health management, and the procedure was uneventful without any pathological biopsy. However, the state of intestinal cleanliness was poor (Boston 2-3-2), and clumps were observed in the feces. Ten hours after the examination, the patient experienced progressive pain in the right lower abdomen and was admitted to the gastroenterology department.

History of past illness

The patient's past medical history was unremarkable.

Personal and family history

The patient denied any possibility of family history-related conditions.

Physical examination

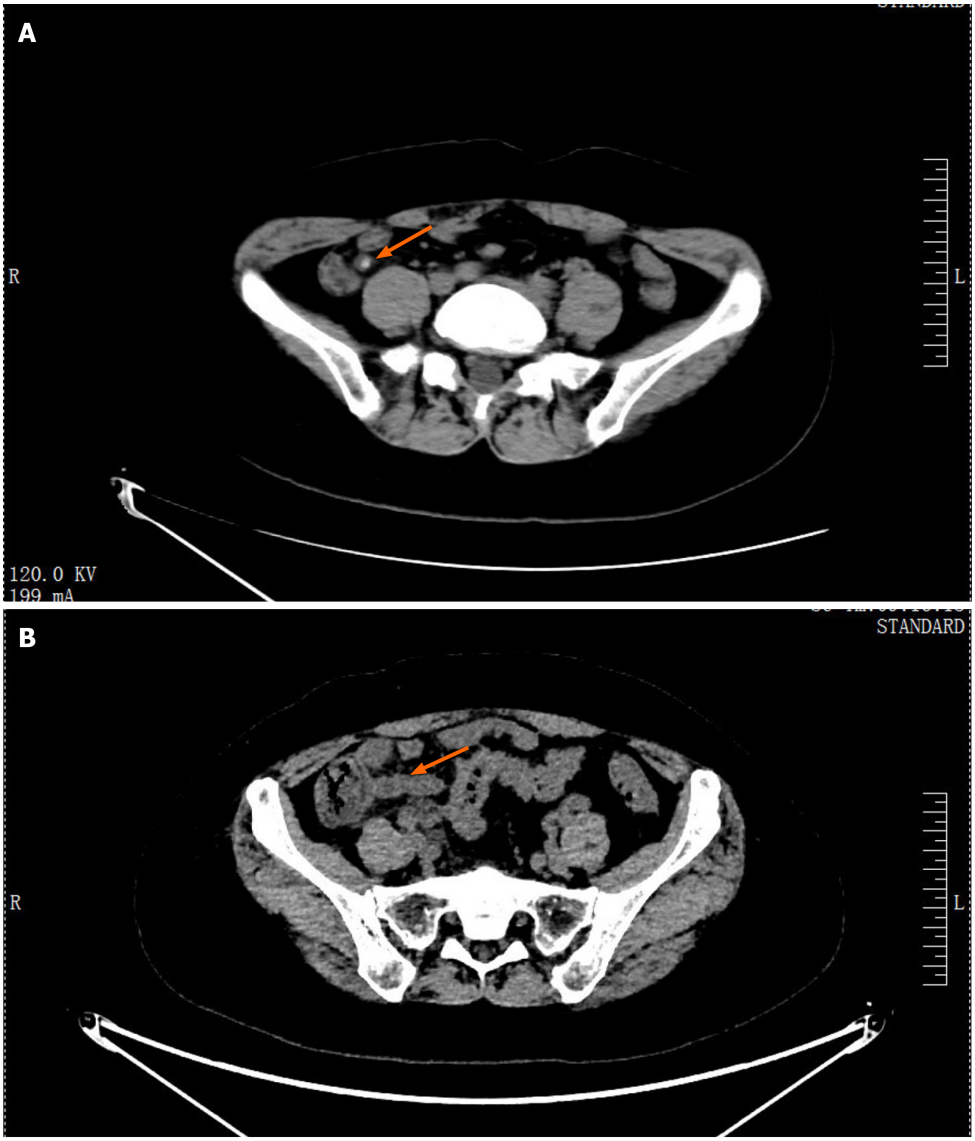
Body temperature was 37.6 °C, blood pressure was 132/75 mmHg, and heart rate was 85 beats/min. Tenderness of the right lower abdomen was evident without total abdominal pain [Murphy (-), Mc (+)].

Laboratory examinations

The white blood cell count, neutrophil count, and C-reactive protein level were 9.54 × 10^9 cells/L, 11.8 × 10^9 cells/L (N%: 90.4%), and 25.3 mg/L, respectively.

Imaging examinations

A computed tomography (CT) scan of the lower abdomen and pelvis revealed a dilated and inflamed appendix with fecoliths (Figure 1A).



DOI: 10.12998/wjcc.v11.i36.8563

Figure 1 Computed tomography scan of the lower abdomen and pelvis. A: Computed tomography (CT) revealed a dilated and thickened appendix with fecoliths (solid arrow: Appendix with fecoliths); B: After 3 d of treatment, the pelvic CT revealed that the appendicolith had disappeared (solid arrow: Dilated appendix without fecolith).

FINAL DIAGNOSIS

Post-colonoscopy acute appendicitis.

TREATMENT

The patient refused surgery and was administered antibiotics. After 3 d of treatment, the pelvic CT revealed inflammation in the appendix, and the appendicolith had disappeared (Figure 1B). Five days later, the patient was discharged in good physical condition.

OUTCOME AND FOLLOW-UP

The patient was followed up for 1 year and no symptoms of appendicitis recurred.

DISCUSSION

Colonoscopy is widely used to examine, diagnose, and treat intestinal diseases. It is associated with rare serious complications, of which bleeding and perforation are the most common. The incidence rate of complications ranges from 0.2% to 3%[8-10]. In recent years, more rare complications have been reported, including splenic and mesenteric vein embolisms. Post-colonoscopy appendicitis (PCA) is a rare complication.

Further, some scholars believe that PCA is a coincidence rather than a complication. Since the first reported case of PCA in 1988, the number of similar cases has increased over the past 20 years; to date, over 50 similar cases have been reported[2,3]. Interestingly, the number of cases reported in the past decade has increased fourfold compared to the previous decade[2], suggesting that this complication has gained increasing awareness among physicians.

Currently, no consensus on the definition, pathogenic factors, or pathogenesis of PCA have been established. Shaw *et al* [11] proposed that PCA should be defined as appendicitis occurring within 72 h of colonoscopy. Currently, there are several hypotheses regarding the pathogenesis of PCA: (1) Air pressure trauma caused by over-inflation[9]; (2) Obstruction and/or inflammation caused by stool pressing on the appendix[12]; (3) Direct trauma caused by unintentional intubation of the appendix tube[13]; (4) Exacerbation of existing subclinical diseases[14]; and (5) Stimulation of residual glutaraldehyde in the endoscope on the mucosa[13].

In the present case, appendicitis may not have been caused by a single factor. Owing to the impact of intestinal air pressure, fecal calculus in the intestinal cavity rushes into the appendix. Meanwhile, rising airway pressure makes it difficult for the airway to roll out, thereby causing appendicitis. In this case, this assumption was based on the fact that the patient's intestinal cleanliness was unremarkable.

The diagnosis of PCA presents certain challenges, particularly because its initial clinical manifestations are generally nonspecific. Therefore, misdiagnosis of intestinal perforation or polypectomy syndrome is common. In the early stages of the disease, changes in biochemical examination results are not evident. However, CT can exclude lesions in other organs and intestinal perforations very early. CT scanning has high sensitivity and specificity for detecting acute appendicitis [15]. Plain abdominal film and ultrasound examinations may not be significantly useful in the early diagnosis and treatment of this disease[16-21]. Therefore, CT has become the primary diagnostic modality for PCA in clinical settings. The duration of PCA from symptom onset to diagnosis varied from several hours to 10 d. A recent study demonstrated that patients undergoing colonoscopy are prone to developing appendicitis within a week[22]. Therefore, patients experiencing abdominal pain after an examination should be cautious and skeptical of their diagnosis.

Based on previous treatment of PCA, laparoscopy is the first treatment choice. Over the past 15 years, the success rate of laparoscopy has reached approximately 89.5%[3]. However, when complicated with extensive peritonitis, open surgery remains a more safe, rapid, and effective treatment modality[23,24]. However, in recent years, nonsurgical treatments have received increasing attention. Furthermore, owing to an improved understanding of PCA, this disease can now commonly be diagnosed at an early stage. Non-surgical treatment is feasible for appendicitis without perforation, gangrene, or suppuration[3].

CONCLUSION

Although PCA is rare, the number of reported cases has increased in recent years. Owing to its nonspecific clinical symptoms and the fact that some mild inflammatory reactions may independently subside, the actual incidence of this disease may be underestimated. However, PCA should be considered in the differential diagnosis of patients with abdominal pain after colonoscopy, especially when intestinal cleanliness is poor.

FOOTNOTES

Author contributions: Song XL designed the research plans and wrote the manuscript; Ma JY contributed to the index detection, collation and analysis of original results; Zhang ZG proposed the feasibility analysis of the research scheme and revised the paper.

Informed consent statement: Written informed consent was obtained.

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: Wang JJ
L-Editor: Filipodia
P-Editor: Zhang XD

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World Journal of Clinical Cases

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World J Clin Cases 2023 December 26; 11(36): 8568-8573

DOI: 10.12998/wjcc.v11.i36.8568

ISSN 2307-8960 (online)

CASE REPORT

Post-laparotomy heterotopic ossification of the xiphoid process: A case report

Seung Soo Lee

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
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Augustin G, Croatia

Received: October 16, 2023
Peer-review started: October 16, 2023
First decision: November 21, 2023
Revised: November 24, 2023
Accepted: December 13, 2023
Article in press: December 13, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Heterotopic ossification (HO) represents all types of extraskeletal ossification in the body. It occurs in various areas, including the skin, subcutaneous tissue, muscle, and joints. Surgical excision is recommended for symptomatic HO. Postoperative radiotherapy, oral nonsteroidal anti-inflammatory drugs, and topical sealants, such as bone wax, have been recommended as preventive measures. As HO is rare in occurrence, these recommendations are based on personal experiences, and there is a lack of information on individualized treatments depending on its location.

CASE SUMMARY

A 62-year-old male was admitted for symptomatic HO along a laparotomy scar. Surgical excision was performed for an 11 cm-sized ossification originating from the xiphoid process, and bone wax was applied to the excisional margin. However, the surgical wound failed to heal. After several weeks of saline-soaked gauze dressing, delayed wound closure was performed. The patient was finally discharged eight weeks after the excision. Because HO can occur in various areas of the body, a treatment strategy that may be effective for some may not be for others. Bone wax has been used as a topical sealant over excisional margins in the shoulder, elbow, and temporomandibular joints. However, in our case, its application on an abdominal surgical wound delayed its primary healing intention. The valuable lesson was that, when choosing a treatment method for HO based on available research data, its location must be considered.

CONCLUSION

Complete excision should be the priority treatment option for symptomatic HO along the laparotomy scar. Bone wax application is not recommended.

Key Words: Heterotopic ossification; Joints; Laparotomy; Waxes; Wound healing; Case report

Core Tip: Heterotopic ossification (HO) represents all types of extraskeletal ossification, and occurs in various areas, including the skin, muscle, and joints. There are some suggested treatment and preventive approaches for symptomatic HO, which include surgical excision and preventive measures such as postoperative radiotherapy, oral nonsteroidal anti-inflammatory drugs, and topical sealants (bone wax). However, these recommendations are based on personal experiences limited to HO in certain locations. It is important to individualize our treatment approaches depending on its location. For symptomatic HO along the laparotomy scar, complete surgical excision should be the priority treatment option, and bone wax application is not recommended.

Citation: Lee SS. Post-laparotomy heterotopic ossification of the xiphoid process: A case report. *World J Clin Cases* 2023; 11(36): 8568-8573
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8568.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8568

INTRODUCTION

Heterotopic ossification (HO) refers to the formation of trabecular bone outside the usual skeletal system[1,2]. Therefore, all extraskeletal bone formation in various areas of the body, including the skin, subcutaneous tissue, muscle, joints, and mesentery are included in this uncommon clinical entity[3,4]. As much as it covers all extraskeletal bone formation throughout the body, a wide range of factors contribute to each occurrence. Some of the most mentioned associated factors are trauma, burns, arthroplasty, and abdominal surgery[1,5]. As HO is highly associated with an external insult, the concern is higher in military settings where a high incidence of HO in combat-injured patients has been reported[2].

HO has been reported in various sites of the human body, and some hypotheses have been presented for its pathogenesis[6]. The generally recommended treatment for symptomatic HO has been selective surgical excision[2,7]. Some cases have been treated with open resection[8,9], and others, especially cases of HO in the joints, have been treated with arthroscopy[1]. Regardless of the HO site, recurrence has always been a concern for surgeons, and some preventive measures, such as postoperative radiotherapy[10], oral nonsteroidal anti-inflammatory drugs (NSAIDs)[11], and topical sealant (bone wax) over the osteotomy plane[1,7,12], have been recommended.

We experienced a case of symptomatic HO along a laparotomy scar following gastrectomy for gastric cancer. To search for the best treatment options, we vigorously reviewed the previous reports that were available at the time. While realizing that HO is a collective term representing all types of extraskeletal ossifications, we found a lack of information stating the need for individualizing our treatment efforts depending on the HO location. Our choice of treatment, which was a combination of surgical excision and the application of bone wax, did not turn out to be the best option.

CASE PRESENTATION

Chief complaints

A 62-year-old Asian man complained of persistent difficulties in bending his waist forward for six months.

History of present illness

The patient underwent a curative surgery for gastric cancer about a year earlier and had been making routine visits to our outpatient department for regular surveillance. After the gastrectomy, he continued to display a tendency toward excessive anxiety about his health. He kept complaining about memory loss, hair loss, and constipation, which were somewhat different from the usual postgastrectomy complaints, such as diarrhea, nausea, vomiting, and other gastrointestinal symptoms. Four months after the gastrectomy, he started complaining of stiffness along the surgical scar but received little medical attention at the time. The symptoms worsened over the next two months, and the patient started experiencing difficulties in bending his waist forward. The patient had a normal weight (62.7 kg) and body mass index (20.9 kg/m^2). Postgastrectomy weight loss was minimal (weight loss of 1.3 kg). There were no signs of cancer recurrence.

History of past illness

The patient underwent distal subtotal gastrectomy, D2 lymphadenectomy, and Billroth II anastomosis for gastric cancer a year earlier. He did not undergo adjuvant chemotherapy as the surgical specimen confirmed stage I cancer according to the 8th edition of the Union for International Cancer Control classification. The patient had no history of smoking, alcohol

abuse, or previous illnesses except for well-controlled hypertension and type 2 diabetes.

Personal and family history

The patient had no significant personal or family history.

Physical examination

The vital signs were unremarkable. Abdominal physical examination revealed no distension or rigidity. Bowel sound was normal. There was a firm, fixed palpable mass along the surgical incision that was about 10 cm in size. There was no pain or tenderness.

Laboratory examinations

Routine blood and urine analysis results were normal. Serum tumor markers including carcinoembryonic antigen and carbohydrate antigen 19-9 were normal with 3.4 ng/mL and 21.4 U/mL, respectively.

Imaging examinations

An abdominal computerized tomography (CT), taken for 6-mo postgastrectomy surveillance, revealed a 10 cm-sized ossification along the surgical incision (Figure 1). The latest CT, taken for 1-year postgastrectomy surveillance just before the admission, confirmed an 11 cm-sized ossification along the surgical incision.

FINAL DIAGNOSIS

Based on the patient's medical history, physical examination, and CT findings, the final diagnosis was HO, originating from the xiphoid process.

TREATMENT

Surgery for symptomatic HO was performed under general anesthesia. At laparotomy, an 11 cm-sized ossification, originating from the xiphoid process, was noticed between the linea alba and preperitoneal adipose layer (Figure 2). The structure was densely adhered to the surrounding tissue. After careful dissection of the adhered tissue and separation of the bony attachment at the xiphoidal end, we completely removed the structure. As an extra precaution for bone hemostasis and HO recurrence, bone wax was applied to the excisional margin. The surgical wound was closed layer by layer.

OUTCOME AND FOLLOW-UP

Histological examination of the surgical specimen confirmed HO. However, there was extensive discharge from the surgical wound over the following two weeks. The nature of the discharge slowly changed from serous to turbid, and we decided to open the surgical wound. The wound was somewhat waxy, and massive wound irrigation was performed. After three weeks of applying saline-soaked gauze dressings, delayed wound closure was performed, and the patient was finally discharged eight weeks after the HO excision. He underwent a follow-up CT two years postgastrectomy, which was about a year after the HO excision, and there were no signs of recurrence (Figure 3).

DISCUSSION

HO is rare and, yet, broad in that it represents all types of extraskeletal ossifications in the body. Therefore, depending on its location, a treatment strategy that may be effective for some may not be for others. An extensive literature search led us to the application of bone wax along the laparotomy scar following surgical HO excision. However, this turned out to be a grave misapplication of our treatment efforts.

Two pathogenesis hypotheses for the HO of abdominal scar tissue have been suggested[6]. The first and more favored hypothesis is an aberrant inflammatory process in wound healing, leading to the differentiation of mesenchymal stromal cells into osteoblasts. This is highly favored in those with HO located at a distance from the adjacent bone. The second hypothesis emphasizes the iatrogenic spillage of periosteal cells from the adjacent bone during surgery. In our case, HO was connected with the xiphoid process, and we could not exclude the possibility of the iatrogenic spillage of periosteal cells from the xiphoid process.

Whatever the pathogenesis hypothesis, surgical excision has been recommended for symptomatic HO. Our literature search delved deeper into HO prevention. The search returned some recommendations for preventing HO recurrence, and bone wax was one of them. Bone wax is a nonabsorbable substance composed of beeswax and petroleum jelly, and has been used to achieve hemostasis after bone resection[13]. While it functions as a mechanical barrier to stop bleeding, using it to suppress bone formation in the resection surface has also been reported[14]. Despite concerns about a chronic

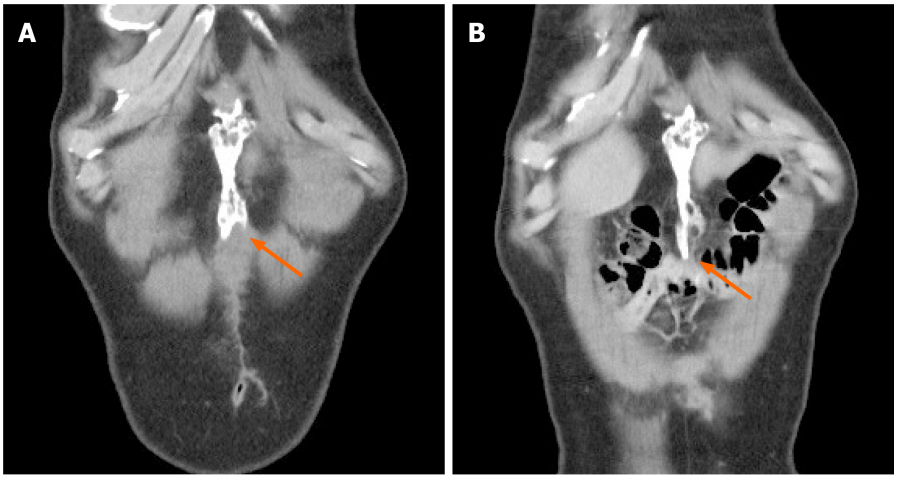

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Figure 1 Computerized tomography images showing heterotopic ossification (arrow). A: A 10 cm-sized ossification was located along the laparotomy scar six months after surgery; B: A slight increase in size was observed one year after surgery.

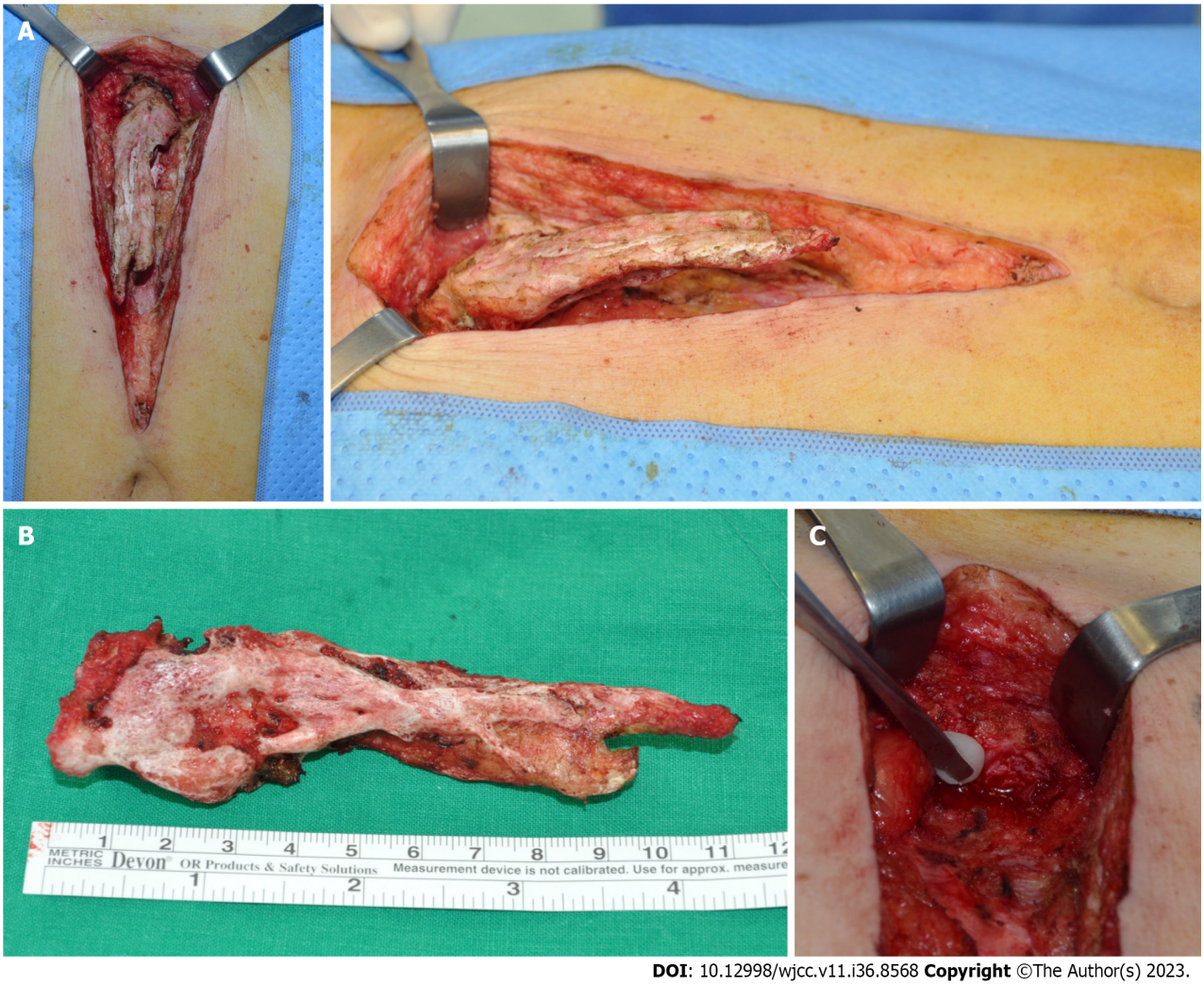

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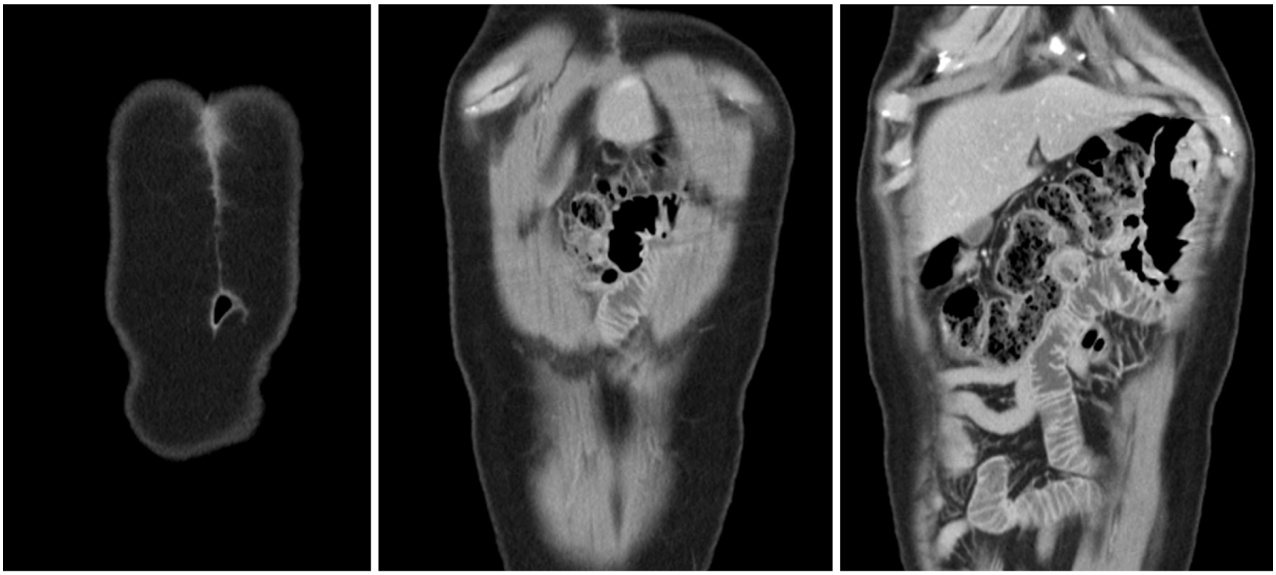
Figure 2 Excision of heterotopic ossification. A: The structure originated from the xiphoid process, extending inferiorly along the midline of the abdomen; B: The 11 cm-sized ossification was excised completely; C: Bone wax was applied to the excisional margin.



DOI: 10.12998/wjcc.v11.i36.8568

Figure 3 An abdominal computerized tomographic scan, taken one year after excision, showing no sign of recurred heterotopic ossification.

inflammatory reaction following the intraarticular use of bone wax[15], bone wax has been used as a topical sealant to prevent HO in shoulders[1], temporomandibular joints[7], and elbows[12].

Besides bone wax, postoperative radiotherapy and oral NSAIDs have been recommended as feasible preventive measures for HO[10,11]. However, we chose none of these because they are highly associated with gastrointestinal symptoms[16,17]. Gastric cancer survivors are known to experience gastrointestinal symptoms for years after surgery [18]. Our patient underwent distal subtotal gastrectomy a year earlier and was not free of gastrointestinal symptoms. Therefore, the clinical application of either radiotherapy or oral NSAIDs would have exacerbated postgastrectomy symptoms.

After much deliberation, we decided to use bone wax. Unfortunately, the outcome was an eight-week-long hospital stay and additional surgery for delayed wound closure. The application of bone wax on the abdominal surgical wound delayed its primary healing intention. A previous study reported the clinical use of bone wax in dermatologic surgery by exploiting such a distinguishing trait[19]. Bone wax has been used to cover deep tissue defects and create an ideal occlusive environment for secondary healing intention. In our case, our efforts to prevent HO recurrence left the surgical wound in a condition that was suitable only for secondary healing intention.

Complete excision may be a sufficient management strategy for HO along a laparotomy scar. We eventually made huge efforts to remove the bone wax as much as possible by massive wound irrigation and repeated cleansing with wet gauze, and there was no sign of recurrence after a year. Nevertheless, uncertainty regarding the remaining bone wax and its implication on HO prevention is a limitation of this finding. The strength would be sharing the valuable lesson that we need to be very careful about choosing a treatment method for HO using available research data and treatment should be individualized depending on the HO location. Previous reports suggesting the beneficial effect of bone wax against HO recurrence have focused on HO in joints[1,7,12]. Our effort of applying bone wax to an abdominal wound could have failed because we did not realize the distinction in treatment between different areas.

CONCLUSION

In conclusion, HO represents all types of extraskeletal ossifications in the body, and treatment approaches must be individualized depending on the surroundings. Complete surgical excision should be the priority treatment option for HO along a laparotomy scar, and the application of bone wax is not recommended.

FOOTNOTES

Author contributions: Lee SS contributed to conceptualization, design of the study, acquisition and analysis of data, drafting and revising the manuscript, and final approval of the version to be submitted.

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

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: 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 December 26; 11(36): 8574-8580

DOI: 10.12998/wjcc.v11.i36.8574

ISSN 2307-8960 (online)

CASE REPORT

Balloon displacement during caesarean section with pernicious placenta previa: A case report

Deng-Feng Gu, Chao Deng

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
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Yarmahmoodi F, Iran

Received: October 17, 2023
Peer-review started: October 17, 2023
First decision: November 20, 2023
Revised: November 26, 2023
Accepted: December 15, 2023
Article in press: December 15, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

For the past few years, preventive interventional therapy has been widely used domestically and overseas, bringing great benefits to pregnant women at high-risk for complications, such as pernicious placenta previa (PPP) and placenta accreta. Nevertheless, there are still few reports on surgical complications related to interventional therapy, and its safety should be a concern.

CASE SUMMARY

We report a 36-year-old pregnant woman with PPP who underwent balloon implantation in the lower segment of the abdominal aorta before caesarean section. However, the balloon shifted during the operation, which damaged the arterial vessels after filling, resulting in severe postpartum haemorrhage in the patient. Fortunately, after emergency interventional stent implantation, the patient was successfully relieved of the massive haemorrhage crisis.

CONCLUSION

It seems that massive postoperative bleeding has been largely avoided in preventive interventional therapy in high-risk pregnant women with placenta-related diseases, but surgical complications related to intervention therapy can also cause adverse consequences. It is equally important for clinical doctors to learn how to promptly identify and effectively treat these rare complications.

Key Words: Pernicious placenta previa; Caesarean section; Abdominal aortic balloon; Case report

Core Tip: It is well known that postpartum haemorrhage is one of the most serious complications in malignant placenta previa caesarean section, and it is also the most concerning problem for medical staff. Currently, preventive interventional therapy has been able to prevent postpartum haemorrhage to a large extent, but its surgical complications need to be acknowledged, given that they are often overlooked. This article introduces a case of adverse consequences caused by a interventional therapy complication to provide some information for medical staff's clinical work.

Citation: Gu DF, Deng C. Balloon displacement during caesarean section with pernicious placenta previa: A case report. *World J Clin Cases* 2023; 11(36): 8574-8580
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8574.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8574

INTRODUCTION

Pernicious placenta previa (PPP) is placenta previa that occurs at the uterine scar incision from a previous caesarean section[1]. Uncontrolled and fatal postpartum haemorrhage is the main threat to such pregnant women. Research statistics have shown that[2] it is common for patients with placenta previa undergoing caesarean section to experience intraoperative bleeding of up to 3000 mL, this occurs in up to 90%, and approximately 10% of them even experience bleeding exceeding the rare 10000 mL. Massive postpartum haemorrhage can easily lead to complications such as haemorrhagic shock, disseminated intravascular coagulation, and multiple organ failure, endangering the safety of pregnant women and newborns[3]. Even in severe cases, some patients have to undergo hysterectomy, which can cause great harm to their physical and mental health[4]. In recent years, the use of abdominal aortic balloons to control bleeding has been widely used in caesarean section for placenta previa[5,6]. Temporarily filling the arterial balloon before stripping the placenta not only effectively reduces intraoperative blood loss, and provides a clear surgical field, but also more importantly, reduces the rate of hysterectomy[7]. However, this kind of intervention also has corresponding surgical complications[8], such as vascular injury, pseudoaneurysm, arterial thrombosis[9], ischaemia reperfusion injury, and foetal radiation exposure. We describe a rare complication that occurred during abdominal aortic balloon occlusion combined with caesarean section in a pregnant woman with PPP and give some opinions on this phenomenon.

CASE PRESENTATION

Chief complaints

A 36-year-old woman was admitted to the hospital to terminate her pregnancy due to a recurrence of brucellosis after 20 + 4 wk of pregnancy.

History of present illness

The patient experienced an elevated body temperature two weeks earlier, even reaching a maximum of 41 ℃. She took antibiotics and antipyretic analgesics for symptomatic treatment of her brucellosis. At the same time, this pregnant woman reported that the foetal movement response significantly decreased 10 d ago. Due to fear of medication leading to foetal intrauterine death or abnormalities, after her body temperature returned to normal, she went to our hospital to ask for termination of pregnancy.

History of past illness

The patient was diagnosed with brucellosis 6 mo ago. After symptomatic treatment in other hospitals, her condition improved, and since then, the patient stopped taking the medicine herself.

Personal and family history

The patient denied any infectious disease and any relevant family history of placenta previa.

Physical examination

On physical examination, the patient's vital signs were as follows: Body temperature, 36.1 ℃; blood pressure (BP), 113/79 mmHg; heart rate (HR), 91 beats per min; respiratory rate, 16 breaths per min, height, 165 cm; weight, 70 kg. Specialist inspection: The pregnant woman's abdomen showed a gestational bulge with an abdominal circumference of 96 cm, and her pelvic floor was at the navel level. At this time, the foetal HR was 148 beats/min, but the contractions were not palpable. In gynaecological diagnosis, the cervical canal was not ruled out, the uterine orifice was not open, and the foetal membrane was not broken.

Laboratory examinations

Routine blood tests showed a haemoglobin level of 85 g/L and a C-reactive protein level of 19.95 mg/L. Blood

biochemical analysis indicated an albumin level of 28.5 g/L and a blood alkaline phosphatase level of 189.0 mmol/L.

Imaging examinations

Prenatal ultrasound examination revealed that the pregnant woman had central placenta previa and currently had subchorionic haemorrhage.

Marital and reproductive history

The patient was married at the age of 21 years. She had been pregnant a total of 5 times thus far, with two previous deliveries being caesarean sections (in 2008 and 2017) and two induced abortions.

FINAL DIAGNOSIS

The patient was diagnosed with placenta accreta without bleeding, central placenta previa, pregnancy with uterine scars, mid-term induced abortion, brucellosis, subchorionic haematoma, pregnancy with liver damage, pregnancy with hypoproteinaemia, pregnancy with anamia and pregnancy 5, delivery 2, and pregnancy 20 + 4 wk.

TREATMENT

The patient experienced fever again after admission and sustained lower abdominal pain without any underlying cause. Urgent pelvic ultrasound examination revealed local detachment of the placenta. Considering the changes in the patient's condition, it is recommended to undergo caesarean section and embryo removal surgery. Due to the clear diagnosis of central placenta previa and placenta accreta in the patient, there is a high possibility of acute massive bleeding during surgery. Therefore, to reduce the amount of bleeding, a balloon placement surgery in the lower segment of the abdominal aorta (Figure 1) was performed before the caesarean section, and immediately after the intervention surgery, a "transverse incision caesarean section for embryo retrieval in the lower segment of the uterus" was performed.

After entering the abdomen, it was found that the bladder peritoneum was tightly adhered to the the previous uterine scar. The placenta was implanted in the scar of the previous caesarean section of the uterus, and the surface blood vessels were dilated (Figure 2), making it impossible to push down the bladder peritoneum. The uterus was transversely cut 1cm above the scar, and a large amount of brownish-red purulent thread-like blood gushed out of the uterine cavity. After puncturing the amniotic membrane, a 470 g baby boy was delivered, but the foetus died, most likely due to intrauterine infection, then the pungent, pale yellow-green was immediately aspirated. After the delivery of the dead foetus, extensive implantation and adhesions of placental tissue were observed in the posterior wall, left and right walls, and lower segment of the uterus. Bleeding was active at the dissection site, and the obstetrician immediately filled the abdominal aortic balloon at this time. The blocking effect was observed to be poor, and the amount of bleeding did not decrease. Then, after the tourniquet was tied in the vascular free zone of the broad ligament in the lower segment of the uterus, the ascending branches of the bilateral uterine arteries were ligated, the posterior wall and the lower segment of the uterus were sutured with "8" shaped sutures for haemostasis and symptomatic treatment to promote uterine contraction, and the bleeding of the wound caused by the separation of uterus and placenta was reduced. Due to the time of filling of the abdominal aortic balloon up to 15 min, the balloon was immediately emptied. At this time, the patient's BP suddenly dropped to 60/30 mmHg. Blood transfusion and fluid replacement were immediately performed to treat shock. At the same time, bilateral appendages and abdominal cavities were examined, and a dark red haematoma with a diameter of approximately 10 cm was found on the right side of the sacral promontory of the posterior peritoneum, with irregular range and significant fluctuations and no significant increase in BP after deep pressure treatment. We palpated the patient's bilateral dorsalis pedis arteries, and the pulsation of the right artery was significantly weaker than that of the left. We had reason to suspect that the patient's abdominal aortic balloon shifted and injured the artery after filling it. Immediate angiography was performed to confirm the diagnosis, and it was observed that the patient's right common iliac artery was torn and bleeding, with blood extravasation forming a haematoma (Figure 3). Immediately, we requested that an interventional physician perform the right common iliac artery covered stent implantation surgery. Postoperative angiography showed that the lumen of the right common iliac artery was unobstructed, the stent was well unfolded, and no definite contrast agent leakage was observed. The ruptured vessel was successfully repaired (Figure 4), and the patient's vital signs gradually stabilized. The total duration of this surgery was 5 h, with a blood loss of approximately 3000 mL. During the surgery, 10 U of red blood cell suspension and 1000 mL of plasma were transfused.

OUTCOME AND FOLLOW-UP

After the surgery, the patient was transferred to an intensive care unit for continued close monitoring, and received active treatment, such as anti-infection therapy, promotion of uterine contractions, and correction of anaemia. After recovery, the patient was discharged from the hospital.

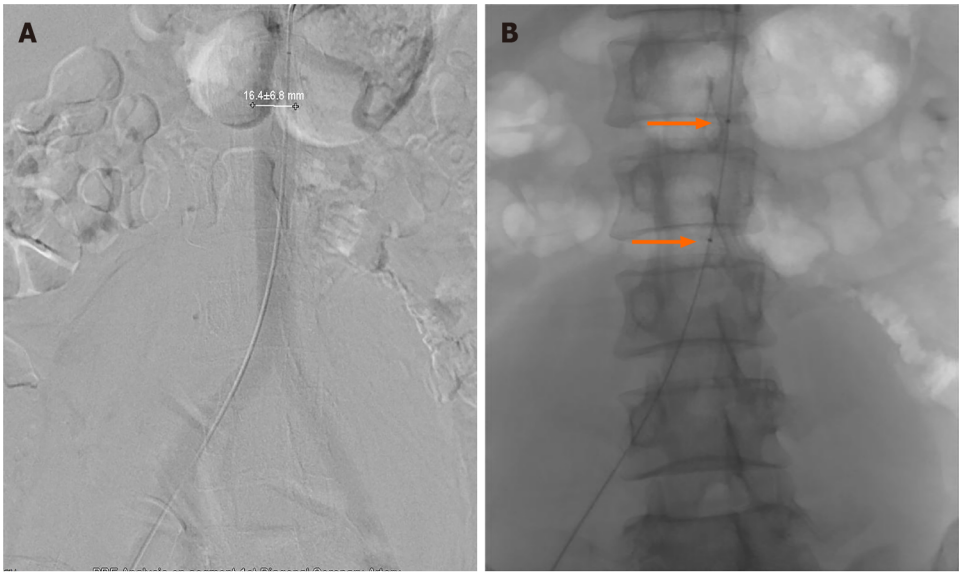

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Figure 1 Prophylactic placement of the abdominal aortic balloon before cesarean section. A: Abdominal aortography; B: Balloon catheter marker point (orange arrows).

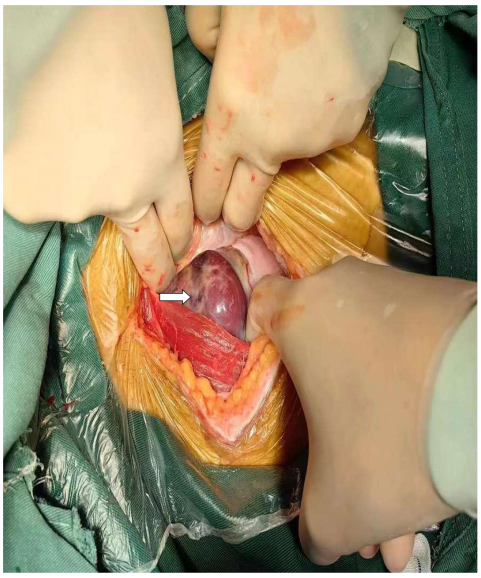

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Figure 2 Placenta is implanted in the scar of the previous cesarean section (white arrow).

DISCUSSION

With the reform of China's family planning policy, the number of caesarean sections and the difficulty of surgery are constantly increasing, especially for high-risk pregnant women with placenta previa and placenta accreta spectrum (PAS) diseases. It has been reported that the incidence rate of PPP patients in China is 0.31%-0.89%, and approximately 53.3% of PPP patients have PAS[10], which means that obstetricians and anaesthesiologists face greater challenges. For pregnant women with placenta previa or placental implantation diseases, preoperative preventive intervention treatments such as abdominal aortic balloon implantation and uterine artery embolization allow doctors rescue patients with postpartum haemorrhage and have achieved significant results both domestically and internationally[11]. However, inevitably, there are still many worrisome aspects to interventional therapy, such as whether X-ray exposure is harmful to the foetus, whether preventive intervention surgery can completely avoid postpartum haemorrhage, and whether arterial blockade can cause ischaemi damage to other organs, which are all worthy of attention.

The main feature of our case is the occurrence of a rare complication, injury to the common iliac artery caused by filling the abdominal aortic balloon after unforeseen displacement.

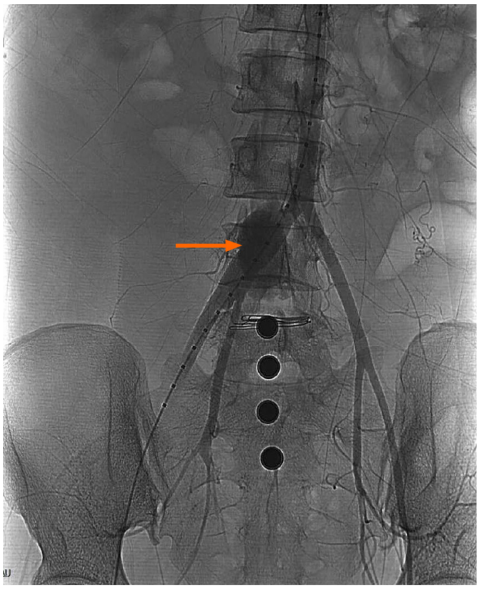

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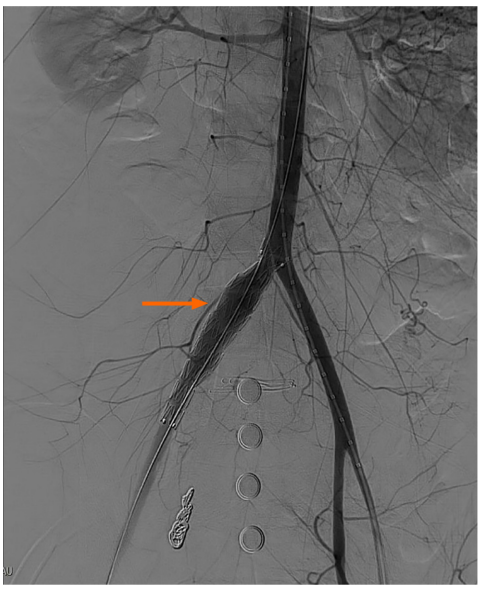
Figure 3 Blebleeding of the right common iliac artery (orange arrow).



DOI: 10.12998/wjcc.v11.i36.8574

Figure 4 Right common iliac vessel stent placement (orange arrow).

The possible reasons for the occurrence of this rare complication are as follows: (1) The preoperative abdominal aortic balloon implantation surgery for patients undergoing caesarean section is performed using digital subtraction angiography equipment in the interventional surgery room. After completion, the patient needs to be transported to the operating room for caesarean embryo removal. During this period, multiple handling of the patient is inevitable, and frequent and nonstandard bed transfer processes lead to the displacement of the abdominal aortic balloon; (2) during caesarean section, the delivery of the foetus requires external force to compress the fundus of the uterus, and the surgeon usually pushs directly above the abdominal aortic balloon. Inappropriate force may also be one of the reasons for balloon displacement; (3) pregnant women have a different abdominal pressure from ordinary people. When the foetal placenta is delivered and amniotic fluid flows out, the uterine volume decreases, and the abdominal pressure drops suddenly. The changes in pressure before and after can cause the fixed balloon to shift; (4) after the balloon was correctly placed in position, the arterial sheath at the femoral artery puncture point and balloon catheter were not well fixed. Although the adhesive used for fixation during the surgery in this case did not fail, it is still possible that the catheter had moved outwards and (5) the discrepancy between the size of the balloon catheter and the patient's blood vessels, as well as the inadequate placement of the balloon catheter, are also reasons for this shift.

Summary of experience and lessons learned from this case: (1) For the delivery foetuses of pregnant women with PPP accompanied by placental implantation, it is necessary to pay attention to the prevention and treatment of severe postpartum haemorrhage, and multidisciplinary cooperation is essential. All departments should make comprehensive preoperative preparations and take corresponding measures, including preinstall abdominal aorta or bilateral common iliac artery balloon blockers in the interventional radiology department to prevent bleeding during placenta removal. The obstetrics department should develop a rigorous surgical plan and be equipped with sufficient qualified and experienced surgeons. The anaesthesia department should prepare for the rescue of intraoperative massive bleeding, such as invasive BP monitoring, multiple infusion pathways, rapid airway establishment plans, blood products, and liquid resuscitation supplies. At the same time, the intensive care department and nursing team should conduct rigorous postoperative observations and meticulous care; (2) at present, preoperative arterial balloon implantation has been performed under ultrasound guidance instead of X-ray[12]. Ultrasound monitoring equipment not only prevents physicians and patients from receiving radiation but also foetuses. Moreover, this technology does not require specialized hybrid operating rooms, greatly saving operating time and reducing the occurrence of balloon catheter displacement due to transportation. At the same time, ultrasound can be used to dynamically monitor the position of the balloon, adjust the position deviation in a timely manner, avoid complications caused by this, and ensure the safety of the mother and baby; (3) the catheter needs to be fix in a more meticulous manner, such as marking the catheter and skin at the puncture point after successful placement, to observe its position at any time, determine whether it is dislodged and determine whether the balloon is displaced; and (4) even a perfect preoperative preparation cannot completely avoid the occurrence of all unexpected situations. PPP and balloon displacement can both lead to the occurrence of severe bleeding in patients. As in this case, the combination of two risk factors further increases the risk and volume of bleeding, leading to uncontrollable massive bleeding during surgery, making the patient's condition even more dangerous. Therefore, surgeons should maintain a vigilant mentality, handle possible critical situations with cautious and meticulous surgical operations, and summarize experiences and lessons in a timely manner. Only in this way can we ensure the safety of patients' lives.

CONCLUSION

Pregnant women with PPP often need preventive interventional therapy before undergoing caesarean section, which can significantly reduce the incidence of postpartum haemorrhage and a series of serious adverse consequences. However, the patient experienced a rare complication of balloon displacement, which led to more severe postpartum haemorrhage. Yet, after timely identification and multidisciplinary collaboration in diagnosis and treatment, the life of this pregnant woman was ultimately saved. Thus, any treatment method has complications, so regardless of the probability of occurrence, clinical doctors should remain vigilant, be prepared to face all possible critical situations, gain clinical experience, and protect the patient's life.

FOOTNOTES

Author contributions: Gu DF contributed to manuscript writing and editing, Deng C contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

Supported by Curriculum Case Base Construction Project of the First Affiliated Hospital of Xinjiang Shihezi University, No. 2021Y-AL15.

Informed consent statement: Informed consent was obtained from the patients for publication of this case report details.

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: Qu XL
L-Editor: A
P-Editor: Qu XL

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World Journal of Clinical Cases

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

World J Clin Cases 2023 December 26; 11(36): 8581-8588

DOI: 10.12998/wjcc.v11.i36.8581

ISSN 2307-8960 (online)

CASE REPORT

Synchronous carotid endarterectomy and coronary artery bypass graft: Four case reports

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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
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Lakusic N, Croatia; Ueda H, Japan

Received: October 18, 2023
Peer-review started: October 18, 2023
First decision: November 13, 2023
Revised: November 19, 2023
Accepted: December 13, 2023
Article in press: December 13, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

One of the major perioperative complications for coronary artery bypass graft (CABG) is stroke. The risk of perioperative stroke after CABG is approximately 2%. Carotid stenosis (CS) is considered an independent predictor of perioperative stroke risk in CABG patients. The optimal management of such patients has been a source of controversy. One of the possible surgical options is synchronous carotid endarterectomy (CEA) and CABG. Here, we have presented 4 cases of successful synchronous CEA and CABG.

CASE SUMMARY

Our center's experience with 4 cases of significant carotid artery stenosis, which were successfully managed with combined CEA and CABG, are detailed. The first case was a female who presented for CABG after a ST-elevation myocardial infarction. She had right internal carotid artery (ICA) occlusion and 90% left ICA stenosis. The second case was a male who was electively admitted for CABG. It was discovered that he had left ICA occlusion and 90% right ICA stenosis. The third case was a male with a history of stroke, two months prior to admission. He presented with non-ST-elevation myocardial infarction. Preoperatively, it was

discovered that he had > 90% right ICA stenosis. The final case was a male who was electively admitted for CABG. It was discovered that he had bilateral > 90% ICA stenosis. We have also reviewed the current evidence and guidelines for managing CS in patients undergoing CABG.

CONCLUSION
Our case series demonstrated that synchronous CEA and CABG was safe. A multicenter study with additional patients is needed. It is necessary for clinicians to screen for CS in high-risk patients with features.

Key Words: Carotid artery stenosis; Carotid endarterectomy; Coronary artery bypass grafting; Coronary artery disease; Synchronous; Case report

Core Tip: The risk of perioperative stroke after coronary artery bypass graft (CABG) is 2%. A hemodynamically significant carotid artery stenosis is found in 7% of patients undergoing CABG. Carotid stenosis is considered an independent predictor for the risk of perioperative stroke in CABG patients. The optimal management of such patients has been a source of controversy, but one of the possible surgical options is combined carotid endarterectomy and CABG. Our case series suggested that this option is safe for the management of this population of patients.

Citation: AlGhamdi FK, Altoijry A, AlQahtani A, Aldossary MY, AlSheikh SO, Iqbal K, Alayadhi WA. Synchronous carotid endarterectomy and coronary artery bypass graft: Four case reports. *World J Clin Cases* 2023; 11(36): 8581-8588
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8581.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8581

INTRODUCTION

Ischemic heart disease and ischemic stroke are the two leading causes of death worldwide[1]. Due to similar pathophysiologic processes, coronary artery disease and carotid artery disease can coexist. A hemodynamically significant carotid artery stenosis (> 50% stenosis) is found in 7% of patients undergoing coronary artery bypass grafting (CABG)[2]. One of the major perioperative complications for CABG is stroke. The risk of perioperative stroke after CABG is around 2%[2]. Carotid stenosis (CS) is considered an independent predictor for the risk of perioperative stroke in CABG patients[3]. The optimal management of such patients has been a source of controversy. One of the possible surgical options for treatment is synchronous carotid endarterectomy (CEA) and CABG. In this work, we reported the experience of 4 cases of successful combined CEA and CABG at a single center and briefly reviewed the literature.

CASE PRESENTATION

Chief complaints

Case 1: A 64-year-old female presented with typical ischemic chest pain.

Case 2: A 76-year-old male presented with the complaint of chronic chest discomfort that was related to physical exertion.

Case 3: A 63-year-old male presented with severe chest pain that started 6 h prior to presentation to the emergency department.

Case 4: A 71-year-old male presented with shortness of breath and orthopnea that started the morning of his presentation.

History of present illness

Case 1: The patient presented to our emergency department with chest pain that was retrosternal and radiating to the left. She previously had similar pain that was related to physical activity. The previous pain was aggravated by physical activity and relieved by rest. However, the pain at presentation was more severe and occurred during rest.

Case 2: The patient presented to the clinic with a 6-mo history of chest discomfort and tightness that was triggered by physical exertion and relieved by rest. He denied any shortness of breath, palpitations, or loss of consciousness. The patient was electively admitted to our center for diagnostic coronary angiography (CAG).

Case 3: The patient presented to our emergency department with severe left-sided chest pain that was radiating to the back and left shoulder. The chest pain started while the patient was at rest and was associated with shortness of breath

and sweating. He was admitted with an initial diagnosis of non-ST elevation myocardial infarction (NSTEMI).

Case 4: The patient presented to our emergency department with shortness of breath that started that morning while at rest. He was also experiencing chest heaviness and sweating. He was admitted with an initial diagnosis of NSTEMI.

History of past illness

Case 1: The patient had diabetes, which was poorly controlled, and hypertension. In addition, she had hypothyroidism. She previously had an infected foot ulcer that was treated by amputation of the right big toe.

Case 2: The patient had end-stage renal disease and hypertension.

Case 3: The patient had hypertension. He also had a history of pulmonary embolism that was treated with oral anticoagulation medication. He suffered a stroke 2 mo prior to presentation and experienced residual left-sided weakness.

Case 4: The patient had hypothyroidism and bilateral carotid artery stenosis.

Personal and family history

There were no family history of cardiac disease or stroke of all patients.

Physical examination

Case 1: The patient was alert, conscious, and oriented with stable vital signs. She had normal bilateral vesicular breathing sounds. Heart sounds were normal with no murmurs or added sounds. Peripheral pulses were palpable with normal volume on both upper and lower limbs.

Case 2: The patient was alert, conscious, and oriented with stable vital signs. He had normal bilateral vesicular breathing sounds. Heart sounds were normal with no murmurs or added sounds. Peripheral pulses were palpable with normal volume on both upper and lower limbs. He had an arteriovenous fistula on his left arm that was used for dialysis.

Case 3: The patient was alert, conscious, and oriented with stable vital signs. He had normal bilateral vesicular breathing sounds. Heart sounds were normal with no murmurs or added sounds. Peripheral pulses were palpable with normal volume on both upper and lower limbs. The motor power of the patient's upper and lower limbs on the left side was reduced. However, sensation and proprioception were preserved.

Case 4: The patient was alert, conscious, and oriented with stable vital signs. He had normal bilateral vesicular breathing sounds. Heart sounds were normal with no murmurs or added sounds. Peripheral pulses were palpable with normal volume on both upper and lower limbs.

Laboratory examinations

Case 1: The patient's routine blood work was normal with the exception of the hemoglobin A1c level, which was 9.9% (normal range: < 5.7%).

Case 2: The patient's routine blood work was normal with the exception of the creatinine level, which was 575 mmol/L (normal range: 53-106 mmol/L). The estimated glomerular filtration rate was very low (8.4 mL/min/1.73 m^2; normal range: ≥ 90 mL/min/1.73 m^2).

Case 3: The patient's routine blood work was normal with the exception of the high-sensitivity troponin-T level which was 126 ng/L (normal range: 0.0002-58.9 ng/L).

Case 4: The patient's routine blood work was normal with the exception of the high-sensitivity troponin-T level which was 200 ng/L. The patient's hemoglobin A1c level was slightly elevated (6.1%).

Imaging examinations

Case 1: Echocardiography showed a 30%-35% left ventricular ejection fraction (LVEF) with no significant valvular abnormalities. CAG showed triple vessel disease. Carotid Doppler showed total occlusion of the right internal carotid artery (ICA) and > 90% stenosis of the left ICA (Figure 1).

Case 2: Echocardiography showed a > 50% LVEF with mild mitral regurgitation. CAG showed triple vessel disease. Carotid Doppler showed total occlusion of the left ICA and > 90% stenosis of the right ICA (Figure 2).

Case 3: Echocardiography showed a 30% LVEF with mild aortic regurgitation. CAG showed left main coronary artery stenosis (> 50%). Carotid Doppler showed 90%-99% stenosis of the right ICA and normal left ICA (Figure 3).

Case 4: Echocardiography a 35%-40% LVEF with mild mitral regurgitation. CAG showed significant triple vessel disease. Carotid Doppler showed 90% stenosis of the left ICA and > 90% stenosis of the right ICA (Figure 4).

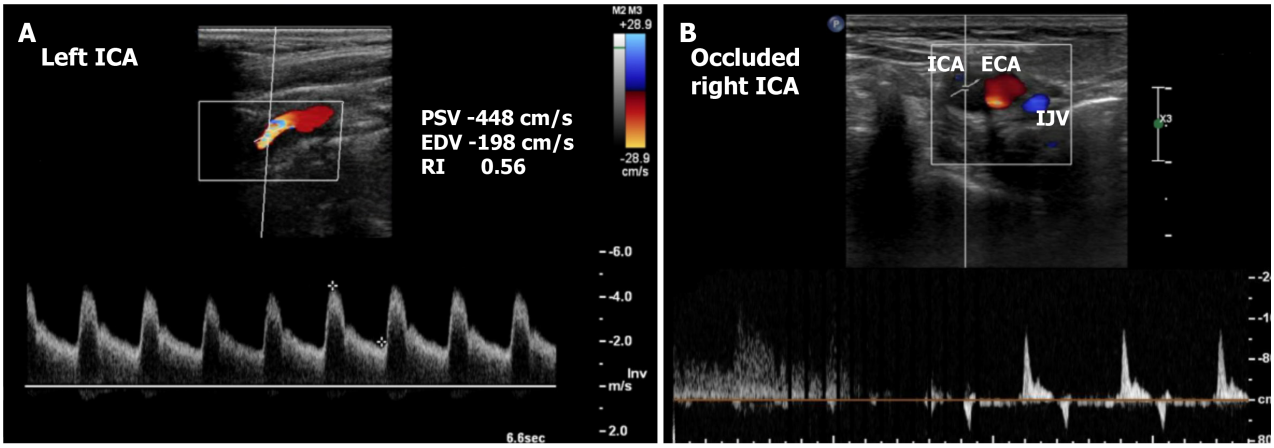

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Figure 1 Preoperative carotid ultrasound duplex in case 1. A: Left internal carotid artery stenosis of > 90%; B: Totally occluded right interval carotid artery. ECA: External carotid artery; EDV: End-diastolic velocity; IJV: Internal jugular vein; PSV: Peak systolic velocity; RI: Resistance index; ICA: Internal carotid artery.

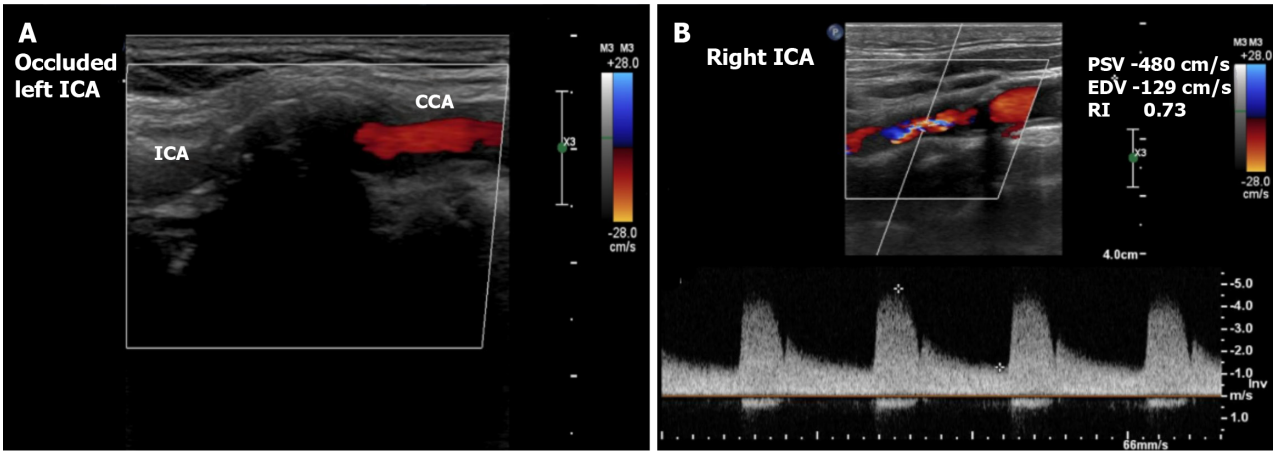

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Figure 2 Preoperative carotid ultrasound duplex in case 2. A: Totally occluded left internal carotid artery; B: Right interval carotid artery stenosis of > 90%. CCA: Common carotid artery; EDV: End-diastolic velocity; PSV: Peak systolic velocity; RI: Resistance index; ICA: Internal carotid artery.

FINAL DIAGNOSIS

Case 1: The patient was diagnosed with triple vessel coronary artery disease with low ejection fraction and total occlusion of the right ICA and 90% stenosis of the left ICA.

Case 2: The patient was diagnosed with triple vessel coronary artery disease with preserved ejection fraction and total occlusion of the left ICA and > 90% stenosis of the right ICA.

Case 3: The patient was diagnosed with left main coronary artery stenosis with reduced LVEF, NSTEMI, and > 90% stenosis of the right ICA.

Case 4: The patient was diagnosed with triple vessel coronary artery disease presenting as NSTEMI with reduced ejection fraction and bilateral > 90% ICA stenosis.

TREATMENT

Case 1: The patient underwent left CEA and on-pump CABG.

Case 2: The patient underwent right CEA and on-pump CABG.

Case 3: The patient underwent right CEA and on-pump CABG.

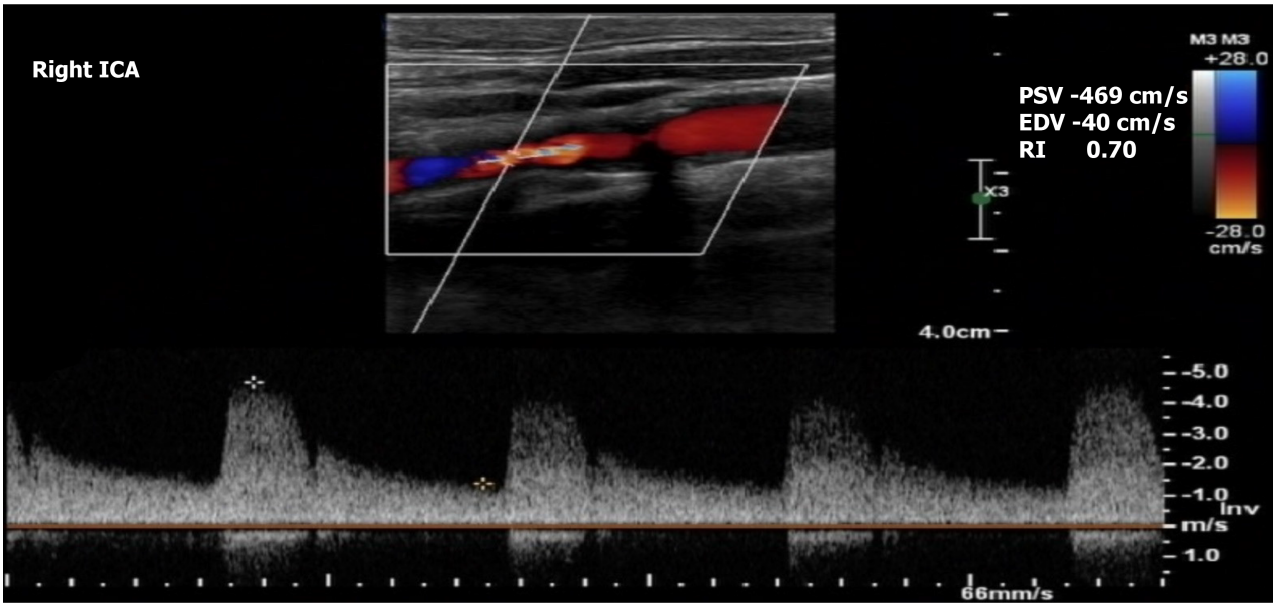

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Figure 3 Preoperative carotid ultrasound duplex showed right internal carotid artery stenosis of > 90% in case 3. EDV: End-diastolic velocity; PSV: Peak systolic velocity; RI: Resistance index; ICA: Internal carotid artery.

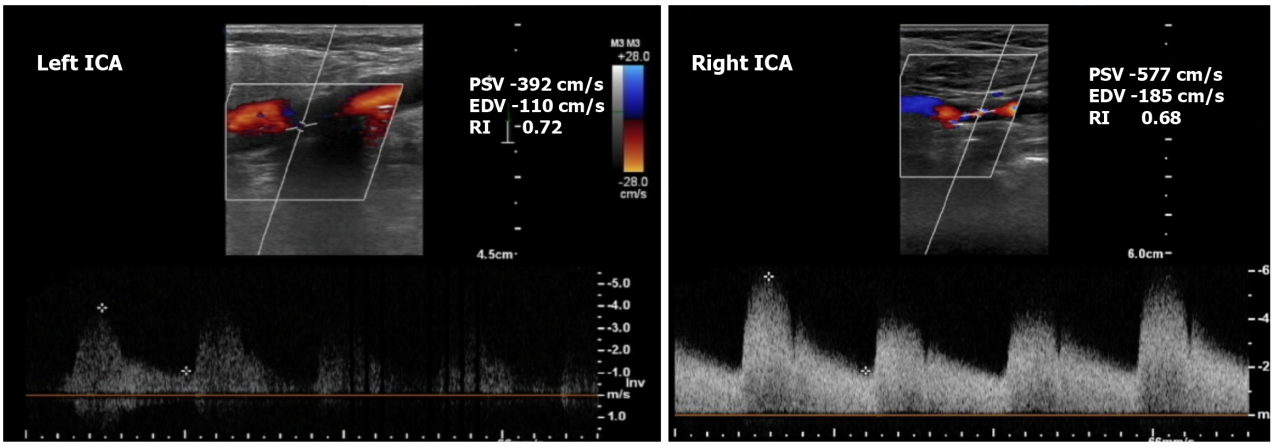

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Figure 4 Preoperative carotid ultrasound duplex in case 4. Bilateral internal carotid artery stenosis of > 90%. EDV: End-diastolic velocity; PSV: Peak systolic velocity; RI: Resistance index; ICA: Internal carotid artery.

Case 4: The patient underwent left CEA and on-pump CABG, with planned right CEA 12 mo after the CABG.

OUTCOME AND FOLLOW-UP

Case 1: The patient's postoperative course was uneventful and was discharged 1 wk after her surgery. Her last follow-up was 5 years after the surgery. She did not experience stroke or myocardial infarction (MI) during the follow-up period.

Case 2: The patient's postoperative course was uneventful, he was discharged after 2 wk. His last follow up was 4 years after the surgery. He did not experience stroke or MI during the follow-up period.

Case 3: The patient had no complications postoperatively and was discharged 5 d after the surgery. His last follow up was 1 year after the surgery. He did not experience stroke or MI during the follow-up period.

Case 4: The patient's intensive care unit stay was uneventful and he was transferred to the ward 4 d after the surgery and discharged on the 6th d postoperatively. His last follow-up was 1 year after the surgery. He did not experience stroke or MI during the follow-up period.

DISCUSSION

The risk of perioperative stroke in patients who are treated with CABG is around 2%[2]. CS is considered an independent predictor for the risk of perioperative stroke in CABG patients[3]. There are multiple causes of perioperative stroke in patients undergoing CABG, including CS, aortic embolism during manipulation, cannulation and decannulation, graft anastomosis to the aorta, platelet aggregation on cardiopulmonary bypass, hypercoagulable states, postoperative arrhythmias, and hemodynamic instability[4]. CS > 80% is found in 7% of CABG patients[2]. The risk of perioperative stroke in CABG patients with > 50% and > 80% CS is 7% and 9%, respectively[5]. The impact of perioperative stroke on patient survival is significant when compared to the survival of cardiac surgery patients with no stroke. In a meta-analysis of 174000 cardiac operations, the operative mortality of patients who suffered perioperative stroke was 29.0% *vs* 2.4% in patients who did not suffer from perioperative stroke ($P < 0.001$)[6].

The routine screening of CS in patients who are candidates for cardiac surgery is controversial. Most of the international societies support selective screening for high-risk patients[4,7]. The European Society of Cardiology (ESC) recommends screening patients who are undergoing CABG with duplex ultrasound if they have a history of recent (< 6 mo) transient ischemic attack (TIA) or stroke[4]. They also recommend screening patients with no history of recent TIA or stroke but are ≥ 70-years-old, have multivessel coronary artery disease, have concomitant peripheral arterial disease, or have carotid bruit on examination[4]. The ESC does not recommend screening patients if they require urgent CABG and have no history of recent TIA/stroke[4]. The European Society for Vascular Surgery (ESVS) recommends screening patients who are aged > 70-years-old, have a history of TIA or stroke, carotid bruit, or left mainstem disease[7].

Prophylactic carotid intervention in patients with carotid artery stenosis is controversial. There is no strong evidence to support carotid intervention in all CABG patients with asymptomatic CS[4]. Select patients may benefit significantly from carotid intervention because it could reduce their risk of stroke-related morbidity and mortality and of a prolonged hospital stay[2]. Patients who could benefit are at a high risk of postoperative stroke, such as patients with asymptomatic severe (70%-99%) bilateral stenosis, asymptomatic severe stenosis with contralateral occlusion, or a history of prior stroke or TIA[4,7].

The surgical and endovascular options for patients are staged CEA then CABG, staged CABG then CEA, synchronous CEA plus CABG, staged carotid artery stenting (CAS) then CABG, and same day CAS then CABG. Most of the data comparing these options are from observational studies and meta-analyses. In a meta-analysis that involved 25021 patients who had undergone either combined or staged CEA and CABG, there was no difference between the two approaches in early mortality (relative risk: 1.36; 95% confidence interval: 0.78-2.36; $P = 0.27$) and postoperative stroke (relative risk: 1.14; 95% confidence interval: 0.99-1.31; $P = 0.07$)[8].

There are only two randomized controlled trials that evaluated synchronous or staged CEA in CABG patients with unilateral asymptomatic CS. Illuminati *et al*[9] randomized 185 patients with severe unilateral asymptomatic CS to one of three groups: CEA synchronous with CABG; staged CEA before CABG; or isolated CABG then delayed CEA. They concluded that staged CEA then CABG or synchronous CEA and CABG prevented stroke better than delayed CEA. The CABACS (*i.e.*, Coronary Artery Bypass graft surgery in patients with Asymptomatic Carotid Stenosis) trial randomized 129 CABG patients from 17 centers. The enrolled patients had unilateral asymptomatic severe (80%-99%) CS. They were randomized to either synchronous CEA and CABG or CABG alone. The 30-d death/stroke rate among patients who underwent the synchronous procedure was 18.5% *vs* 9.7% in patients with isolated CABG[10]. Unfortunately, this trial was terminated prematurely after funding withdrawal. However, the authors concluded that the very high rate of perioperative stroke does not justify the synchronous approach in patients with severe asymptomatic CS[10].

One of the options to manage this population of patients is either same-day or staged CAS. This modality may be beneficial because it is less invasive compared to conventional CEA. However, CAS can complicate the management of CABG patients because dual-antiplatelet therapy is needed after CAS. This could increase the risk of bleeding during the CABG procedure or increase the risk of MI if CABG was delayed for the administration of dual-antiplatelets. In a systematic review that included 11 studies that evaluated the outcome of 760 staged or same-day CAS plus CABG procedures, the majority of the patients (87%) were asymptomatic. The overall mortality rate was 5.5%, and the risk of suffering any stroke was 4.2%[11]. This review also observed that CABG performed within 48 h of a CAS procedure was not associated with a significant risk compared to CABG performed 2 wk after a CAS procedure[11].

The most recent guidelines emphasize that the management of patients should be individualized and determined by a multidisciplinary team[4]. The ESC recommends that patients who will be treated with a CABG procedure and who have a recent history of stroke or TIA should be considered for carotid revascularization if there is 50%-99% CS, without specifying the means for revascularization[4]. They also recommend that prophylactic carotid revascularization may be considered in a patient with bilateral 70%-99% CS or 70%-99% CS and contralateral occlusion[4]. On the other hand, the most recent ESVS guidelines were more specific in regard to the modality and timing of revascularization[7]. The ESVS recommends staged or synchronous CEA and CABG in patients who have a recent history of TIA or stroke with ipsilateral 50%-99% CS[7]. It also recommends staged or synchronous CAS/CEA and CABG in patients who are asymptomatic and who have either bilateral 70%-99% CS or 70%-99% CS and contralateral occlusion[7].

CONCLUSION

In conclusion, CS is prevalent among patients with coronary artery disease who are undergoing CABG. Screening for CS is indicated in patients with high-risk features, such as old age and left mainstem disease. The indications, modality, and timing for carotid revascularization in CABG patients is still controversial, and more evidence is needed to decide on the

best management plan for this patient population.

FOOTNOTES

Author contributions: AlGhamdi FK, Altoijry A, AlQahtani A, Aldossary MY, AlSheikh SO, Iqbal K, and Alayadhi WA contributed to the study design, literature review, and manuscript writing; AlGhamdi FK, AlQahtani A, and Aldossary MY contributed to the data collection and analysis; and all authors read and approved the final manuscript.

Informed consent statement: Written informed consent was obtained from all of the patients for publication of this case series and accompanying images. A copy of the written consent is available for review upon request.

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

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

World J Clin Cases 2023 December 26; 11(36): 8589-8594

DOI: 10.12998/wjcc.v11.i36.8589

ISSN 2307-8960 (online)

CASE REPORT

Intraoperative cardiogenic shock induced by refractory coronary artery spasm in a patient with myasthenia gravis: 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): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liu YC, China

Received: October 26, 2023
Peer-review started: October 26, 2023
First decision: November 22, 2023
Revised: November 24, 2023
Accepted: December 7, 2023
Article in press: December 7, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Coronary artery spasm (CAS) is a rare but critical condition during surgery. Clinical manifestations can vary from only subtle electrocardiography change to sudden death. In this case report, we present the case of a patient with myasthenia gravis (MG) who developed refractory CAS-related cardiogenic shock during thymoma surgery.

CASE SUMMARY

A 61-year-old man had a history of cigarette smoking and coronary artery disease with a bare metal stent placed. Three months ago, he suffered from coronary spasms, with three vessels involved, after surgery for cervical spine injury. He started having progressive dysphagia 4 wk prior and was diagnosed with MG *via* serologic tests, and computed tomography declared a thymoma in the anterior mediastinum. After the symptoms of MG subsided, he was referred for thymectomy. The operation was uneventful until the closing of the sternal wound. Electrocardiography showed sudden onset ST elevation, followed by ventricular tachycardia and severe hypotension. Cardiopulmonary cerebral resuscitation was initiated immediately with electrical defibrillation, extracorporeal membrane oxygenation was performed due to refractory cardiogenic shock, and the patient was transferred to an angiography room. Angiography showed diffuse CAS with three vessels involved. Intracoronary isosorbide dinitrate and adenosine were administered, and then the patient was transferred to the intensive care unit.

CONCLUSION

Our case highlights the importance of being prepared for clinical situations such as the one described here and suggests the necessity of developing an appropriate anesthesia plan that includes proactive analgesia and preemptive coronary vasodilators.

Key Words: Coronary spasm; Myasthenia gravis; Thymectomy; Shock; Case report

Core Tip: In previous literature reviews, it has been noted that a correlation exists between myasthenia gravis (MG) and cardiac complications, such as coronary artery spasm (CAS), which frequently manifests as chest pain in affected patients. Nevertheless, when MG coincides with thymoma, surgical intervention is often necessary. The diagnosis of CAS while the patient is under general anesthesia poses a considerable challenge. Our case report aims to underscore scenarios of this nature and suggests an optimal anesthesia strategy in such cases.

Citation: Hsu CW, Chang CC, Lin CS. Intraoperative cardiogenic shock induced by refractory coronary artery spasm in a patient with myasthenia gravis: A case report. *World J Clin Cases* 2023; 11(36): 8589-8594
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8589.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8589

INTRODUCTION

Coronary artery spasm (CAS) was recently recognized as a cause of myocardial infarction with nonobstructive coronary arteries[1]. The transient cessation of the coronary blood supply causes clinical manifestations that mimic ischemic heart disease. Perioperative CAS can be challenging for anesthesiologists, especially when patients are sedated or under general anesthesia. We present a case of myasthenia gravis (MG) that developed coronary spasm-related cardiogenic shock during thymoma surgery.

CASE PRESENTATION

Chief complaints

A 61-year-old man was diagnosed with MG and thymoma. He was scheduled for median sternotomy to undergo resection of the thymoma.

History of present illness

The patient started having progressive dysphagia 4 wk prior, and the associated symptoms included diplopia, ptosis, general weakness, and easy choking. He denied chest pain, bloody sputum, and fever. Serologic tests were positive for antibodies against the acetylcholine receptor (serum level: 88.3 nmol/L). Computed tomography revealed a 5.4 cm enhanced lobular mass in the anterior mediastinum, which was declared to be a thymoma. He was diagnosed with MG, and intravenous immunoglobulin was administered at a dose of 600 mg/kg once-daily for 5 consecutive days. The symptoms of MG subsided after 20 d, and he was referred for surgical intervention. Preoperative echocardiography revealed preserved systolic function and normal wall motion without major valvular dysfunction. Thus, a medium sternotomy for anterior mediastinum tumor resection was arranged.

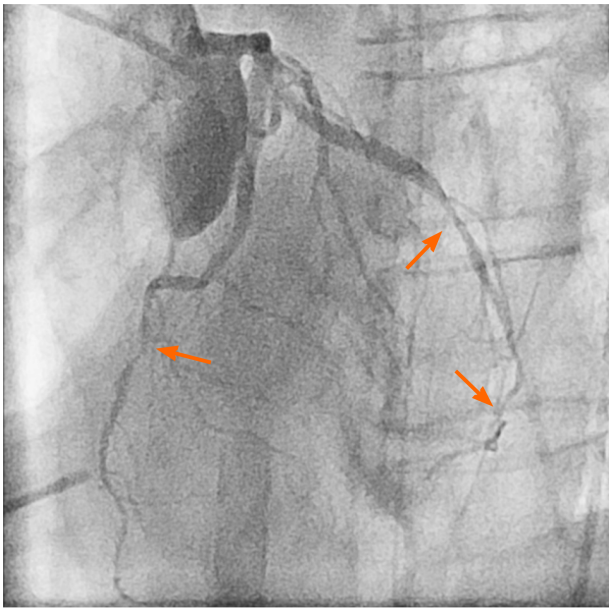
In the operating theater, general anesthesia was induced with lidocaine 60 mg, thiamylal sodium 300 mg, fentanyl 50 μg, and rocuronium 40 mg. A 37-Fr double lumen endotracheal tube was intubated, and then an arterial line and a central venous catheter were placed smoothly. The operation was uneventful until the closing of the sternal wound. Electrocardiography showed sudden onset ST elevation, followed by ventricular tachycardia and severe hypotension. Cardiopulmonary cerebral resuscitation was initiated immediately with electrical defibrillation (200 J), and the surgeon started to perform direct cardiac massage. However, ventricular tachycardia/fibrillation and hypotension persisted. Extracorporeal membrane oxygenation (ECMO) was performed 40 min after the initiation of cardiopulmonary cerebral resuscitation.

History of past illness

The patient had a history of cigarette smoking and coronary artery disease with a bare metal stent placed 11 years prior. In January 2021, he suffered from a cervical spine injury with disc fracture at C5–6 and central cord syndrome from a traffic accident. He underwent cervical discectomy and interbody fusion with a cervical cage. After transfer to the intensive care unit, chest pain was mentioned. Then, sudden onset bradycardia following ventricular tachycardia and cardiac arrest occurred. Coronary angiography showed spasms in three vessels without obvious atherosclerotic lesions. He was transferred to a normal ward 10 d later and then discharged after rehabilitation was completed.

Personal and family history

The patient denied any family history of MG.



DOI: 10.12998/wjcc.v11.i36.8589

Figure 1 Diffuse spasm involving the left anterior descending artery and left circumflex artery (arrows).

Physical examination

After ECMO insertion, the patient's arterial blood pressure was approximately 90/50 mmHg. The heart rate was around 70 beats per minute and respiratory rate was set at 12 breaths per minute. Capnography showed a low end tidal CO_2 level (under 20 mmHg).

Laboratory examinations

Arterial blood gas data showed acidosis (PH = 7.304) with elevated $PaCO_2$ (70.4 mmHg) and $HCO3^-$ (35.3 mEq/L). Serum lactate level also increased (8.5 mmol/L). Serum creatine kinase (CK) and CK muscle and brain isoenzyme levels were in normal range but troponin-T level was elevated (0.039 ng/mL).

Imaging examinations

Electrocardiography indicated a return to sinus rhythm with ST elevation within 10 min. Subsequent transesophageal echocardiography exhibited global hypokinesia. Further assessment through angiography unveiled diffuse CAS with three vessels involved (Figure 1).

FINAL DIAGNOSIS

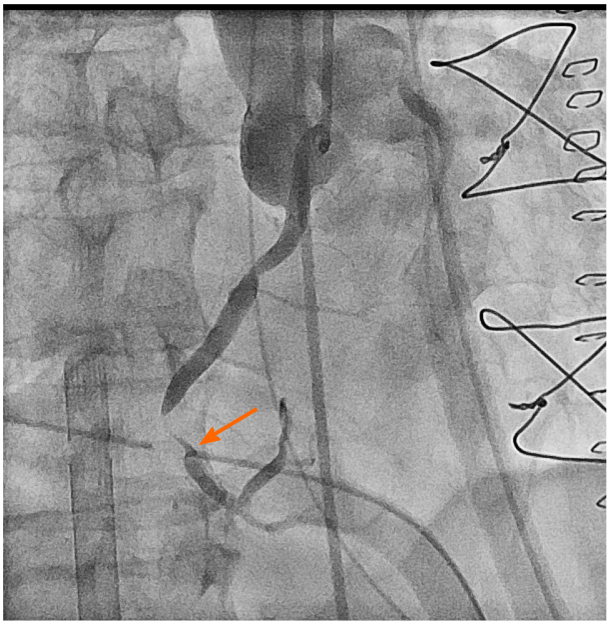
Cardiogenic shock due to diffuse CAS with three vessels involved.

TREATMENT

A total of 1600 mg intracoronary isosorbide dinitrate and 360 mg adenosine were administered. After transient relief, refractory spasm was noted at the right coronary artery (Figure 2); thus, a bare metal stent was placed (Figure 3). An intra-arterial balloon pump was placed due to poor contraction of the left ventricle, and then the patient was transferred to the intensive care unit.

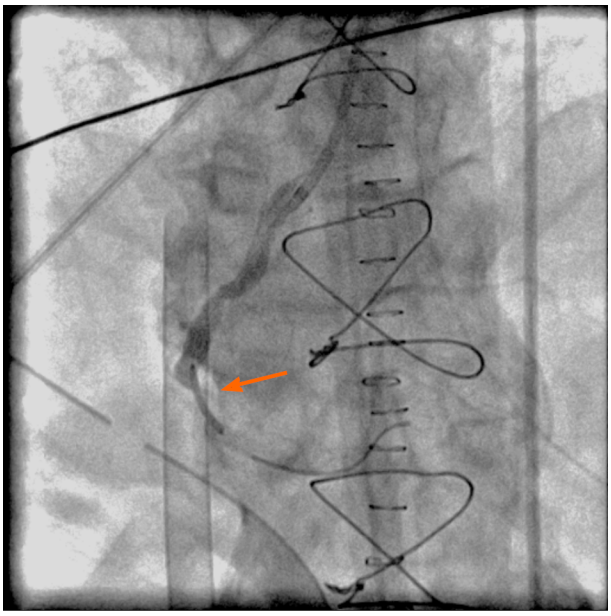
OUTCOME AND FOLLOW-UP

The patient regained consciousness on the following day. A week later, echocardiography revealed improved left ventricular systolic function; thus, the intra-arterial balloon pump and ECMO were removed. He was then transferred to a ward for a rehabilitation program and discharged. However, he had pneumonia and progressed into sepsis 5 mo later and expired due to multiorgan failure.



DOI: 10.12998/wjcc.v11.i36.8589

Figure 2 Refractory spasm of the right coronary artery after intracoronary isosorbide dinitrate and adenosine administration (arrow).



DOI: 10.12998/wjcc.v11.i36.8589

Figure 3 A bare metal stent was placed at the right coronary artery (arrow).

DISCUSSION

CAS is a rare condition, and its diverse manifestations can sometimes be critical, especially perioperatively. Some risk factors for CAS have been identified, such as age, sex, smoking, and physical and mental stress, and the usage of sympathomimetic and parasympathomimetic agents can be precipitating factors. The pathophysiology of CAS can be multifactorial, including endothelial dysfunction, autonomic nervous system disorder, and oxidative stress. One study reviewed 115 cases with perioperative CAS, and most cases of CAS occurred during abdominal or thoracic surgery. The authors considered inadequate depth of general anesthesia, use of vasopressors, and vagus nerve stimulation as possible contributing factors. Most patients had normal preoperative electrocardiograms. However, almost every patient (97%) presented ST segment changes when CAS occurred, and approximately 20% were associated with ventricular fibrillation or cardiac arrest[2].

MG is an autoimmune neuromuscular disease, and antibodies to acetylcholine receptors at neuromuscular junctions cause muscle weakness. Usually, antibodies bind only to the skeletal system. However, in patients with MG combined

with thymoma, specific striational antibodies bind to heart muscle, which may be related to the myocarditis and myositis that occur in MG patients[3]. Several case reports have presented the occurrence of CAS in patients with MG after cholinesterase inhibitor or intravenous immunoglobulin treatment[4]. Acetylcholine, as a parasympathetic neurotransmitter of the endothelium, is usually related to coronary dilation; however, it can induce vasospasm through vascular smooth muscle constriction when the endothelium is damaged[5,6]. While the precise mechanism is not fully understood, MG and its treatments can influence myocardial and coronary function through different pathways, causing patients to be at risk of cardiovascular events.

To the best of our knowledge, this is the first reported case of intraoperative coronary spasm in a patient with MG who underwent thymectomy. Our case had several risk factors for CAS, including cigarette smoking and atherosclerotic coronary artery disease. He also suffered from coronary spasm after traumatic cervical spine injury. He was diagnosed with MG and administered anticholinergic and intravenous immunoglobulin treatments. Thus, we cannot simply attribute the cause to a single factor. In our case, high-quality cardiopulmonary cerebral resuscitation and successful ECMO cannulation were crucial, and the patient recovered without complications. A previous study announced that prophylactic coronary vasodilators may bring benefits that reduce the risk of CAS[7]. To avoid noxious stimuli, an adequate anesthesia depth is necessary. The epidural catheter technique is widely used in thymectomy as an effective analgesia method. However, it can also induce coronary spasm, so the risks and benefits need to be determined[2,8]. We suggest that sugammadex should be used for the reversal of neuromuscular function if postoperative extubation is indicated. In summary, the potential risk of cardiovascular events should be taken into consideration for patients with MG undergoing surgery.

CONCLUSION

In past literature reviews, an association between MG and CAS has been reported. Patients with these conditions often present with chest pain. However, when MG is combined with thymoma, surgical intervention is frequently required. Diagnosing CAS under general anesthesia can be very challenging. Our case report presented a particularly devastating CAS that necessitated the use of ECMO and an intra-aortic balloon pump. We identified severe heart failure using transesophageal echocardiography and promptly closed the surgical incision to transfer the patient to the catheterization room for further treatment. Reflecting on this case, we propose an appropriate anesthesia plan, including proactive pain management, prophylactic coronary vasodilators, and always keeping the possibility of such complications as a differential diagnosis. Further research is needed to explore this complex relationship in the future.

FOOTNOTES

Author contributions: Hus CW and Chang CC interpreted the patient data and wrote the draft of the manuscript; Lin CS wrote the manuscript as the corresponding author; all authors read and approved the final manuscript.

Informed consent statement: Written informed consent for publication of the clinical details and images was obtained from the relative of the patient.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016) and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Lin C
L-Editor: Wang TQ
P-Editor: Lin C

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World Journal of Clinical Cases

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World J Clin Cases 2023 December 26; 11(36): 8595-8602

DOI: 10.12998/wjcc.v11.i36.8595

ISSN 2307-8960 (online)

CASE REPORT

Effects of video game-based therapy in an adolescent with cerebral palsy: A case report

Huda Aliah Mohd Iqbal, Wei Sheng Ho, Asfarina Zanudin, Hafifi Hisham, Nor Azlin Mohd Nordin

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: Batta A, India

Received: November 3, 2023
Peer-review started: November 3, 2023
First decision: November 13, 2023
Revised: November 25, 2023
Accepted: December 7, 2023
Article in press: December 7, 2023
Published online: December 26, 2023

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Abstract

BACKGROUND

Herein, we report the case of a 13-year-old boy with spastic quadriplegia cerebral palsy (CP) at Gross Motor Function Classification System (GMFCS) level II, engaging in a 6-wk video game-based therapy (VBT) program. This study aimed to offer essential insights regarding VBT's impact on enhancing the physical function and improving the quality of life (QoL) of adolescents diagnosed with CP. This report provides a distinctive viewpoint that can inform and direct future clinical practices and research endeavors.

CASE SUMMARY

The boy presented with moderate mobility, balance, and overall well-being. He faced challenges with diminished lower limb strength, which affected his daily living and physical fitness capabilities. Our participant was diagnosed with spastic quadriplegic CP at GMFCS level II. He participated in a 6-wk program of VBT using a play station. This innovative approach incorporates warm-up exercises, interactive activities, and cool-down routines, targeting various movements, including single-leg stance, weight shifting, kicking, jumping, marching, and squatting. After VBT, the strength of the left hip extensor significantly increased from 199.3 N to 541.3 N. Distance covered as part of a 6-min walk test increased by 82 m. His Paediatric QoL Inventory score increased dramatically by 25.9%.

CONCLUSION

VBT is an innovative, individualized therapy that enhances physical function and QoL in CP, emphasizing its role in ambulatory patients.

Key Words: Video game; Physical function; Quality of life; Cerebral Palsy; Case report

Core Tip: This study examined the potential transformative effects of video game-based therapy (VBT) in adolescents diagnosed with cerebral palsy (CP). The 6-wk VBT program demonstrated notable improvements in lower limb strength, motor function, and overall quality of life. VBT is distinguished by its creative and patient-centric approach, which is customized to meet the unique needs of each individual. This study highlights the need to incorporate technology-driven rehabilitation approaches into treatment methods for ambulatory patients with CP. It emphasizes the significant implications of such an approach and sets the stage for future multicenter trials that consider a range of functional levels.

Citation: Mohd Iqbal HA, Ho WS, Zanudin A, Hisham H, Mohd Nordin NA. Effects of video game-based therapy in an adolescent with cerebral palsy: A case report. *World J Clin Cases* 2023; 11(36): 8595-8602
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8595.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8595

INTRODUCTION

Cerebral palsy (CP) is the most common motor disability among children, with an estimated prevalence of one to nearly four per 1000 live births worldwide, as reported by the Centers for Disease Control and Prevention in 2022. Enhancing the quality of life (QoL) has consistently been a primary objective and robust evaluative criterion in therapeutic interventions for adolescents with CP[1,2]. Considerable research has indicated significant empirical evidence regarding the efficacy of modern physiotherapy approaches currently available for children and adolescents diagnosed with CP. Among the existing approaches, video game-based therapy (VBT) can incorporate all the aforementioned elements in the therapeutic process owing to its distinctive attributes of being centered on video content and recreational activities, while being adaptable based on the user's condition. Furthermore, in addition to the heightened excitement experienced during physical activity, VBT offers instantaneous biofeedback to improve users' movement patterns and experiences.

The current evidence indicates that VBT is a viable therapeutic option for enhancing arm function, postural control, and ambulation in adolescents with CP[3-6]. However, research on the impact of VBT on the physical functioning of children and adolescents with CP, specifically in terms of walking ability, gross motor skills, strength, and QoL, has been lacking. This inadequacy is particularly apparent in the absence of a comprehensive and reliable tool for assessing outcomes. Therefore, this study was conducted to provide essential empirical support for an alternative therapeutic approach for adolescents diagnosed with CP.

This study aimed to produce essential evidence that can assist healthcare professionals in assessing their patients while providing suggestions for their interventions. The present study examined the potential of VBT in enhancing physical function, including lower-limb strength, gross motor skills, walking capacity, and QoL in adolescents diagnosed with CP. The findings of this study provide essential information for healthcare professionals to evaluate their patients and act as a framework for guiding their interventions with patients. The results could potentially influence the physical health and overall well-being of adolescents diagnosed with CP and their respective families.

CASE PRESENTATION

Chief complaints

This case report is based on a boy who was 13 years and 3 months old he was diagnosed with spastic quadriplegia CP. His mother reported of his sedentary preference and inability to walk for long periods, especially outdoors and on inclined surfaces.

History of present illness

When diagnosed, the patient was classified as having Gross Motor Function Classification System (GMFCS) level II. He could walk without assistive equipment by employing a unique knee-gait pattern, and exhibited skills in traversing curbs, uneven surfaces, and barriers. Additionally, he could independently ascend and descend steps within his two-story home with one hand holding the rail.

History of past illness

The participant was born at full term with no other medical complications. He had mild jaundice, which is a common condition in many newborns. However, eventually, the participant's mother observed gross motor developmental deficits, including milestones, such as rolling, compared to his older siblings. Accordingly, the mother sought the expertise of a pediatrician at the hospital.

In 2009, he was referred to our hospital for various medical assessments. In mid-2010, he was officially diagnosed with spastic quadriplegia CP, which mainly explained his motor development impairments. He began his physiotherapy in

2009, following his mother's concerns about gross motor delay. Physiotherapy was conducted on a bi-monthly basis by a pediatric physiotherapist. Physiotherapy aims to provide motor training and home program strategies to effectively target the specific requirements and challenges of the participants.

Prior to VBT, his mother observed an increase in sedentary behavior and his son's difficulties in long-distance walking, especially during outdoor activities and on inclined surfaces. These concerns were the primary motivating factors behind the pursuit of novel strategies to enhance his physical capabilities and overall well-being.

Personal and family history

The patient had no family history of CP or other remarkable neurological conditions as claimed by the mother.

Physical examination

A comprehensive literature review was conducted before selecting assessments for the clinical decision-making process. Muscle strength with respect to body function was assessed using a handheld dynamometer. additionally, general motor ability is evaluated using the Gross Motor Function Measure (GMFM)-88. The 6-min walk test (6 MWT) was used to assess walking capacity, whereas the Pediatric QoL (PedsQL) tool in Malay was used to determine the QoL. Physical examination was performed twice, at baseline and after 4 weeks of VBT.

Muscle strength: Muscle strength was tested using a micro Force Evaluation and Testing 2 (microFET®2) handheld dynamometer (Hogan Health Industries Inc., United States), a small portable device held by the examiner, and placed against the participant's limit during maximal isometric contraction. According to Goudriaan *et al*[7], a knee extension interclass correlation (ICC) value of 0.95 for children with CP indicated that the handheld dynamometer was highly reliable.

According to Neumann[8], a pathology that affects the strength, control, or extensibility of hip muscles can significantly disrupt the fluidity of many routine movements involving both functional and recreational activities. Thus, in our assessment, we focused on the hip abductor, hip extensor, and knee extensor muscles. The test was conducted in a maneuver with an ICC validated by Yazici *et al*[9] (ICC = 0.938-0.986), wherein the examiner was in a stable position, providing maximal ability to resist force by the participant, running at a slow count of four upon maximal muscle contraction. Testing was performed in the following manual muscle testing positions: Prone lying (hip extensor), side lying (hip abductor), and high sitting (knee extensor). Figure 1 shows muscle strength measurements using the MicroFET®2 handheld dynamometer.

Gross motor ability: According to the Center of Childhood Disability Research, the GMFM is a standardized observational instrument designed and validated to measure changes in gross motor function over time in children and adolescents with CP, with most items having specific descriptors for each score. The GMFM-88 has been used to assess the gross motor ability of persons with CP[10]. In our assessments, domains D (standing) and E (walking, running, and jumping) from the GMFM-88 were used to suit our participant category, which, in this case, GMFCS level II, possesses the ability to stand and walk. The items were administered according to the GMFM manual[10].

Walking capacity: The 6 MWT is a submaximal exercise test that involves walking for 6 min. ICC 0.98 was validated in the CP population by Thompson *et al*[11]. The 6 MWT was used to determine the participants walking capacity. The test was administered according to the standard protocol, implementing every instruction in accordance with the guidelines of the American Thoracic Society[12].

QoL: To explore the QoL, we chose a PedsQL parent's proxy questionnaire consisting of a 5-point Likert Scale ranging from 0 to 4, covering four multidimensional functions, namely, physical, emotional, social, and school. Adapting to the local culture, the PedsQL questionnaire was translated into Malay to ease the patient's career comprehension. The questionnaire has been validated with Cronbach's α with a range (0.7–0.98) and factor correlation values ranging from 0.1 to 0.57[13].

Laboratory examinations

The laboratory examinations are not applicable.

Imaging examinations

The imaging examinations is not applicable.

FINAL DIAGNOSIS

The final diagnosis of the case presented is spastic quadriplegia CP.

TREATMENT

The VBT intervention was initiated in the second session after an initial session, in which baseline data assessments were conducted. An interventional session was conducted by a researcher under the guidance of the patient's pediatric physio-

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Figure 1 Muscle strength measurement. A: Knee extensor; B: Hip extensor; C: Hip abductor.

therapist for 6 weeks, consisting of two sessions per week, with each session requiring approximately 1 hour. The principal objective of the program was to enhance engagement in physical activities. Balance, strength, and endurance training exercises were incorporated into the regimen using an X-Box 360 Kinect. The tasks included upper limb movements, marching, side-stepping, weight shifting, single-leg stance (SLS), kicking, squatting, and jumping. All interventions were adapted to be fun and engaging for young adolescents. To make the gaming session more fun and competitive, the researchers also participated in the gaming session during the participants' resting period to motivate them to perform the tasks at their maximal performance.

Each session started with a warm-up of 10–15 min involving upper limb movements and low-intensity exercises such as side-stepping and marching at a low pace. The session was followed by balance training, such as weight shifting, SLS, and dynamic balance training; strength training involving marching, kicking, squatting, and jumping; and endurance training, a combination of all movements and movement strategies with more significant repetitions. Following this, progress was made according to the participants' preferences and the researcher's observations. Throughout the intervention session, participants rested between tasks until they were ready for the next game. The session ended with a cooldown period of 10 min consisting of controlled breathing and stretching of the upper and lower limbs. The components and movements are listed in Table 1.

OUTCOME AND FOLLOW-UP

Initial outcomes

Clinical observation: The patient exhibited moderate thoracic scoliosis on the right side manifesting as an elevated right shoulder relative to the left shoulder. The participant could walk unaided while maintaining a mild jumping knee gait; however, he encountered challenges when sprinting and walking at high speeds. He could only walk in tandem for five steps and a SLS on the right foot for 2 s and 1 s on the left. He was only able to execute single-leg hopping with his right foot once using a double-hand grasp and was unable to conduct single-leg hopping with his left foot.

Outcome and follow-up

Clinical observation: He could run but still had a mild hopping knee gait. He could maintain the right foot SLS for 5.36 s, whereas he maintained the left foot SLS for 1.36 s. For running, he could now complete a distance of 4.5 min and 5.4 s instead of walking fast.

Description of outcomes: Post-intervention, there were marked increases in strength for his tested lower limb muscles, of which, the left hip extensor had gained the most improvement, from 199.3 N to 541.3 N, followed by the left hip abductor, from 201.1 N to 743.3 N.

Table 1 Components and tasks involved in the video game-based intervention

Component	Movements	Game
Warm up	Upper limb movements side	Dance central: Poker face
	Stepping	Kinect adventures: Space pop
	Marching	Motion explosion: Balance beam
Balance	Single leg stance	Kinect adventures: 20000 leaks
	Weight shifting	Kinect sports: Target kick
		Ice age 4: Slip slider
Strength	Kicking	Kinect sports: Target kick
	Jumping	Kinect adventures: River rush
	Marching	Kinect sports: Hurdles
		Kinect sports: Sprint
Endurance	Combination of marching, squatting, jumping, and upper limb movements	Ice age 4: Glacier hopper
		Kinect adventures: Rally ball
Cool down	Upper limb movements Stepping	Kinect adventures: Space pop Motion explosion: Balance beam

The boy's gross motor function in terms of standing and advanced activities, such as walking, running, and jumping demonstrated no improvement nor deterioration. A decreased of one score in GMFM component D. According to his walking capacity, the distance increased from 368 m to 450 m, yielding an improvement of 82 m.

Assessing the QoL of the boy using the mother's proxy, the post-intervention PedsQL total scale score rose from 58.7 to 73.9, marking an increase of 17.06%. All the domains in PedsQL which are physical, emotion, social and schooling showed increased scores. The changes in muscle strength, gross motor ability, and QoL after the VBT intervention are shown in Table 2.

Adherence, adverse events, and participant feedback: The participants in this study showed good adherence to the program with 100% attendance. He did not miss any appointments for the program. No adverse events were observed during the intervention period. According to the participant, VBT was fun, and he did not experience fatigue or muscle soreness after every session. The participant's caregiver also added that her child was more motivated and excited for VBT than the routine physiotherapy appointments.

DISCUSSION

The VBT intervention enhanced the physical function and QoL of a GMFCS level II adolescents with CP, as indicated by the achievement of positive results on almost all outcome measures. Furthermore, our participants demonstrated high adherence to and a desire to engage in all assigned tasks during the VBT sessions. Participants and their caregivers complied with the entire program and adhered to the schedule for each session. Consistent with findings from prior research[14,15], our participants also reported exceptional joy and amusement compared to routine interventions. Following these sessions, the patient exhibited enhancements in bodily structure, function, and QoL. The participant and his pediatric physiotherapist noted that his posture and balance improved after the intervention[14,15].

Our results are consistent with those of Gercek *et al*[16], which showed improved lower-extremity muscle strength from VBT. The bilateral hip extensors, hip abductors, and right knee extensors improved post-intervention, potentially because of the exercises performed during VBT training. The participants performed lower limb-intensive exercises during training, including marching, squatting, kicking, and jumping, at a specific velocity corresponding to the tempo of the events. As the required pace increases, stamina, endurance, and reaction time are required. Voluntary active range of motion, weight-bearing movements, and the functionality and velocity of the movements themselves must have contributed to the increase in muscle strength. Our hypothesis was consistent with findings by van Vulpen *et al*[17], showing an association of improvement in strength with the functionality of the velocity in strength training exercises.

Pre-intervention, the participant was able to perform most of the gross motor activities in GMFM component D (standing); however, he had difficulty in performing the SLS, with the right-foot SLS better than a left-foot SLS (right: 2 s; left: 1 s). After the intervention, SLS time in both feet improved, with right-foot SLS to a greater extent (right: 5.36 s; left: 1.56 s). With respect to component E (walking, running, and jumping), he possesses difficulty in performing tandem walking (5/10 steps), running 4.5 m (fast walking instead), and single leg hopping (right: One hop with two-hand held; left: 0/10 with two-hand held). Post-intervention, the changes were tandem walking (3/10 steps), running 4.5 m (able to run), and single-leg hopping (right: One hop without hand-held; left: 0/10). These changes were consistent with the findings of Gercek *et al*[16], who showed improvements in motor function post-intervention. These changes are likely due

Table 2 Changes after the video game-based therapy in muscle strength, gross motor, and quality of life

Outcome measure		Pre-intervention	Post-intervention	Change (%)
Muscle strength (N)	Left hip extensor	199.3	541.3	34 (> 100)
	Right hip extensor	147.2	535.4	388.2 (> 100)
	Left hip abductor	201.1	743.3	542.2 (> 100)
	Right hip abductor	212.6	752.2	539.6 (> 100)
	Left knee extensor	216.2	1017.9	801. (> 100)
	Right knee extensor	290.1	1035.6	745.5 (> 100)
GMFM-88 score	Dimension D standing (0-39)	36	35	1 (2.7)
	Dimension E walking, running, jumping (0-72)	65	65	-
Walking distance (m)	6 MWT	368	450	82 (5.0)
Quality of life	PedsQL in physical (0-100)	71.9	81.3	9.4 (13.0)
	PedsQL in emotion (0-100)	50.0	60.0	10 (20)
	PedsQL in social (0-100)	35.0	65.0	30 (85.7)
	PedsQL in schooling (0-100)	70.0	85.0	15 (21.4)
	PedsQL in total (0-100)	58.7	73.9	15.2 (25.9)

N: Newton; GMFM: Gross Motor Function Measure; m: Meter; 6 MWT: Six-min walk test; PedsQoL: Pediatric quality of life.

to the nature of virtual reality (VR), which addresses the critical factors of motor training, including intensity, repetition, task orientation, and multisensory environments. According to Brien and Sveistrup[18], enriched environments are known to promote neuronal plasticity changes documented using functional magnetic resonance imaging, and have shown that training in VR offers the potential for long-term learning from adaptive cerebral plasticity consistent with significant functional motor improvements in CP. Despite the minimal changes, we expect to see a more substantial improvement in the participants' gross motor skills with a longer intervention of a minimum of 8 weeks is being performed, especially in the gait component. According to Ghai S and Ghai I[4], a VBT of less than 4 times per week, 20–30 min, for more than 8 weeks can have a maximum effect on gait. Therefore, a trial utilizing these suggestions could be conducted to harness this impact. In addition, the improvement in muscle strength and gross motor function to different extents was consistent with the findings of Shin *et al*[19], who showed no correlation between muscle strength and gross motor function in CP.

Upon pre-intervention, the participant completed a distance of 368 m. After the intervention, an increment of 82 m was obtained. This finding is consistent with a previous study[20] showing that VBT intervention can improve walking capacity in adolescents with CP. Throughout our intervention, the VBT involved repetitive practice and movement correction. As pointed out by Chen *et al*[3] in a similar study utilizing VR, the repetitions used during VR sessions were high, and the child performed up to 150 reaching movements in 3 min without realizing them while playing the video games. Although the repetitions of movement in our study were not recorded, more significant repetitions within a specific time frame are required, which we believe have contributed to the build-up of endurance in the participants, thus resulting in a significant outcome.

QoL improvement as a result of overall improvement in the participants' physical and social functioning were reported with all aspects acquiring significant increment, and out of all, social functioning improved by the most (85.7%). An increase in score (from 4 to 2) was observed in Components 1 (relationships with other adolescents), 4 (inability to perform activities that other adolescents are capable of), and 5 (catching up with other adolescents' pace). Two of the three questions were based on the participants' physical abilities. With improvements in bodily functions shown in the physical functioning domain, which may have contributed to his school functioning domain improvement, the emotional and social aspects of the QoL increased significantly. Although the exact cause-and-effect relationship between these domains is still unknown, our findings indicate that the enhancements in gross motor function, walking ability, and overall physical functions, such as muscle strength, are indeed associated with the improvements observed in the social domain of the PedsQL, which are in line with the findings of Shelly *et al*[21], who stated that the psychological domain of QoL was significantly associated with the functioning level.

In conclusion, increments in muscle strength, particularly hip extensor, 6 MWT, GMFM-88 domains D and E, and PedsQL scores post-intervention, indicated that VBT could improve physical function and QoL of CP with GMFCS level II. Although the improvements are apparent, the results of this case study should be carefully interpreted as the outcomes of a single-subject case study have limited generalizability to a larger population, with limitations such as the short duration of the VBT program and follow-up assessment once participants finish the program. In the future, to ensure an optimal number of participants, recruitment planning should consider the barriers of participants visiting the clinic for VBT for two sessions per week. In addition, the PedsQL Adolescent Report should be employed to provide additional

Table 3 The pros and cons between standard care and video game-based therapy for adolescents with cerebral palsy

	Standard care for cerebral palsy	Video game-based therapy for cerebral palsy
	Functional training; Facilitation of normal patterns of movement; Passive range of motion; Stretching exercise; Strengthening exercise; Positioning; Manual technique; Functional electrical stimulation; Splinting; Maintenance training	Refer to Table 1
Pros	Basic technique and well-known by physiotherapists; Most of the essential equipment available in the physiotherapy department	Active motor training with progressive challenges; Motivational and fun activities; Games were tailored to patients' ability, preference, and functional goals; Bi-weekly training with a structured program and assessments
Cons	Patients tend to get bored with repetitive treatment	Physiotherapists need to be trained on how to operate the games; Not all physiotherapy department has the equipment and space for the VBT

VBT: Video game-based therapy.

validation of the QoL outcomes. Subsequent research should focus on the frequency and durations of VBT interventions, with specific emphasis on the duration, number of sessions per week, and localization of VBT programs.

What this case study adds to evidence-based practice

This is the first case report to examine the effect of VBT intervention in an adolescent with spastic quadriplegia and GMFCS level II CP in a local setting. This study demonstrated the clinical applicability of VBT intervention in elevating physical function with improvements in muscle strength, gross motor function, and walking capacity, ultimately improving the QoL of adolescents with CP. Table 3 sums up the advantages and disadvantages of standard care and VBT in adolescents with CP.

CONCLUSION

In summary, the aforementioned case study involving a 13-year-old boy diagnosed with spastic quadriplegic CP, underscores the need for timely identification and intervention in the field of pediatric neurological disorders. Despite difficulties in the gross motor development, he has sought and engaged in ongoing physiotherapy since 2009, which highlights the compliance and support of both his family and healthcare professionals in addressing his distinct requirements.

The implementation of VBT as a novel intervention shows the potential for improving participants' physical functioning and QoL. The preliminary evaluation indicated his competence in walking while emphasizing his difficulties in navigating outdoor environments and ascending inclined slopes. The VBT, in conjunction with his family's assistance, seeks to mitigate these constraints and enhance holistic welfare.

This case highlights the importance of customized therapies for children diagnosed with CP as well as the potential advantages of rehabilitation methods that include technology. As the intervention progresses, and subsequent assessments are conducted, significant insights will be gained regarding the efficacy of VBT in treating children with spastic quadriplegic CP. These findings serve as valuable resources for informing future treatment approaches for comparable instances.

FOOTNOTES

Author contributions: Mohd Iqbal HA, Ho WS, Hisham H, and Zanudin A contributed to manuscript writing editing; Mohd Iqbal HA, Ho WS, and Zanudin A contributed to data collection; Ho WS, Mohd Iqbal HA, Zanudin A and Mohd Nordin NA contributed to data analysis; Zanudin A and Mohd Nordin NA contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

Supported by the Ministry of Higher Education of Malaysia, No. FRGS/1/2021/SKK06/UKM/03/2.

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

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Lin C
L-Editor: A
P-Editor: Lin C

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World J Clin Cases 2023 December 26; 11(36): 8603-8605

DOI: 10.12998/wjcc.v11.i36.8603

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Lyophilized recombinant human brain natriuretic peptide: A promising therapy in patients with chronic heart failure

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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): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Tokumine J, Japan

Received: September 13, 2023
Peer-review started: September 13, 2023
First decision: December 5, 2023
Revised: December 5, 2023
Accepted: December 12, 2023
Article in press: December 12, 2023
Published online: December 26, 2023

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Abstract

Lyophilized recombinant brain natriuretic peptide (BNP) is an exogenous peptide synthesized by artificial recombination technology, with a similar structure and similar physiological effects with the endogenous natriuretic peptide secreted by the human body. It's main mechanism of action is to increase cyclic guanosine monophosphate by binding with its corresponding receptor in the body, regulating, thus, the imbalance of the vascular system and cardiac hemodynamics, improving the heart's pumping capacity, and inhibiting sympathetic excitability and myocardial remodeling. Moreover, it can promote mitochondrial metabolism and enhance the use of adenosine triphosphate in cardiomyocytes. In the present study, 102 chronic heart failure (HF) patients were randomly assigned to a control and an observation group consisting of 51 patients each. Patients of the control group were treated with standard HF therapy for 3 d including oral metoprolol tartrate tablets, spironolactone, and olmesartanate while patients of the observation group were administered the recombinant human BNP injection for the same time-period, plus the standard HF therapy. The recombinant human BNP group (observation group) demonstrated better physical, emotional, social, and economic scores, as well as cardiac and inflammatory biomarkers such as serum hypersensitive C-reactive protein, N-terminal pro BNP and troponin I levels, compared to the control group. Moreover, cardiac function was also improved, as left ventricular ejection fraction and stroke volume were significantly higher in the observation group than in the control group. Interestingly, adverse reactions were not different between the 2 groups. However, these results are not generalizable and the need of large multicenter randomized controlled trials examining the safety and efficacy of recombinant human BNP in HF patients is of major

importance.

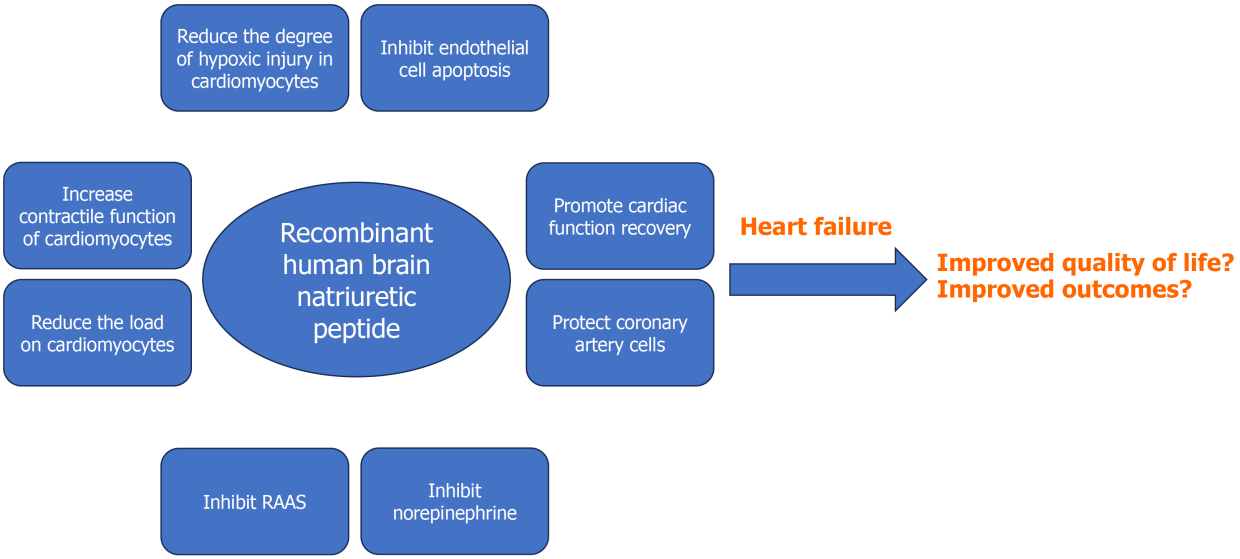
Key Words: Heart failure; Recombinant; Brain natriuretic peptide; Outcomes

Core Tip: Lyophilized recombinant brain natriuretic peptide is an exogenous peptide synthesized by artificial recombination technology, with a similar structure and similar physiological effects with the endogenous natriuretic peptide secreted by the human body. A recent single center, randomized study examined its safety and efficacy in 102 chronic heart failure patients, showing promising results. Larger randomized controlled trials are urgently needed.

Citation: Kourek C, Briasoulis A, Giamouzis G, Skoularigis J, Xanthopoulos A. Lyophilized recombinant human brain natriuretic peptide: A promising therapy in patients with chronic heart failure. *World J Clin Cases* 2023; 11(36): 8603-8605
URL: https://www.wjgnet.com/2307-8960/full/v11/i36/8603.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i36.8603

TO THE EDITOR

We read with great interest the original research article entitled "Lyophilized recombinant human brain natriuretic peptide (BNP) for chronic heart failure (HF) (CHF): Effects on cardiac function and inflammation by Li *et al*[1], published in the September 2023 issue of World Journal of Clinical Cases. In this study, authors investigated the actions of lyophilized recombinant human BNP administration on myocardium and microinflammatory profile in CHF patients. Lyophilized recombinant BNP is an exogenous peptide synthesized by artificial recombination technology, with a similar structure and similar physiological effects with the endogenous natriuretic peptide secreted by the human body[2]. It is widely used in cardiovascular diseases, including acute myocardial infarction and HF, and the main mechanism of action of this recombinant BNP is to increase cyclic guanosine monophosphate, regulating the imbalance of the vascular system and cardiac hemodynamics, improving the heart's pumping capacity, and inhibiting sympathetic excitability and myocardial remodeling[1,2]. As a result, there is an improvement in the quality of life of patients with cardiovascular diseases. Lyophilized recombinant human BNP has been shown to have a significant effect in improving cardiac function and flow-mediated dilatation in patients with acute myocardial infarction[2], acute renal injury induced by endotoxin in canines[3], acute carbon monoxide poisoning[4], as well as patients with weaning-induced cardiac failure[5]. In their study, Li *et al*[1] randomly assigned 102 CHF patients from a single center, with a mean age of 63-80 years, to a control and an observation group consisting of 51 patients each. Patients of the control group were treated with standard HF therapy for 3 d including oral metoprolol tartrate tablets, spironolactone, and olmesartanate while patients of the observation group were administered the recombinant human BNP injection for the same time-period, plus the standard HF therapy. The recombinant human BNP was shown to excel the standard HF therapy in terms of the overall clinical efficacy and quality of life in CHF patients including physical, emotional, social, and economic scores, and further improved significantly cardiac and inflammatory biomarkers such as serum hypersensitive C-reactive protein, N-terminal proBNP and troponin I levels[1]. Moreover, cardiac function was also improved, as left ventricular ejection fraction (LVEF) and stroke volume were significantly increased[1]. Interestingly, adverse reactions were not different between the 2 groups. Overall, the specific therapy (*i.e.*, recombinant human BNP) seemed to be safe and reliable. These findings could be explained by the mechanism of action of the recombinant human BNP on the renin-angiotensin-aldosterone system, through the inhibition of norepinephrine and aldosterone secretion, the protection of the coronary artery cells and cardiomyocytes, and the inhibition of endothelial cell apoptosis, leading to reduced inflammatory factor secretion and myocardial damage[1] (Figure 1). Despite these interesting and promising findings of this study, there are major limitations that need to be highlighted. Firstly, lyophilized recombinant human BNP was implemented in a small number of patients with reduced LVEF (*i.e.*, ≤ 40%). Secondly, the duration of the drug administration was short (*i.e.*, 3 d) and there was no follow-up. Therefore, data on the safety and efficacy of the drug beyond 3 d are lacking. Thirdly, data on the baseline characteristics of the study population were scarce. In conclusion, lyophilized recombinant human BNP could be a quite promising therapy in HF by improving the cardiac function, the microinflammatory status, and thus, the overall quality of patients' life. It seems to be safe and reliable without causing any significant adverse effects at the time of administration. However, these results are not generalizable and the need of large multicenter randomized controlled trials examining the safety and efficacy of recombinant human BNP in HF patients is of utmost importance.



DOI: 10.12998/wjcc.v11.i36.8603

Figure 1 Recombinant human brain natriuretic peptide as a promising therapy in patients with heart failure. Its beneficial effects could be explained by the mechanisms of action of the recombinant human brain natriuretic peptide on the renin-angiotensin-aldosterone system, through the inhibition of norepinephrine and aldosterone secretion, the reduction of the load on cardiomyocytes, the protection of the coronary artery cells, and the inhibition of endothelial cell apoptosis, resulting in reduced inflammatory factor secretion and myocardial damage.

FOOTNOTES

Author contributions: Kourek C conceived and designed the study, acquired the data, and analyzed and interpreted the data; Briasoulis A, Giamouzis G, Skoularigis J, and Xanthopoulos A drafted and made critical revisions to the manuscript; all authors have read and gave final approval of the version of the article to be published.

Conflict-of-interest statement: All the authors state that they have no potential or real conflicts of interest to declare.

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S-Editor: Qu XL
L-Editor: A
P-Editor: Zhao S

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