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Radiation oncology practice during COVID-19 pandemic in developing countries

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Abstract

Radiation therapy (RT) is considered one of the cornerstone modalities of treatment for different cancer types. The preparation and delivery of RT requires a number of staff members from different disciplines within the radiation oncology department. Since the emergence of the corona virus disease 2019 (COVID-19) pandemic, RT, similar to other cancer care modalities, has been adapted to minimize patient and staff exposure without compromising the oncological outcomes. This was reflected in the dramatic practice changes that occurred in the past year to address the lockdown restrictions and fulfill the infection control requirements. RT practices differ across regions based on financial and training levels, and developing countries with limited resources have struggled to maintain radiation treatment services at a level equivalent to that in developed countries while following pandemic control guidelines. The response during the COVID-19 pandemic varied between developing countries according to the infection rate and RT technological capabilities. In this editorial, we review recently published articles addressing radiotherapy practice reports during the COVID-19 pandemic in developing countries.

Key Words: Radiotherapy; COVID-19, Developing countries; Radiation therapy; Pandemic; Low income countries

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Core Tip: This editorial discusses the impact of corona virus disease 2019 (COVID-19) pandemic on radiation oncology practice in developing countries. The challenges and measures taken to mitigate COVID19 and its ramifications.


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INTRODUCTION

The estimated increase in new cancer cases will be more than 24 million in 2030, and this problem is a growing challenge for healthcare systems, especially in low- and middle-income countries[1]. Radiation therapy (RT) is an integral part of multidisciplinary cancer care, and approximately half of all cancer patients will receive radiotherapy during the course of their treatment, whether it is with curative or palliative intent[2,3]. Nevertheless, accessing radiation services is dependent on the availability of these facilities, along with demographic and logistical factors; for instance, in low-income countries, more than 90% of the residents do not have access to radiation treatment[4].

In early 2020, severe acute respiratory syndrome coronavirus 2 infections started to spread uncontrollably. In March 2020, the World Health Organization announced that the coronavirus disease 2019 (COVID-19) outbreak was a pandemic; since then, many countries in the world have been forced to implement partial and complete lockdowns that have lasted for months. Variations in the status of the pandemic and governmental actions coupled with insufficient resources could result in a greater impact and worse poorer outcomes, leading to a higher risk to the safety of health care providers in developing countries that could aggravate the crisis[5].

PRACTICE ADAPTION TO COVID-19

During this time, hospitals worldwide were experiencing an increased number of patients and a lack of medical supplies. Elective surgeries and interventions were postponed due to hospital crowding and the fear of infection. Elective cancer procedures were cancelled or postponed as well, which resulted in delays in cancer diagnosis and treatment and psychological distress on the part of the patients and their families.

RT has changed dramatically during the past year, and these changes were implemented to cope with lockdown restrictions and to fulfill infection control requirements[6]. Developing countries have struggled to maintain radiation treatment services at a level equivalent to that in developed countries while following pandemic control guidelines[7]. In China, during COVID-19 pandemic outbreak; lock down resulted in treatment interruptions in more than 50% of patients who were on active chemoradiation[8].

Changes to RT practices depended on regional factors such as financial and training levels. The implemented modifications included postponing elective radiation treatment, utilizing hypofractionated regimens and encouraging online (remote) access to radiotherapy planning and quality control systems to decrease direct physical contact[9].

The financial burden of cancer care has always been a main concern in low- and middle-income countries, as their healthcare systems already face diverse problems due to the poor infrastructure, lack of funding and absence of effective administrative and strategic planning. The consequences of the COVID-19 pandemic exacerbated these financial problems[10].

The response to the COVID-19 pandemic varied among developing countries according to the infection rate in the region and the RT technological capabilities in the country. The presence of a strong information technology (IT) infrastructure enabled the developed world to switch smoothly to online and remote workflows. In developing countries, the situation was the opposite: a lack of financial and IT support led to a poor response to the pandemic and a failure to quickly adapt practices to the current situation. Developing countries are facing multiple financial and social complications as a result of the pandemic, and prioritizing COVID-19 patients has led to the cancelation and postponement of treatment for many cancer patients. Some countries are affected by war and lack health care systems. All these challenges should be addressed in developing countries. Future planning and international support will be crucial to help developing countries overcome this pandemic.
During the COVID-19 pandemic, most cancer centers around the world have adopted alternative oncological guidelines to adapt to the circumstances, including using a hypofractionated RT regimen or shifting the RT start date. However, hypofractionated regimens usually require careful planning and delivery, as they involve giving a higher dose with a lower number of fractions, which means that the impact of target inaccuracy could have a worse effect on tumor control and increase the risk of damage to adjacent organs. In addition, a delay in RT can sometimes result in poor outcomes. This leads us to question prior to implementing a new practice whether a delay or change is oncologically justifiable[11].

One major change that has occurred in response to the pandemic is the shift towards telemedicine and the development of a virtual clinic workflow for RT. Reducing hospital visits and minimizing contact were not the only advantages of virtual clinics; virtual clinics also provide more flexibility during discussions with patient and family members and eliminate the need for waiting rooms. However, for exams and investigations, the patient still has to present to the clinic in person. Proper planning to make the clinical visit worthwhile should be performed[12,13].

In life-threatening situations such as those involving bleeding and spinal cord compression, in which RT needs to be delivered urgently, the use of a hypofractionated regimen is preferable to achieve a more rapid response; the use of these regimens also adheres to the protocols in place during the COVID-19 pandemic[14]. It may also be possible to omit computed tomography (CT) simulations and to use diagnostic CT as an alternative fast track to RT during emergencies[15], this will help to minimize exposure and short preparation time as shown in Figure 1.

A recent systematic review published by Donkor et al[16] addressed the approaches used to mitigate the impact of COVID-19 on radiotherapy centers in low- and middle-income countries. Eleven studies were included in review, and the methods used to cope with COVID-19 in RT departments were as follows: forming COVID-19 response multidisciplinary teams; increasing the use of telemedicine; modifying the layout of waiting areas; reducing staff; isolating patients suspected of having COVID-19; and adopting triage systems.

**LIGHT AT THE END OF THE TUNNEL**

COVID-19 vaccines are now available, and the number of infections is expected to decrease; as a result, quarantine measures are expected to be eased. Regardless of whether the general public is willing to be vaccinated, cancer patients should be prioritized for vaccination once it becomes available due higher morbidity and mortality among COVID-19 patients with cancer[17,18]. Unfortunately, access to the vaccine is not equal, and wealthy, developed countries are currently receiving the vaccines that are being produced. Unequal access will slow recovery in developing countries and add to the current challenges.
CONCLUSION

Adapted guidelines and protocols should be implemented at the national and institutional levels in RT units in developing countries to cope with the rapid changes in RT practices and to enable them to continue to serve patients. Collecting and sharing data is crucial to building a better understanding. More vaccination campaigns should be implemented in developing countries to minimize the burden of the pandemic on cancer care in general and more specifically on RT.

REFERENCES


Complete mesocolic excision and central vascular ligation in colorectal cancer in the era of minimally invasive surgery

Marzia Franceschilli, Sara Di Carlo, Danilo Vinci, Bruno Sensi, Leandro Siragusa, Vittoria Bellato, Roberto Caronna, Piero Rossi, Giuseppe Cavallaro, Andrea Guida, Simone Sibio

Abstract

Since the 19th century, appropriate lymphadenectomy has been considered a cornerstone of oncologic surgery and one of the most important prognostic factors. This approach can be applied to any surgery for gastrointestinal cancer. During surgery for colon and rectal cancer, an adequate portion of the mesentery is removed together with the segment of bowel affected by the disease. The adequate number of lymph nodes to be removed is standardized and reported by several guidelines. It is mandatory to determine the appropriate extent of lymphadenectomy and to balance its oncological benefits with the increased morbidity associated with its execution in cancer patients. Our review focuses on the concept of “complete mesenteric excision (CME) with central vascular ligation (CVL),” a radical lymphadenectomy for colorectal cancer that has gained increasing interest in recent years. The aim of this study was to evaluate the evolution of this approach over the years, its potential oncologic benefits and potential risks, and the improvements offered by laparoscopic techniques. Theoretical advantages of CME are improved local-relapse rates due to complete removal of the intact mesocolic fascia and improved distance recurrence rates due to ligation of vessels at their origin (CVL) which guarantees removal of a larger number of lymph nodes. The development and worldwide diffusion of laparoscopic techniques minimized postoperative trauma in oncologic surgery, providing the same oncologic results as open surgery. This has been widely applied to colorectal cancer surgery; however, CME entails a technical complexity...
INTRODUCTION

Cancer represents a social disease related to lifestyle habits, environmental pollution, and aging societies, and its incidence has progressively increased during the last several decades, since 20% of men and 15% of women will be diagnosed with cancer in their lifetime and 12% and 10%, respectively, will die of the disease, namely from metastatic progression[1]. For this reason, preventing metastatic spread is of key importance in cancer treatments. Currently, these treatments are highly integrated, combining neoadjuvant and adjuvant chemotherapy with radiotherapy and early or subsequent surgery in several different settings[2].

The keystone of surgery is removal of an adequate number of lymph nodes that can limit its wide minimally-invasive application. This review analyzes results of these procedures in terms of oncological outcomes, technical feasibility and complexity, especially within the context of minimally invasive surgery.

Key Words: Complete mesenteric excision; Central vascular ligation; Colorectal cancer; Lymphadenectomy; Laparoscopy; Minimally invasive surgery

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Core Tip: An optimal lymphadenectomy is the cornerstone of oncologic surgery. The concept of “optimal” or “adequate” relies on the balance between oncologic advantages and increased morbidity. The extent of lymphadenectomy in colorectal cancer surgery is a highly debated issue. The concept of “central vascular ligation” and “complete mesocolic excision” for radical lymphadenectomy in the era of minimally invasive surgery for colorectal cancer have been investigated.

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INTRODUCTION

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The keystone of surgery is removal of an adequate number of lymph nodes that have both staging and prognostic value. Biological bases of lymphatic spread are theorized by the Halsted and Fisher models. The former describes a highly organized and progressive proximal to distal spread of metastases, whereas the latter suggests an early and completely random spread of metastases[2,3]. Regardless, the adequate extent of lymphadenectomy is always advocated in cancer surgery and worldwide consensus guidelines state the minimal number of lymph nodes to be removed for each type of cancer. In this landscape, complete mesocolic excision with central vascular ligation procedures have been developed to optimize lymph node removal and improve the radicality of surgery. Complete mesocolic excision (CME) is based on a dissection conducted on the embryological plane separating the right mesocolon and the retroperitoneum and a high tide of ileocolic, right colic, and right branch of the middle colic vessels[4,5]. A key point of the CME technique is the retrieval of an unbreached mesocolon package as the result of careful dissection between mesocolon and retroperitoneum along the Toldt’s layer together with central vascular ligation to remove the largest amount of lymph nodes.

To be more specific, D1 lymph node resection represents transection of the feeding vessel just proximal to the marginal vessels; D2 resection is a more traditional resection of the main feeding vessels to a given colonic segment and lymphadenectomy that includes the origin of the feeding vessels[6]; D3 represents an extended lymphadenectomy that includes dissection of the lympho adipose tissue covering the medial side of the superior mesenteric vein (SMV) and dissection of the lympho adipose tissue covering the head of the pancreas after section of the superior right colic vein (SRCV) at its confluence in the gastrocolic trunk of Henle (GCTH) if necessary (Figure 1). The latter is a fundamental surgical landmark defined as the venous confluence of the following three veins: right gastroepiploic vein, anterosuperior...
Figure 1 Complete mesocolic excision during right colectomy. A: Lympho-adipose tissue covering the head of the pancreas after sectioning of the superior right colic vein (SRCV) at its confluence in the gastrocolic trunk of Henle (before dissection), and right branch of the middle colic artery; B: Lympho-adipose tissue covering the head of the pancreas after sectioning of the superior right colic vein at its confluence in the gastrocolic trunk of Henle (after dissection), and right branch of the middle colic artery (Courtesy of Prof. Giuseppe Sica, Tor Vergata University of Rome).

CME and D3 lymphadenectomy share common oncologic results, and as first described by Hohenberger et al[7], CME and CVL offer better results if performed together. The authors proposed a nodal dissection even more extended than the standard D3 proposed by Japanese surgical societies, known as CVL[7].

Furthermore, in recent years, the wide spread of minimally invasive techniques in colorectal surgery has introduced new issues regarding technical complexity and increased morbidity of these procedures[8]. Concerns have been raised, especially about the proper extent of laparoscopic lymphadenectomy and its feasibility.

**COLORECTAL CANCER**

Curative treatment of colorectal cancer (CRC) is focused on surgery. The development of cancer is supposed to be a result of interactions among environmental factors, genetic alterations, and immune response that can promote or inhibit tumor cell growth[1-16].

Once developed, CRC cells can diffuse away from the primary tumor by means of the embryological envelope constituted by the primitive dorsal mesenterium, a double layered fibrofatty mesenchymal tissue. The concept of radicality in CRC must include complete excision of this “meso-structure,” which represents the main procedure able to prevent local recurrence. On the other hand, distant metastases spread has to be prevented by means of an extended local lymph nodes removal. From this point of view, CVL is able to provide extensive lymph node dissection, limiting regional recurrence and systemic dissemination rates, thus providing improved survival in stage I-III colonic cancer[17].
Regarding rectal cancer, the concept of total mesorectal excision (TME) introduced by Heald[4] demonstrated as a complete excision of mesorectal fascia yields better outcomes and it has become the gold standard for rectal surgery (Figure 2). Again, the underlying concept is that complete removal of lymphatic drainage together with the primary tumor, while preserving the integrity of enveloping fascial layers is able to provide improved local control of disease and lower distant diffusion rates[18].

Definitely, the integrity of the dissection plane described by Heald, remains the principal predictive factor for local recurrence as clearly stated in recent meta-analyses and reviews comparing TME plus lateral lymph node dissection (LLND) vs TME alone [19-22]: to perform LLND doesn’t provide significant reduction of recurrence rates or improvement in survival; indeed, LLND is reported to require longer operation time (360 min vs 294.7 min; \( P = 0.02 \)) and increased complication rates (odds ratio [OR] = 1.48, 95% confidence interval [CI]: 1.18-1.87; \( P < 0.001 \)) such as urinary dysfunction[19].

In recent years, the same concept of extensive dissection adhering to embryological planes (CME) and central vascular ligation (CVL) have also been introduced for colonic resections[23]. CME is a well standardized procedure providing increased DFS in right colectomy[24], while little is known about perioperative morbidity and mortality when it is associated with CVL[25].

Kanemitsu et al[26] examined 370 consecutive patients who had right colectomy with D3 lymphadenectomy for right colon cancer; 3% of patients had N3 nodal involvement (patients with T3-T4 tumors) and 13.2% had N2 nodal involvement. The 5-year DFS was 36.4% for the patient with N3 nodal involvement vs 83.5% for N2 nodal involvement, suggesting that patients with proximal nodal metastasis exhibit a different tumor biology than patients with more intermediate-level nodal metastasis. Nagasaki et al[27] suggested that lymph nodes are a key element of the tumor-node-metastasis staging system and are considered a significant factor for predicting disease-free survival (DFS) and overall survival (OS) in patients with CRC without distant metastasis. Integrity of the surgical field provided by dissection conducted along the embryological planes is also very important to limit the amount of cancer cells exfoliating from traumatized tissues. In fact, in CRC surgery, intraperitoneal-free cancer cells presence is not routinely investigated but data exist on worse survival for patients who show a positive peritoneal wash[28-30].

The wide application of CME and CVL techniques seem to be also limited by the large number of CRC patients who present in emergency: a recent study demonstrated that disease free survival for patients with pT3 mucinous and signet ring cell tumor is possible (Figure 2) and might allow a "bridge to surgery" strategy (if possible) might provide better oncologic outcomes in T3 patients[31] and might allow application of CME and CVL also in these patients, if successfully shifted to elective surgery.

However, the correct extent of lymphadenectomy is still debated: 2019 guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) recommend D3 lymph node dissection for clinical stage II/III CRC[32]. However, when performing a left hemicolectomy, it is still unclear whether D3 lymph node dissection with preservation of the left colic artery (LCA) is different in terms of clinical outcomes, compared to D3 without LCA preservation. The advantages in D3 without LCA preservation have been identified in the prevention of the micrometastatic cell spillage through the en bloc lymph node dissection of the root of the inferior mesenteric artery (IMA); disadvantages include a higher possibility of anastomotic leakage and the sacrifice of the autonomic nerves around the IMA; no significant differences in terms of operation time and blood loss have been found. Despite a higher incidence of complications, D3 with LCA preservation was associated with a higher OS[33-37].

Moreover, while Kotake et al[38] demonstrated no difference in the OS of patients who had T2 colon cancers treated with D2 or D3 resection, Slanetz et al[39] showed that the level of mesenteric resection influenced outcomes only for patients who had moderate or well-differentiated cancer with intermediate-level nodal involvement. Patients with more than four positive lymph nodes or poorly differentiated tumors had poor survival regardless of the extension of lymphadenectomy. These studies had limitations such as outdated staging methods, lack of modern chemotherapy, and no audit of the pathology specimen.
LAPAROSCOPY AND CENTRAL VASCULAR LIGATION: IS IT FEASIBLE?

Minimal invasive surgery, such as robotic and laparoscopic techniques, has revolutionized the approach to gastrointestinal surgery, especially in colorectal surgery, notably lowering surgical and post-operative trauma and shortening post-operative course\[40,41\]. The concept of extended lymphadenectomy might appear in contrast with this leading point of view. Technical complexity as well as increased morbidity are important issues to be solved in order to consider these procedures in the scope of minimal invasive surgery. Regarding safety of laparoscopy from a general point of view, several trials reported promising results when comparing it to open surgery: the COST trial\[42\], COLOR I and II trials\[43,44\], CLASICC trial\[45,46\], and COREAN\[47\] demonstrated non-inferior outcomes to open surgery. A Cochrane Review clearly showed the laparoscopic approach features advantages such as decreased blood loss, quicker oral intake, decreased narcotic use, and lower rates of surgical site infections \[48\]. Furthermore, Arezzo \textit{et al}\[49\] in a meta-analysis including 4539 patients found decreased mortality (2.4% vs 1.0%; \(P = 0.048\)) and morbidity (35.4% vs 31.8%; \(P < 0.001\)) in the laparoscopic group.

Regarding the correct performance of CME and CVL, a recent systematic review reported no differences in the local and distant recurrence rate, the 3- and 5-year OS rates and the DFS rates between the laparoscopic and open CME groups\[48\]. Furthermore, the quality of the surgical specimen from laparoscopic CME/CVL seems to be similar to that obtained with the open technique\[50-53\]. In one of the few randomized controlled trials, Yamamoto \textit{et al}\[54\] compared laparoscopic and open D3 colonic resections demonstrating lower morbidity rates in the laparoscopic group with the usual benefits of minimally invasive surgery.

CONCLUSION

Central vascular ligation can be considered a widely accepted reality in colorectal surgical oncology with clear benefits in terms of oncologic outcomes. Concerns remain regarding increased rate of postoperative complications\[7,24,55\]. Different awareness on the benefits and feasibility of these extended dissections is reported for rectal and colonic cancer. Nowadays, TME is considered the gold standard in rectal cancer and it provides an optimal local disease control confining tumor deposits as well as nodal involvement within the mesorectal fascia. Complete excision of the mesorectum should be performed on bloc with the rectum by dissecting along the rectal fascia in the plane that separates this from the parietal pelvic fascia (the so called “holy plane”), thereby preserving integrity of the rectal fascia and mesorectal contents, and sparing the autonomic pelvic nerves and plexuses\[5\].

In agreement with this principle, the same concept of preservation of the embryological envelope has been applied to colonic resections\[24\]. For what concerns right colectomy, it is the author’s opinion that a true CME does not exist without CVL and extended dissection along the vascular plane offered by the anterior surface of the SMV and SMA.
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Fecal diversion in complex anal fistulas: Is there a way to avoid it?

Pankaj Garg, Vipul D Yagnik, Sushil Dawka

Abstract

Temporary fecal diversion by a diverting colostomy or ileostomy is occasionally performed for serious complex fistulas. The main indications are highly complex and extensive cryptoglandular anal fistula, anal fistula associated with severe anorectal Crohn’s disease, recurrent rectovaginal fistula, radiation-induced fistula and anal fistula with associated necrotizing fasciitis. The purpose of stoma formation is to divert the fecal stream away from the anorectum and the perianal region so as to control the infective process and prevent trauma to the operated repaired tissues. Once the fistula has healed, the diverting stoma is closed. However, two questions are relevant. First, is it certain that the same disease would not relapse (or the fistula would not recur) once the colostomy is closed? Second, is there a non-surgical method which can obviate the need for a diverting colostomy? An attempt is made to answer both these questions in this review.

Key Words: Anal fistula; Fecal diversion; Diverting stoma; Colostomy; Crohn’s disease; Rectovaginal fistula

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Core Tip: Fecal diversion is performed for severe and uncontrolled anal fistula disease. Though usually done as a last resort, it significantly increases morbidity and cost. We speculated on whether fecal diversion is actually the last resort, is it effective and can it be avoided? A novel non-surgical protocol [LOOP: L: Liquid diet with no fiber; O: Oral rehydration salt; O: Oral vitamins and protein powder/supplements; P: Phosphate]
INTRODUCTION

Anal fistulas can be simple or complex. As the name suggests, complex fistulas are complicated and pose a significant management challenge. A good proportion of fistulas in any series can be complex; at referral tertiary centers this may be as much as 50% of all reported fistulas[1]. At times, the fistula can be so complex that all routine treatment options fail to provide relief[2]. In such cases, temporary fecal diversion (diverting colostomy or ileostomy) is considered as the “last resort” management option[2]. However, this option is associated with significant morbidity which comprises physical discomfort as well as psychological distress. Diverting colostomy is quite depressing for the patient especially when performed for a non-malignant condition especially as the time of stoma closure is uncertain. Not uncommonly, patients have to live with the colostomy for the rest of their life. Last but not the least, the additional surgical procedures increase the cost of treatment significantly. Therefore, the indications and benefits of diverting stomas in perianal fistulas needs to be reviewed and an alternative less morbid (preferably non-surgical) method needs to be considered.

WHY IS A DIVERTING STOMA NEEDED IN PERIANAL FISTULAS?

A diverting stoma is needed in perianal fistulas for two reasons: (1) Uncontrolled sepsis with risk of septicemia: At times, the fistula may be associated with conditions which lead to marked sepsis like severe anorectal Crohn’s disease[3,4], anal fistula with associated necrotizing fasciitis or Fournier’s gangrene[5,6], anal fistula with large pelvirectal abscess, etc.[2]. It is believed that fecal diversion would prevent the bacterial load (fecal matter) from reaching the site of sepsis and would thus help in better and easier control of the fulminant infection; and (2) Highly refractory fistula: Another indication of diverting stoma is to increase the chances of fistula healing. At times, there are high perianal fistulas (supralevator or pelvirectal fistulas)[2], rectovaginal fistulas[7,8], radiation-induced fistulas[7,9] and Crohn’s fistulas[3] which recur repeatedly and refuse to heal even after repeated surgeries. Fecal diversion can help in these patients by preventing fecal matter, hence possible infection, from reaching the fistula site (surgery site in operated patients). Secondly, the risk of physical trauma by the stool mass to the surgical site is also curtailed due to which the healing of the surgical wound is expected to be better. These are the two main categories for which temporary fecal diversion is performed in patients of perianal fistulas.

HOW EFFECTIVE IS FECAL DIVERSION?

The important point to discuss is the efficacy of the diverting stoma in achieving the primary purpose for which the diversion is done. Unfortunately, the literature highlights that fecal diversion does not serve the purpose in a significant proportion of cases[10]. In many cases, either the disease does not improve at all[8] or it does improve with diversion but recurs once the diverting colostomy is closed, thereby necessitating permanent diversion[3,10-12].
In a study of 86 patients suffering from anal fistula due to Crohn’s disease, 62% required temporary fecal diversion and out of these, 49% ultimately ended with permanent diversion[13]. In patients with refractory anorectal Crohn’s disease for whom temporary fecal diversion was done, only 63.8% patients reported improvement in clinical symptoms within 3-6 mo[14,15]. The restoration of bowel continuity could only be attempted in 34.5% of these patients and was successfully achieved in only 16.6% patients[14,15]. Of patients in whom bowel continuity could be restored successfully, re-diversion was needed in 26.5% patients due to relapse of severe symptoms[14]. Improvement in the rectal and the perianal disease was the single most important and consistent factor responsible for restoration of bowel continuity[14,16]. On the other hand, there are studies which demonstrated that the quality of life seemed similar or potentially superior in diverted patients suffering from Crohn’s perianal fistulas compared with patients in whom the diversion was not done[17]. A diverting stoma, therefore, has the potential to improve quality of life in patients, especially with severe perianal Crohn’s disease[17]. Though medical treatment remains the mainstay of perianal Crohn’s fistulizing disease, aggressive surgical management should be considered only for severe or recurrent disease[18]. Therefore, in patients with perianal Crohn’s disease, both medical and surgical treatments should be used judiciously and the disease be managed by a multidisciplinary team[19].

Thus, the popular belief that fecal diversion would lead to rapid resolution of symptoms, rapid improvement in the disease process, and full recovery from the disease may not be true in all cases, and there is evidence in the literature which does not support this[14]. In one of the largest series of anal fistula patients who underwent surgery, half of the patients had high complex fistulas, and amongst these high fistulas, about 30% were supralevator fistulas[1]. The long-term success rate of 93.5% could be achieved in this series without needing to do fecal diversion in any patient[1]. This implies that temporary fecal diversion should be done more sparingly and after much deliberation in patients of complex perianal fistulas. Moreover, whenever it is considered, the minimal impact of fecal diversion on long-term disease prognosis as well as the possibility of inability to restore the bowel continuity should be discussed with the patient in detail. This would be even more relevant for the patients who are resistant to the prospect of permanent fecal diversion from the very beginning.

IS THERE A NON-SURGICAL WAY WHICH CAN OBVIATE THE NEED FOR FECAL DIVERSION?

As discussed above, the indications of fecal diversion need to be pruned but it would be worthwhile if its need could also be curtailed by a method which is less morbid and preferably non-surgical.

One of the methods already in vogue is loose (draining) seton insertion. In patients of complex fistulas with large deep abscesses or severe sepsis, seton insertion can lead to adequate drainage and resolution of sepsis. Along with this, it can also prevent recurrence of abscess over extended periods of time. Therefore, in highly complex cryptoglandular fistulas and patients with severe fistulizing Crohn’s disease, a draining seton can help prevent the need of fecal diversion in many cases[19]. However, there would be cases with severe disease in whom the passage of fecal matter through the anus and contact of fecal matter with the fistula keeps worsening the disease process. In these patients, another novel method can be helpful in many, if not all patients, to prevent fecal diversion.

The aim of temporary fecal diversion is to prevent contact of fecal matter with the anorectum and perianal tissues for a few days to weeks. If the same endpoint can be achieved by a non-surgical method, then the need of diversion might be mitigated. LOOP does precisely that; LOOP is an acronym for L - Liquid diet with no fiber, O - Oral rehydration solution (ORS), O - Oral vitamins and protein powder supplements, P - Phosphate (sodium phosphate) enema at the start of the treatment (Table 1). The basic principle behind LOOP is that the patients do not pass any bowel motions at all for few days to weeks while all their nutritional needs are taken care of.

As the diet has zero fiber, stool formation would be nil or minimal. The electrolytes (sodium, potassium, chloride, citrate) are taken care of by ORS. The proteins are given at 1 gm/kg body weight/d by oral protein powder supplement. The patient can take clear fluids (with zero fiber) like juices, coconut water, clear soups with butter, soft drinks, glucose water, tea, coffee etc. An oral multivitamin tablet is given daily to replenish vitamins and minerals. Along with these dietary recommendations, an enema (sodium phosphate or any other enema preferred by the patient) is given on the
Table 1 LOOP concept

| L | Liquid diet with no fiber | Clear fluids (with zero fiber) like juices, coconut water, clear soups with butter, soft drinks, glucose water, tea, coffee, etc. |
| O | Oral rehydration solution | The electrolytes (sodium, potassium, chloride etc.) are taken care by this |
| O | Oral vitamins and protein powder supplements | The proteins are given at 1 gm/kg body weight/d by oral protein powder supplement |
| P | Phosphate enema at the start of the treatment | Enema (whichever preferred by the patient) is given on the first day of the treatment so as to evacuate the rectum and clear the bowels. Otherwise, the residual stool in the rectum can harden and can cause problems later |

first day of the treatment so as to evacuate the rectum and clear the bowels. Otherwise, the residual stool in the rectum can harden over the next few days (when the patient is on LOOP and not passing stool) and these hardened stools could cause problems and pain when the normal diet and bowel motions are resumed after a few days.

LOOP can be implemented for a few days to weeks (2-4) depending upon the patient’s tolerance. If the patient can tolerate it well, then it can be extended as needed without any negative consequences as all the nutritional requirements are fully taken care of while the patient is on LOOP.

LOOP was initially developed to provide relief by a non-surgical method in anorectal conditions which get aggravated by passage of stool. These include intractable bleeding from hemorrhoids in patients on anti-coagulants that cannot be withheld, acute refractory anal fissure, acute painful thrombosed hemorrhoids etc. LOOP was found to be highly successful in these patients and, barring a few, it was comfortably tolerated.

The application of the LOOP protocol can be logically extended to patients requiring fecal diversion as the endpoint of both temporary fecal diversion and LOOP is the same – fecal matter should not come in contact with perianal tissues. LOOP may not be able to replace fecal diversion in all indications but can do so in conditions which require fecal diversion for a short period.

The indications of fecal diversion can be divided in three parts: (1) Acute conditions: Surgical repair of refractory rectovaginal fistula or high cryptoglandular fistulas (supralevator or pelvirectal), anal fistula with huge abscess with septicemia, anal fistula with associated necrotizing fasciitis or Fournier’s gangrene; (2) Acute exacerbation of a chronic controlled condition: Abscess formation in Crohn’s disease otherwise well controlled with medications; and (3) Chronic debilitating condition: Severe widespread Crohn’s disease, severe radiation proctitis with anal fistula.

The first two indications require fecal diversion for a short period (days to a few weeks) and in these conditions, LOOP can replace fecal diversion in most cases. However, for the third indication (chronic debilitating conditions), it would perhaps be difficult to replace fecal diversion with LOOP. Moreover, this is the category of patients who end up having a permanent stoma.

Thus, the LOOP protocol is logical, simple, easy to execute, has no drawbacks, can be interrupted anytime, is tolerated well by most patients, and can be repeated as required. It has been shown to be effective in avoiding surgery in other acute anorectal conditions. Against this background, it is recommended that LOOP be tried in order to avoid fecal diversion by stoma creation for the indications listed above.

CONCLUSION

Temporary fecal diversion in the management of perianal fistulas is utilized where it is intended that fecal matter should not come in contact with the anorectum and perianal tissues for a short period of time. It is done for highly complex cryptoglandular anal fistula, severe anorectal Crohn’s disease, recurrent rectovaginal fistula, radiation-induced fistulas, anal fistula with associated necrotizing fasciitis etc. However, the main drawbacks of fecal diversion are questionable impact of fecal diversion on disease resolution, uncertainty over the time-frame and success of restoration of bowel continuity, risk of having a permanent stoma, and significant increase in morbidity and cost. Therefore, fecal diversion should be used sparingly in clinical practice. A novel protocol, LOOP (patient kept on zero fiber diet with full oral nutritional support so as to avoid passage of bowel motions for a few days to weeks), has been shown to be successful in treating several acute anorectal conditions. LOOP can be tried as a
non-surgical method to avoid fecal diversion in many, if not all, conditions where temporary fecal diversion is done. If found effective, LOOP will prevent significant morbidity and reduce cost in the management of this dreaded disease.

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Regulatory roles of extracellular vesicles in immune responses against *Mycobacterium tuberculosis* infection

Zhi Yan, Hua Wang, Lan Mu, Zhi-De Hu, Wen-Qi Zheng

**Abstract**

Extracellular vesicles (EVs) are cystic vesicles naturally released by most mammalian cells and bacteria. EV contents include proteins, lipids, and nucleic acids. EVs can act as messengers to transmit a variety of molecules to recipient cells and thus play important regulatory roles in intercellular signal transduction. EVs, released by either a host cell or a pathogen, can carry pathogen-associated antigens and thus act as modulators of immune responses. EVs derived from *Mycobacterium tuberculosis* (Mt) infected cells can regulate the innate immune response through various pathways, such as regulating the release of inflammatory cytokines. In addition, EVs can mediate antigen presentation and regulate the adaptive immune response by transmitting immunoregulatory molecules to T helper cells. In this review, we summarize the regulatory roles of EVs in the immune response against Mt.

**Key Words:** Extracellular vesicles; Exosomes; *Mycobacterium tuberculosis*; Infection; Antigen; Immune regulation

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### Core Tip
Extracellular vesicles (EVs) are nanoscale membrane-bound structures released by mammalian cells and bacteria and play essential regulatory roles in intercellular signal transduction and the immune response. In this review, we discuss...
the regulatory role of EVs released by *Mycobacterium tuberculosis* (*Mtb*)-infected cells in the anti-*Mtb* immune response. Specifically, we focus on providing the most cutting-edge information on EVs released by *Mtb*-infected cells regulating the body’s immune response, including the regulatory roles in innate and acquired immune responses. In addition, we describe the basis for EV-mediated regulation of the immune response in detail, i.e., the EVs released by *Mtb*-infected host cells contain *Mtb*-associated antigens.

**INTRODUCTION**

Tuberculosis (TB) is one of the major lethal infectious diseases caused by *Mycobacterium tuberculosis* (*Mtb*). According to the World Health Organization’s global TB report of 2020, approximately 10 million people were infected with *Mtb* in 2019, causing approximately 1.4 million deaths[1]. Although several public health measures have been taken to prevent the spread of *Mtb*, the situation is concerning[2]. Drug-resistant *Mtb*, especially rifampicin-resistant *Mtb*, has become one of the deadliest pathogens in the world[1,2]. Therefore, the development of novel anti-*Mtb* reagents or vaccines is urgent and essential. Investigating the molecular mechanism of the immune response against *Mtb* is of great value because this information is the basis for preventive and therapeutic approach developments.

Extracellular vesicles (EVs) are nanoscale membrane-bound structures released by mammalian cells and bacteria. They contain proteins, lipids, and nucleic acids. EVs can be categorized into four types according to their biological origin, release pathway, size, and content: Exosomes, microparticles, microvesicles, and apoptotic bodies. Exosomes are mainly formed through the fusion of multivesicular bodies with the plasma membrane and the extracellular release of intracavitary vesicles, with a diameter of 30–100 nm and a buoyancy density of 1.13-1.19 g/mL. Exosomes are cup-shaped under a transmission electron microscope and characterized by the expression of CD63 and CD61[3]. The term “exosome” was first proposed by Trams et al[4] in 1981. Johnstone and Harding first isolated exosomes while studying the transferrin cycle[5,6]. Exosomes can be secreted by various eukaryotic cells, including macrophages, dendritic cells (DCs), neutrophils, lymphocytes, epithelial cells, mast cells, mesenchymal stem cells, and cancer cells[7,8]. Microparticles are 100-500 nm in diameter and share many characteristics with exosomes. They express member markers such as TyA, C1a, and CD35. Microvesicles are larger than exosomes and 100-1000 nm in diameter. They originate from the outer bud of the cytoplasmic membrane and carry selectins and integrins on the surface. The diameter of apoptotic bodies is 1-5 μm, and these EVs are the result of the disintegration of apoptotic cells[9]. Accumulated studies have indicated that EVs can be taken up by recipient cells and subsequently release their content to regulate gene expression in the recipient cells[9,10]. Therefore, EVs are critical regulators of various biological processes, such as embryonic development, angiogenesis, and the immune response. This review aims to summarize the research progress on the regulatory role of EVs in the immune responses against *Mtb*.

**SUMMARY OF THE IMMUNE RESPONSE AGAINST MTB**

After being inhaled into the respiratory tract, *Mtb* is first recognized by antigen-presenting cells (APCs) resident in the lungs, including alveolar macrophages, pulmonary macrophages, and DCs[11]. The pattern-recognition receptors expressed on the APC surface sense pathogen-associated molecular patterns and endocytose *Mtb* to form a phagolysosome. Simultaneously, the innate immune response is initiated,
and several inflammatory cytokines are released to promote the clearance of \textit{Mtb} in APCs. Subsequently, the APCs migrate to the lymph nodes and initiate an adaptive immune response through antigen presentation and cytokine secretion\textsuperscript{[12-14]}. However, \textit{Mtb} has a variety of immune evasion strategies\textsuperscript{[15]}. For example, it can inhibit the acidification and maturation of phagolysosomes via multiple virulence factors, such as protein tyrosine kinase\textsuperscript{[16]}, protein tyrosine phosphatase\textsuperscript{[17]}, and lipoarabinomannan (LAM)\textsuperscript{[18]}. \textit{Mtb} can also affect the adaptive immune response by regulating antigen presentation. For example, \textit{Mtb} lipoarabinomannan mannose can bind to CD209 on DCs and inhibit DC maturation\textsuperscript{[19]}, promote the release of interleukin (IL)-10, reduce the synthesis of IL-12, and ultimately inhibit the release of interferon-γ (IFN-γ) by T helper (Th) cells\textsuperscript{[20]}. The immune evasion mechanisms of \textit{Mtb} are beyond the scope of this review; for more details, please refer to the review by Lerner et al\textsuperscript{[11]}.

### EVS RELEASED BY HOST CELLS CONTAIN \textit{MTB}-ASSOCIATED ANTIGENS

Some \textit{in vitro} experiments have indicated that \textit{Mtb} infection can increase the exosome yield and alter the protein composition of EVs released by host cells. For example, the exosome yield of mouse macrophages increases approximately two-fold after \textit{Mtb} infection\textsuperscript{[21]}. However, not all types of cells produce increased amounts of exosomes after \textit{Mtb} infection. For example, Diaz et al\textsuperscript{[22]} found that the exosome yields of THP-1-derived macrophages infected with \textit{Mtb} or left uninfected were comparable.

\textit{Mtb} infection can alter the protein profile of exosomes released by a host cell. A study applying liquid chromatography-tandem mass spectrometry revealed that there were 355 host proteins in the exosomes released by \textit{Mtb}-infected macrophages. Most of the proteins were membrane proteins, and 41 of the proteins, including Hsp90, vimentin, Coronin 1 C, and moesin, were increased after \textit{Mtb} infection\textsuperscript{[22]}. In addition, \textit{Mtb} itself can also release vesicles, which are termed bacterial vesicles (BVs)\textsuperscript{[23,24]}. BVs are rich in \textit{Mtb} antigens, such as SodB, EsxN, and Ag85b\textsuperscript{[23,24]}. The protein composition of BVs is different from that of \textit{Mtb} itself\textsuperscript{[23]}. Furthermore, there is great overlap between the protein profiles of vesicles released by \textit{Mtb}-infected cells and BVs in aseptic culture\textsuperscript{[22,23,25-27]}. Several studies have confirmed that exosomes released by \textit{Mtb}- or \textit{Mycobacterium bovis} (\textit{M. bovis}) BCG-infected cells contain \textit{Mtb}-related antigens and thus are potentially immunogenic. For example, THP-1 cells infected with \textit{M. bovis} BCG can release exosomes containing \textit{Mtb} 19-kDa lipoprotein and LAM, two \textit{Mtb} antigens\textsuperscript{[25]}. J774 cells stimulated with \textit{M. bovis} BCG also release exosomes containing the Ag85 complex\textsuperscript{[26]}, the most common secretory protein in \textit{Mtb} culture medium\textsuperscript{[28]}. In addition, \textit{Mtb} DNA was also observed in exosomes released by \textit{Mtb}-infected RAW264.7 cells\textsuperscript{[29]}. Notably, a study revealed that there are two subtypes of EVs (mostly exosomes) released by \textit{Mtb}-infected mouse macrophages. One subtype expressed CD69 and CD9 but did not contain \textit{Mtb} antigens, while the other expressed \textit{Mtb} antigens, such as lipomannan (LM) and LAM\textsuperscript{[27]}. These two subtypes of exosomes could be separated by sucrose density gradient centrifugation. These findings were validated by a subsequent study\textsuperscript{[24]}. Notably, no \textit{Mtb} antigens have been observed in exosomes released by mouse macrophages infected with heat-inactivated or γ-ray-inactivated \textit{Mtb}\textsuperscript{[27,30]}, while the exosomes produced by J774 cells treated with \textit{Mtb} culture filtrate protein 10 were shown to contain \textit{Mtb} antigens\textsuperscript{[30]}. In addition, heat-inactivated \textit{Mtb} cannot release BVs when cultured alone\textsuperscript{[31]}. Taken together, these findings imply that the \textit{Mtb} antigens in \textit{Mtb}-infected cell-released exosomes are induced by live \textit{Mtb} or \textit{Mtb} secreted proteins rather than mycobacterial lysis within the infected cell.

A previous study revealed that the \textit{Rab27a} gene is essential for the synthesis of mammalian exosomes\textsuperscript{[32]}. \textit{In vitro} experiments indicated that \textit{Rab27a} knockout could decrease the exosome yield and the content of \textit{Mtb} proteins in exosomes\textsuperscript{[21]}. Furthermore, compared with wild-type mice, \textit{Rab27a} knockout mice had decreased serum exosome levels after \textit{Mtb} infection\textsuperscript{[21]}. The bacterial load was also shown to be increased in \textit{Rab27a} knockout mice, suggesting that exosomes participate in the immune response against \textit{Mtb}\textsuperscript{[21]}. In another study, Bhatnagar et al\textsuperscript{[25]} infected mice with \textit{M. bovis} BCG and found that the exosomes in the bronchial lavage fluid contained both human components (Hsp70) and \textit{Mtb} proteins, such as LAM and 19 kDa lipoproteins.
Mtb antigens have also been found in the serum exosomes of TB patients. Kruh-Garcia et al.[33] used the multiple reaction monitoring technique to analyze the protein profiles of serum exosomes from patients with active TB. They found that there were 76 peptides (33 proteins) in the serum of TB patients, and 20 of them were increased when compared to the levels in TB-negative patients. These proteins were derived from Mtb and are critical to the survival of Mtb.

In conclusion, in vitro, animal, and clinical studies have revealed that Mtb can induce the release of exosomes that contain Mtb proteins. These exosomes may play crucial roles in the anti-Mtb immune response.

REGULATORY ROLE OF EVS IN THE INNATE IMMUNE RESPONSE AGAINST MTB

As mentioned above, EVs released by cells infected with Mtb or M. bovis BCG carry Mtb proteins, such as LAM[24,25,27], the Ag85 complex[26,30], lipoproteins (LpqH and LprG)[21,27], and 19 kDa lipoproteins[25,30]. Therefore, these EVs can trigger an inflammatory response after being taken up by APCs. In addition, these EVs have been confirmed to promote the migration of macrophages, neutrophils, and lymphocytes to the lungs both in vivo and in vitro[34].

Exosomes released from Mtb- or M. bovis BCG-infected J774 cells, THP-1 cells, and RAW264.7 cells can trigger mouse macrophages to release inflammatory cytokines, such as IL-1β, IL-6, IL-12p70, tumor necrosis factor-α (TNF-α), and regulated upon activation normal T cell expressed and secreted factor, and upregulate the expression of inOS[25,30,31,34]. Exosomes from the serum of mice infected with M. bovis BCG can also promote the expression of inflammatory factors in mouse macrophages[34]. The induction of IL-1β and IL-6 is mediated by Toll-like receptor (TLR) 2, while the release of IL-10 and CCL3 is independent of TLR2[31]. The induction of TNF-α is also MyD88 and TLR4 dependent[25]. In addition, exosomes can promote the phosphorylation of p38 and IκB in mouse bone marrow-derived macrophages[25], suggesting that p38 and IκB are also involved in the production of inflammatory cytokines.

IFN-γ can enhance the clearance of Mtb in three ways: (1) Promoting the clearance of intracellular pathogens by supporting macrophages to enhance the response to reactive oxygen species or reactive nitrogen[35]; (2) Promoting the adaptive immune response by enhancing the expression of major histocompatibility complex II (MHC II) [36]; and (3) Promoting an autophagic response against pathogens[37]. The exosomes released by Mtb-infected RAW264.3 cells can inhibit the upregulation of MHC II and CD64 induced by IFN-γ in uninfected mouse macrophages through TLR2 and MyD88 [24,38]. The inhibitory effect of exosomes is associated with the cargo Mtb lipoprotein, as exosomes produced by RAW264.7 cells infected with lspa knockout (unable to synthesize lipoprotein) Mtb fail to inhibit CD64 expression induced by IFN-γ[38].

The expression of mir-18a is increased in Mtb-infected RAW264.3 cells[39], while the expression of miR-20b-5p is decreased[40]. These two microRNAs can regulate the survival, apoptosis, and proliferation of macrophages[39,40]. Both of these microRNAs were also found to be elevated in exosomes released by Mtb-infected RAW 264.3 cells, but it remains unknown whether these exosomes can be taken up by uninfected macrophages. Two studies compared the microRNA profiles of exosomes released by cells infected with Mtb or M. bovis BCG or left uninfected and verified many differentially expressed microRNAs[29,41]. Bioinformatic analysis showed that these differentially expressed microRNAs are involved in the regulation of multiple signaling pathways, including central carbon, fatty acid, and sugar metabolism[42], but whether these microRNAs can regulate the immune response remains unclear.

REGULATORY ROLE OF EVS IN THE ADAPTIVE IMMUNE RESPONSE AGAINST MTB

As mentioned earlier, Rab27a is a key regulator of the fusion of exosomes and the plasma membrane[32]. Smith et al[21] found that Mtb-infected Rab27a gene-deficient mice released decreased amounts of exosomes and consequently had an increased bacterial load and a significantly reduced activated CD4+ T cell population in the spleen, indicating that exosomes promote the adaptive immune response against Mtb in vivo. Furthermore, exosomes promote the T cell response during Mtb mouse infection. Since IFN-γ is mainly produced by Th1 cells during Mtb infection[43], these
studies suggest that exosomes are involved in the adaptive immune response against Mtb and can promote an antigen-specific T cell response[21].

The exosomes secreted by M. bovis BCG-infected J774 macrophages can enhance the expression of CD83, CD86, IL-12p40, and MHC II in mouse bone marrow-derived dendritic cells (BMDCs) and thus promote BMDCs mutation[26]. The release of IL-12p40 by DCs can promote the Th1 response[44,45]. Therefore, exosomes containing Mtb antigens can promote a subsequent Th1 response via DCs. In addition, Mtb itself can also release EVs (termed BVs) in culture, and these vesicles can upregulate the expression of CD86, MHC I, and MHC II in mouse BMDCs, which thereby enhances the release of IL-2 by Ag85-specific T cells[24]. Ramachandra et al[46] found that macrophages infected with Mtb could release EVs containing MHC II, including microvesicles and exosomes, in which ATP greatly enhanced the release of vesicles. Microvesicles and exosomes have the ability to present Mtb peptide–MHC II complexes to T cells[46]. These results suggest that innate immune cells can deliver Mtb antigens to T cells outside the infected site by releasing microvesicles and exosomes.

The exosomes released from M. bovis BCG-infected J774 cells can promote the proliferation of T cells and upregulate the expression of CD69[26], which is a marker of T cell activation[47]. In addition, these exosomes can directly enhance IFN-γ release from CD4+ and CD8+ T cells in M. bovis BCG-immunized mice[26]. These biological functions can be further enhanced in the presence of DCs[26]. In vivo studies have indicated that treating mice with exosomes can increase the proportion of spleen effector T cells (CD62L-low, CD44-high)[26]. These findings were further validated by subsequent studies. Exosomes from Mtb antigen-treated cells (Mtb CFp-treated J744 cells[30] or Mtb CFp-treated RAW264.7 cells[48]) can also activate T cells from Mtb antigen-immunized mice and enhance T cell production of IFN-γ[26,30] and IL-12[48]
in vitro. Interestingly, adjuvants have little effect on the production of IFN-γ and IL-12 [26,30], indicating that these exosomes may contain some types of substances similar to adjuvants. Furthermore, these exosomes can induce the production of memory T cells in mice [26,30] and reduce the susceptibility of mice to Mtb [48].

Athman et al [49] found that EVs released by macrophages from mice infected with Mtb and Mtb-BVs could directly inhibit the anti-CD3 and anti-CD28 antibody-induced activation of naive T cells and effector T cells. This inhibitory effect was mainly attributed to Mtb antigens in the EVs, including LAM, LM, PIM1/2, and PIM6. Previous studies have shown that these Mtb antigens can inhibit the activation of T cells, which represents one of the immune evasion mechanisms of Mtb [50]. EVs can transmit Mtb antigens to T cells and promote the expression of GRAIL [49], a negative regulator of T cell activation [51,52]. Therefore, EVs can regulate the adaptive immune response against Mtb in at least two ways: Modulating the antigen presentation process and directly regulating T cells.

CONCLUSION
In recent years, several studies have been performed to explore the characteristics and potential biological functions of EVs in the immune response against Mtb. However, our understanding of the immunomodulatory role of EVs in Mtb infection is still in its early stages. The regulatory roles of EVs in the immune response against Mtb are summarized in Figure 1. The EVs released by Mtb-infected host cells contain Mtb-related proteins and nucleic acids, which establishes the foundation for a regulatory role in the immune response against Mtb. EVs regulate both the innate and adaptive immune responses against Mtb through various pathways. Therefore, EVs may represent a key factor in the development of an Mtb vaccine.

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Aortic stenosis and Heyde’s syndrome: A comprehensive review

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Core Tip: We summarize the literature on the aortic valve replacement in aortic stenosis

Heyde’s syndrome is an under reported systemic disease of gastrointestinal and cardiac manifestation in older adults. It is characterized by a triad of aortic stenosis, angiodysplasia with bleeding and acquired von Willebrand syndrome. It is characterized by proteolysis of high molecular weight multimers of von Willebrand Factor and loss of platelet mediated homeostasis. Heyde’s syndrome is a treatable condition in most cases, especially in the current era of evolution in interventional cardiology and gastroenterology. There are currently no established guidelines in the management of this condition due to paucity of high quality studies, which warrant future trials. High index of suspicion and increasing the awareness of the syndrome among the general practitioners and sub-specialists will improve the diagnostic potential of Heyde’s syndrome. Future studies may change the management aspect of Heyde’s syndrome and pave a path for drawing specific guidelines and algorithms. The aim of our review article is to summarize the basic pathophysiology, diagnostics and management of Heyde’s syndrome with a special attention to Transcatheter aortic valve replacement.

Key Words: Heyde’s syndrome; Aortic stenosis; Angiodysplasia; Transcatheter aortic valve replacement; Gastrointestinal bleed; Anti platelet
and angiodysplasia (Heyde’s syndrome). This is a very attractive area of interest for interventional gastroenterologists and cardiologists. Future studies may change the management aspect of Heyde’s syndrome and pave a path for drawing specific guidelines and algorithms.

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INTRODUCTION
Heyde’s syndrome is a multi-system disorder of the cardiovascular, gastrointestinal (GI) and hematological system that is commonly described as a triad of aortic stenosis, gastrointestinal bleeding from angiodysplasia and acquired von Willebrand syndrome (Figure 1). Dr. Edward Heyde first described the association between aortic stenosis and gastrointestinal (GI) bleeding in 1958[1]. However, it was late in the 1980s to early 1990s that the role of coagulopathy in the form of acquired von Willebrand Disease was hypothesized to be a pathophysiologic mechanism of Heyde’s syndrome[2,3]. Angiodysplasia is characterized by abnormal and tortuous small blood vessels in the mucosal and submucosal layers of GI tract (upper GI, small bowel, colon). These are pathologically dilated communications between veins and capillaries[4]. Angiodysplasia is the second leading cause of lower gastrointestinal bleeding in the elderly[5]; accounts for 4%-7% of upper GI bleed and is the most common cause of obscure lower GI bleed in up to 50% of cases[6]. The terms angiodysplasia, arteriovenous malformations (AVMs), vascular ectasia have been used interchangeably. Aortic stenosis is the most common degenerative valvular heart disease in the elderly. Prevalence of aortic stenosis in patients with bleeding angiodysplasia has been shown to be between 7% to 41%[7-9]. The contrary is also true in that, patients with aortic stenosis have a greater potential for gastrointestinal (GI) bleeding. Clinically significant GI bleeding is estimated to occur in 1%-3% of patients with moderate to severe aortic stenosis[10-12]. Controversies exist in this regard, as to whether these two conditions occurring together in elderly, is a mere coincidence or if there is a causal relationship. However, improvement in understanding of the pathophysiology of acquired von Willebrand disease (as described later) and observation of resolution of GI bleed in patients with angiodysplasia who underwent aortic valve replacement strongly support the existence of Heyde’s syndrome[13-15]. In this article, we review the epidemiology, pathogenesis and management of Heyde’s syndrome in the era of interventional cardiology and gastroenterology.

EPIDEMIOLOGY
Heyde’s syndrome predominantly occurs in the elderly population (> 65 years) and is probably under reported. The prevalence of aortic stenosis is around 7% in population aged 75 years or older and increases to 10% in those over 80 years[16,17]. The severity of aortic stenosis also increases with age, with about 1.8% of population over 75 years having moderate to severe aortic stenosis[18,19]. A retrospective study from Cleveland clinic which looked into the association between GI Arteriovenous malformations (AVMs) and Aortic stenosis, showed a 51.7% prevalence of Aortic stenosis in patients with AVMs[8]. Another large single center study from Germany[20] involving a cohort of aortic stenosis patients with transcatheater aortic valve replacement (TAVR) showed that GI bleeding existed in 11% with endoscopically proven bleeding from angiodysplasia in 3% of the study population before TAVR. Angiodysplasia predominantly occurs in people over 60 years[6,21]. Although the true prevalence of angiodysplasia is difficult to estimate, a report from pooled prospective studies showed a prevalence of 0.83% of colonic angiodysplasia in population of healthy asymptomatic adults > 50 years[21]. However, its prevalence is thought to be higher in patients with GI bleed, end stage renal disease and von Willebrand disease[22,23]. Angiodysplasia can also be an incidental finding in healthy older adults without GI bleed during screening.
endoscopic procedures or procedures done for other purposes. It is also important to note that while the risk of bleeding in incidentally diagnosed angiodysplasia is not well established, a bleeding angiodysplasia is at increased risk for subsequent bleeding [24].

**PATHOGENESIS**

Acquired von Willebrand syndrome (vWS) is a key pathogenetic factor in Heyde’s syndrome. Acquired vWS encompasses a broad category of syndromes caused by shear induced proteolysis; antibodies to vWF, aberrant vWF binding to tumor cells; decreased vWF synthesis; or drug related [25,26]. vWF is a large glycoprotein, synthesized in megakaryocytes and endothelial cells, and plays a vital role in hemostasis (Figure 2) by mediating platelet adhesion to the sub endothelium and stabilizing factor VIII[27]. Heyde’s syndrome is characterized by the loss of the largest multimers of vWF[12,25,28,29]. Shear forces induce structural changes in the vWF while passing through the stenotic aortic valve, making it more sensitive to the action of a specific von Willebrand protease (ADAMTS 13)[2]. This results in proteolysis of high molecular weight multimers of vWF and loss of platelet mediated hemostasis (acquired von Willebrand syndrome vWS) [12,30] (Figure 3). Similar pathophysiology involving shear forces has been observed in hypertrophic cardiomyopathy, Left ventricular Assist Device (LVAD) placement, extra corporeal life support and severe mitral regurgitation[31-33]. Acquired vWS is common in patients with severe aortic stenosis. Decrease in high molecular weight vWF multimers has been shown in up to 68%-79% of cases with severe aortic stenosis[12,34]. vWF is also thought to play a role in suppressing angiogenesis[35,36] through integrin mediated signaling and vascular endothelial growth factor (VEGF) signaling[37,38]. Loss of vWF multimers leads to increased angiogenesis. This is hypothesized to be another mechanism of bleeding from angiodysplasia through increase in angiogenesis with acquired vW syndrome.

**CLINICAL FEATURES AND DIAGNOSIS**

In general, the triad of aortic stenosis, bleeding angiodysplasia and evidence of acquired vWS should be sought for while evaluating suspected Heyde’s syndrome. Isolated aortic valve stenosis or GI bleeding in the setting of alternative etiologies including peptic ulcer disease, malignancies, diverticular bleed., etc., are the other differentials to be considered. History and physical exam in a patient with suspected Heyde’s syndrome should focus on evidence of aortic stenosis, GI bleeding and impaired hemostasis suggestive of acquired vWS (Table 1). In addition to a complete medical history, prior episodes and etiologies of GI bleeding, use of concomitant drugs that can accentuate GI bleed including NSAIDS, anti-coagulants, aspirin and other anti-platelet agents should be taken into account. Echocardiogram will provide insight into the severity of aortic stenosis (ventricular-aortic gradient and the valve area) and will direct treatment options.

Patients with GI bleed can present with a wide range of clinical symptoms, from asymptomatic to hematemesis, hematochezia, melena, abdominal pain, pallor or blood on digital rectal examination. Acute bleeding with hypotension is rare in Heyde’s syndrome. Orthostasis may be present. Bleeding if present is typically painless, and usually chronic or recurrent. Fecal occult blood testing is a useful diagnostic tool in asymptomatic and occult GI blood loss. Symptoms can stem from aortic valve disease. Dyspnea on exertion, syncope, fatigue and exertional chest pain can occur. Physical
Table 1 Clinical features of Heyde’s syndrome

<table>
<thead>
<tr>
<th>Due to</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI bleed</td>
<td>Hematemesis; Hematochezia; Melena; Abdominal pain</td>
<td>Pallor; Blood on rectal exam; Orthostasis</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>Dyspnea on exertion; Syncope; Fatigue; Exertional chest pain</td>
<td>Low volume slow rising; carotid pulse; Ejection systolic murmur; Absence of physiologic S2 split</td>
</tr>
<tr>
<td>Acquired vWS</td>
<td>Easy bruisability; Mucosal bleeding; Heavy menstrual bleeding</td>
<td>Hemarthrosis; Hematoma</td>
</tr>
</tbody>
</table>

GI: Gastrointestinal; vWS: von Willebrand syndrome.

Figure 2 Hemostasis.

Figure 3 Pathogenesis of Heyde’s syndrome. GI: Gastrointestinal.

examination should include complete cardiac exam with special note pertinent to features of aortic stenosis such as low volume and slow-rising carotid pulse, a loud mid-to late-peaking systolic murmur in the right intercostal space and a single second heart sound (absence of physiologic splitting of S2). Easy bruisability and hemarthrosis are suggestive of impaired hemostasis (acquired vWS).

LABORATORY

Labs including complete blood count (CBC) with platelet count and coagulation testing including a prothrombin time (PT) and an activated partial thromboplastin time (aPTT) should be obtained. Metabolic panel and test for fecal occult blood should be included as well. In individuals with acquired vWS, prolonged PTT may be observed as a result of low factor VIII levels. However normal PTT levels do not rule out acquired vWS. Platelets counts are not affected in acquired vWS, however there
may be a coexisting condition or drug use that has to be accounted for.

**VWF MULTIMER ASSAY AND PLATELET FUNCTION ASSAY**

Reduced levels of large HMW multimers of VWF by gel electrophoresis is a sensitive test for acquired vWS, but is time consuming (7-10 d) and expensive. Another commercially available test of primary hemostasis platelet function assay (PFA)-100 to quantify primary hemostasis (closure time to collagen-ADP) is a useful screening test. VWF antigen and ristocetin cofactor activities are usually normal. PFA is often used as an initial screening test for acquired vWS, as it is completed in a few hours. If abnormal, then VWF multimer assay can be done as a confirmatory test.

**MANAGEMENT**

Management of Heyde’s syndrome basically includes management of the GI bleeding and appropriate consideration for aortic valve repair. In many cases it would mean a multi-team approach coordinated by cardiology, gastroenterology and primary care physician or inpatient hospitalist or geriatrician. There are no specific guidelines drawn for the management of Heyde’s syndrome and is rather based on expert consensus. vWF replacement therapies including vWF, factor VIII or octreotide/desmopressin therapy are not found be of benefit in the management of Heyde’s syndrome.[39].

**MANAGEMENT OF GI BLEEDING**

Initial approach to GI bleeding in suspected Heyde’s syndrome does not vary from a general approach for any case of GI bleed. Initial resuscitative measures should include intravenous fluids and appropriate blood transfusion to ensure hemodynamic stability prior to identifying the source of bleed or endoscopic interventions. As previously noted, bleeding angiodysplasia is the second most common cause of lower GI bleed in the elderly, however not without diagnostic difficulties or uncertainties. In cases of obscure GI bleeding caused by small bowel angiodysplasia, conventional techniques of upper and lower GI endoscopy might not be sufficient and warrant deep enteroscopy or video capsule studies. CT Angiography may be preferred in the setting of active bleeding, followed by angiography and embolization after localization. Rarely surgical resection or intraoperative enteroscopy might have to be undertaken in life threatening bleed. Actively bleeding angiodysplasia identified during endoscopy should be treated. Argon plasma coagulation (APC) is the most commonly employed non contact technique utilizes energy from ionized argon. Bipolar cautery can also be effective albeit with a low risk of perforation. Mechanical hemostasis using endoscopic clips, injection sclerotherapy and radio frequency ablation are the other less commonly employed techniques. Non-bleeding angiodysplasia in the setting of occult bleed or severe iron deficiency anemia, unexplained by other etiology should be treated as well. Incidentally found angiodysplasia in asymptomatic patients (without GI bleed or iron deficiency anemia) are usually thought to be low risk for bleeding and are not treated, and they don’t fall under Heyde’s syndrome.

**APPROACH TO AORTIC STENOSIS IN HEYDE’S SYNDROME**

Aortic stenosis, if severe can be an independent factor for valve replacement despite the presence or absence of GI bleeding. Cardiology guidelines on management of Aortic stenosis should nevertheless be employed in all cases. Comprehensive echocardiographic evaluation should be performed to assess the disease severity. There is no robust data on aortic valve correction in Heyde’s syndrome based on the existing literature. There is a lack of data on randomized trials comparing conservative management vs aortic valve correction in suspected or proven Heyde’s syndrome. Most of the literature supporting aortic valve replacement in Heyde’s syndrome is from case reports, case series and retrospective studies[13,15,40-48] (Table 2). Recurrent and uncontrollable GI bleeding seems to be the most common indication for AVR
Table 2 Aortic valve replacement in Heyde’s syndrome

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Type of study</th>
<th>No of patients</th>
<th>Type of aortic valve replacement</th>
<th>Outcome (Positive)</th>
<th>Outcome (negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Love et al[13]</td>
<td>1982</td>
<td>Case series</td>
<td>3</td>
<td>Surgical</td>
<td>Complete resolution of GI bleed</td>
<td></td>
</tr>
<tr>
<td>Scheffer et al [15]</td>
<td>1986</td>
<td>Case report</td>
<td>1</td>
<td>Surgical-porcine</td>
<td>No GI bleeding during 9 mo follow up</td>
<td></td>
</tr>
<tr>
<td>Cappell et al [40]</td>
<td>1986</td>
<td>Case series</td>
<td>2</td>
<td>Surgical</td>
<td>No further bleeding with negative stool guaiac in one pt at 18 mo follow up; Disappearance of angiodysplasia by endoscopy with no further bleeding in 2 nd patient at 15 mo follow up</td>
<td></td>
</tr>
<tr>
<td>Abi-akar et al [41]</td>
<td>2011</td>
<td>Case report</td>
<td>1</td>
<td>Surgical-bio prosthetic</td>
<td>No bleeding or blood transfusion at 9 mo follow up</td>
<td></td>
</tr>
<tr>
<td>Thompson et al [42]</td>
<td>2012</td>
<td>Retrospective review (1971-2001)</td>
<td>57</td>
<td>Surgical bioprosthesis(47); mechanical(10)</td>
<td>45 patients (79%) had no recurrence of GI bleeding in 15 year follow up</td>
<td>12 patients had persistent GI bleeding post AV replacement</td>
</tr>
<tr>
<td>Kadkhodayan et al[43]</td>
<td>2012</td>
<td>Case report</td>
<td>1</td>
<td>TAVR</td>
<td>No further episodes of GI bleeding post discharge</td>
<td></td>
</tr>
<tr>
<td>Balbo et al[44]</td>
<td>2016</td>
<td>Case report</td>
<td>1</td>
<td>TAVR</td>
<td>No GI Bleeding at 3 and 6 mo of follow up post TAVR</td>
<td></td>
</tr>
<tr>
<td>Alshuwaykh et al[45]</td>
<td>2018</td>
<td>Case report</td>
<td>1</td>
<td>TAVR</td>
<td>No further bleeding with stable Hemoglobin at 6 mo follow up</td>
<td>Melena requiring blood transfusion at 2 wk follow up</td>
</tr>
<tr>
<td>Garcia et al[46]</td>
<td>2019</td>
<td>Case report</td>
<td>1</td>
<td>Surgical, mechanical</td>
<td>No new episodes of GI bleeding post valve replacement</td>
<td></td>
</tr>
<tr>
<td>Famularo et al [47]</td>
<td>2020</td>
<td>Case report</td>
<td>1</td>
<td>TAVR</td>
<td>No GI bleeding at 3 follow up post TAVR</td>
<td></td>
</tr>
<tr>
<td>Godino et al[48]</td>
<td>2012-13</td>
<td>Retrospective (2007-2012)</td>
<td>7</td>
<td>TAVR</td>
<td>During a mean follow-up interval of 22 ± 15 mo, 6 patients (86%) had no recurrence of GI bleeding</td>
<td>One patient had TAVR failure with re hospitalization and blood transfusion</td>
</tr>
</tbody>
</table>

GI: Gastrointestinal; TAVR: Transcatheter aortic valve replacement.

CORRECTION OF HEMOSTATIC ABNORMALITIES (ACQUIRED VON WILLEBRAND SYNDROME) WITH AORTIC VALVE REPLACEMENT

The severity of vWF abnormality is noted to directly correlate with the severity of aortic stenosis measured by transvalvular gradient[12,49,50]. Correction of valve abnormalities or other conditions associated with high shear force (e.g., ventricular assist device) leads to resolution of GI bleeding[13,14,15,48]. Nevertheless, the hemostatic abnormalities and therefore bleeding can recur if there is a mismatch between the patient and prosthesis, (e.g., paravalvular leak)[12]. TAVR (Transcatheter aortic valve replacement) has also been shown to be effective in this regard, especially in surgically high risk patients, with resolution of GI bleeding[48], and recovery of high molecular weight vWF multimers after successful TAVR[20,48,51].

SURGICAL VALVE REPLACEMENT VS TAVR

Aortic valve stenosis is corrected either by surgical techniques (bio-prosthetic or mechanical) or by TAVR. Bio-prosthetic valve may have an upper hand over mechanical valve in preventing recurrent GI bleed theoretically, as the latter will need anticoagulation. In a retrospective analysis of Heyde’s syndrome and surgical aortic valve replacement, recurrent GI bleed was shown to be significantly lower with bioprosthetic when compared to mechanical prosthesis (15% vs 50%)[42]. The two most commonly used scores to determine the candidacy for surgical vs TAVR are the
STS (Society of Thoracic Surgeons)[52] risk score and the EuroScore[53]. TAVR is currently the treatment of choice in patients with intermediate[52] to high risk for the conventional surgical valve replacement. In a recent randomized control trial with intermediate-risk patients, TAVR was similar to surgical aortic-valve replacement with respect to the primary end point of death or disabling stroke with a significantly lower rate of life threatening bleeding at 30 d in TAVR group (10.4% vs 43.4%)[54]. Recent studies have shown that TAVR is non-inferior to surgical valve replacement even in low risk surgical patients[55,56]. TAVR (in the context of angiodysplasia associated GI bleeding) has been shown to have fewer peri-operative complications including myocardial infarction and stroke and decreased rates of blood transfusion than surgical valve replacement[57]. Overall, TAVR is becoming a popular and alternative method to surgery for valvular heart diseases. While it may appear reasonable to consider TAVR or aortic valve surgery for Heyde’s syndrome, one cannot make a strong recommendation based on the current available literature. We also proposed an algorithm for management for Heyde’s syndrome (Figure 4).

ANTI-PLATELETS/ANTI COAGULANT USE WITH TAVR

Bleeding and thromboembolic complications are the major concerns in the post TAVR period. Several factors can determine the use of anti-platelets and/or anti-coagulants including history of coronary artery disease, cardiac stent, atrial fibrillation, stroke, etc. Attempts should be made to minimize the use and/or duration of anti-coagulants and anti-platelet agents in patients with suspected or proven Heyde’s syndrome in appropriate situations. Current guidelines recommend a dual anti-platelet therapy (DAPT) of 3-6 mo after TAVR[38,59]. Recent randomized control trials in TAVR have questioned the use of DAPT against single anti platelet therapy (SAPT), with less bleeding risk with SAPT and no difference in thromboembolic events[60-63]. In a recent randomized trial on TAVR in low risk patients, the use of low dose aspirin plus warfarin did not increase short-term bleeding (30 d)[64]. The option of SAPT with TAVR seems to be promising, especially in the setting of Heyde’s syndrome.

OUTCOMES OF GI BLEEDING POST AORTIC VALVE REPLACEMENT

Several factors may determine the outcomes of GI bleeding post aortic valve replacement including the duration and number of anti-platelet agents/anticoagulants, age, co-morbidities, frailty and type of aortic valve replacement. Peri-procedural bleeding can also be related to access site bleeding. Theoretically, correction of acquired Von Willebrand syndrome with Aortic valve replacement (as described in above section) can lead to control or resolution of GI bleeding. Current data on the outcomes of GI bleeding post aortic valve replacement in Heyde’s syndrome is mostly from case reports and show favorable outcomes[13,15,40,41,43-47] (Table 2). There are a few retrospective studies[42,47] which show favorable outcomes with no recurrence of GI bleed in 79%-86% of patients post TAVR. Thompson et al[42], in a retrospective analysis of 57 patients with Heyde’s syndrome who underwent AVR, found that in a 15 year follow-up, 79% had no recurrence of GI bleeding.

GI bleeding may complicate TAVR regardless of its existence pre TAVR, and the rates of GI bleeding vary according to literature (1.4%-11.8%). Spiewak et al[65], in a retrospective analysis of 482 patients hospitalized for TAVR showed that GI bleed was only 1.4% in the immediate post TAVR period, with 40.6% of the population on DAPT and 29% on oral anticoagulation[65]. However, the risk of GI bleeding post TAVR is may be significantly higher (up to 10 fold, 11.8%) in the setting of triple therapy with DAPT and oral anticoagulant use as shown in a large cohort study by Stanger et al[66]. A large retrospective analysis on readmission rates for late GI bleeding following TAVR vs surgical aortic valve replacement showed that it was higher in TAVR cohort (3.3%) than surgical cohort (1.5%) with average time to readmission similar in both groups (approximately 90 d)[67]. Another large retrospective study from France, involving a cohort of 372 patients receiving TAVR, showed that major GI bleeding occurred in up to 11.3% of population with a median follow-up of 383 d[68]. For patients with high CHADS2-VASc score and clinically high risk for bleeding (HAS-BLED score)[69] with anti-coagulants or anti-platelet agents, WATCHMAN device (left atrial appendage closure) is another option. WATCH-TAVR is a prospective, multi-center, randomized controlled trial currently enrolling patients in 32 centers in United States, aiming at the prevention of stroke and bleeding in patients with atrial
CONCLUSION

Heyde’s syndrome, a complex multi system disorder is often overlooked and under reported, especially in the growing era of geriatric population. Heyde’s syndrome should be suspected in patients with intestinal bleeding and aortic stenosis. A high index of suspicion will improve the diagnosis. With evolution in interventional cardiology and gastroenterology the prognosis of this syndrome appears to be excellent. Future randomized controlled trials comparing clinical outcomes with and without aortic valve correction in Heyde’s syndrome will help formulate guidelines for aortic valve correction in Heyde’s syndrome.

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Retrospective Study

Key determinants of misdiagnosis of tracheobronchial tuberculosis among senile patients in contemporary clinical practice: A retrospective analysis

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Author contributions: Fan XY, Lyu LP and Tang F contributed study concept and design; Tang F, Ye W, Zha XK, Cheng Y, Wu YF and Wang YM contributed acquisition of subjects and/or data; Lin LJ and Tang F contributed analysis and interpretation of data; Tang F contributed preparation of manuscript; All authors read and approved the final manuscript.

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Institutional review board statement: The study was approved by the ethics committee of the Anhui Chest Hospital. All procedures performed in studies involving human participants were

Abstract

BACKGROUND
Tracheobronchial tuberculosis (TBTB) is a common subtype of pulmonary tuberculosis. Concomitant diseases often obscure the diagnosis of senile TBTB.

AIM
To characterize senile patients with TBTB and to identify the potential causes of misdiagnosis.

METHODS
One hundred twenty patients with senile TBTB who were admitted to the Anhui Chest hospital between May 2017 and May 2019 were retrospectively analyzed. Patients were classified as diagnosed group (n = 58) and misdiagnosed group (n = 62). Clinical manifestations, laboratory results, radiographic data, and endoscopic findings were compared between the two groups.

RESULTS
Patients in the misdiagnosed group were most commonly diagnosed as
in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent statement: Due to the retrospective nature of this study, informed consent was waived.

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

Data sharing statement: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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urinary tuberculosis (non-TTB, 29/62, 46.8%), general pneumonia (9/62, 14.5%), chronic obstructive pulmonary disease (8/62, 12.9%), and tracheobronchial carcinoma (7/62, 11.3%). The time elapsed between disease onset and confirmation of diagnosis was significantly longer in the misdiagnosed group [median (first quartile, third quartile): 6.32 (4.94, 16.02) mo vs 3.73 (2.37, 8.52) mo]. The misdiagnosed group had lower proportion of patients who underwent bronchoscopy [33.87% (21/62) vs 87.93% (51/58)], chest computed tomography (CT) scan [69.35% (43/62) vs 98.28% (57/58)], and those who showed CT signs of tuberculosis [27.91% (12/62) vs 50% (29/58)] as compared to that in the diagnosed group (P < 0.05). There were no significant between-group differences with respect to age, gender, occupation, clinical manifestations, or prevalence of comorbid chronic diseases (P > 0.05).

CONCLUSION
Insufficient or inaccurate radiographic or bronchoscopic assessment was the predominant cause of delayed diagnosis of TTB. Increased implementation and better interpretation of CT scan and early implementation of bronchoscopy can help reduce misdiagnosis of senile TTB.

Key Words: Senile tracheobronchial tuberculosis; Misdiagnosis; Clinical characteristics; Pulmonary tuberculosis; Tuberculosis

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Core Tip: Tracheobronchial tuberculosis (TBTB) is commonly misdiagnosed in clinical practice, especially among senile patients. To identify the determinants of misdiagnosis of TTB, we systematically compared the clinical features and diagnostic workup between senile patients with TTB that had been correctly diagnosed and those that had been misdiagnosed. Insufficient or inaccurate radiographic or bronchoscopic assessment was the predominant cause of delayed diagnosis of TTB. Clinical features like age, gender, occupation, clinical manifestations, or prevalence of comorbid chronic diseases were not related to the misdiagnosis of TTB.

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DOI: https://dx.doi.org/10.12998/wjcc.v9.i25.7330

INTRODUCTION
Pulmonary tuberculosis (PTB) remains a major global public health issue. According to the 2019 global tuberculosis (TB) report by the World Health Organization[1], the estimated global caseload of TB exceeds 1.7 billion; an estimated 10.0 million new cases were diagnosed, and an estimated 1.2 million people died of TB in the year 2018. The TB-related burden varies enormously among countries, and China is among the top 22 countries that are hard-hit by TB. According to the China Health Statistics Yearbook [2], more than 0.83 million new cases of TB were diagnosed in China in 2018, with the estimated morbidity rate in the same year exceeding 60.53/100000. According to an epidemiological survey, the major peak of incidence was in the age-group of 75-80 years[3,4]. Senile patients typically have multiple comorbid conditions and are immunocompromised; therefore, the diagnosis and management of senile PTB is an even more challenging issue.

Tracheobronchial TB (TBTB) is a common subtype of PTB that mainly affects the mucosa, submucosa, smooth muscle, cartilage, and even the outer membranes of the trachea or bronchii[5]. Owing to the airway involvement, patients with TBTB commonly develop obstructive pneumonia and pulmonary atelectasis, resulting in high mortality and lower cure rate as compared to the other subtypes of PTB[5].

Tracheobronchial TB (TBTB) is a common subtype of PTB that mainly affects the mucosa, submucosa, smooth muscle, cartilage, and even the outer membranes of the trachea or bronchii[5]. Owing to the airway involvement, patients with TBTB commonly develop obstructive pneumonia and pulmonary atelectasis, resulting in high mortality and lower cure rate as compared to the other subtypes of PTB[5].
Despite the high incidence, early diagnosis of TBTB is a challenge; this is largely attributable to the atypical manifestations and the lack of specific approaches for assessment [6,7]. Moreover, presence of concomitant diseases (especially other respiratory diseases) in senile patients further obscures the diagnosis of senile TBTB[6]. In this study, we sought to characterize the potential causes of missed diagnosis and misdiagnosis of TBTB in senile patients. Insights from our study may help improve the diagnostic workup for TBTB in clinical practice.

MATERIALS AND METHODS

Study population
Data pertaining to a total of 120 senile patients with TBTB who were hospitalized at the Anhui Chest Hospital between May 2017 and May 2019 were retrospectively analyzed. Patients that met all the following criteria were included: (1) Age ≥ 60 years; met diagnostic criteria for TBTB as described in the Diagnosis and treatment guidelines for TBTB 2012[8]; (2) had a previous diagnosis and treatment experience related to the current disease; and (3) complete medical records pertaining to previous diagnosis and treatment. The study population was classified into two groups: diagnosed group (n = 58, diagnosis of TBTB was confirmed before admission) and misdiagnosed group (n = 62, patients who were misdiagnosed before admission). The study was approved by the ethics committee of the Anhui Chest Hospital. Due to the retrospective nature of this study, the requirement for informed consent was waived.

Data collection
Data pertaining to demographic characteristics including age, gender, occupation, area of residence (rural/urban), and onset time (time elapsed from disease onset to the admission in our hospital) were collected. Medical records, including clinical manifestations (signs and symptoms), presence of concurrent extrapulmonary TB and other underlying diseases, were obtained. Results of radiographic assessment or bronchoscopy performed before admission were also collected.

Statistical analysis
Statistical analysis was performed using the Statistical Package for Social Science (SPSS 21.0). Normally distributed continuous variables are presented as median ± SD and between-group differences were assessed using the unpaired t test. Non-normally distributed continuous variables are presented as median (interquartile range) [M (QR)], and between-group differences were assessed using the Mann-Whitney U test. Dichotomous or categorical variables are expressed as frequencies (percentage) and between-group differences were assessed using the Chi-squared or Fisher exact test. For all statistical analysis, P values < 0.05 were considered indicative of statistical significance.

RESULTS

TBTB misdiagnosis in senile patients
Among the 120 included patients who were finally confirmed as TBTB, 62 patients (51.7%) were previously incorrectly diagnosed. These patients were most commonly misdiagnosed as pulmonary TB (non TBTB, n = 29, 46.8%), general pneumonia (n = 9, 14.5%), chronic obstructive pulmonary disease (n = 8, 14.5%), tracheobronchial carcinoma (n = 7, 11.3%), chronic bronchitis (n = 5, 8.1%), foreign body in bronchus (n = 2, 3.2%), bronchial asthma (n = 1, 1.6%), and non-tuberculous mycobacterial lung disease (n = 1, 1.6%).

General characteristics of patients in the diagnosed and misdiagnosed groups
We compared the basic characteristics of patients in the two groups to identify potential factors that may contribute to the misdiagnosis of TBTB. We found no significant differences between the two groups with respect to age, gender, occupation, or area of residence (Table 1). The onset time of the disease (time elapsed between disease onset and the present admission) in the misdiagnosed group was significantly longer than that in the diagnosed group (P < 0.001, Table 1); this indicated that misdiagnosis could jeopardize the early diagnosis and treatment of the disease.
Table 1 Comparison of general characteristics of patients in the two study groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Categories</th>
<th>Misdiagnosed group, n = 62</th>
<th>Diagnosed group, n = 58</th>
<th>$\chi^2$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>24 (38.71)</td>
<td>27 (46.55)</td>
<td>0.754</td>
<td>0.385</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>38 (61.29)</td>
<td>31 (53.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60-70</td>
<td>48 (77.42)</td>
<td>39 (67.24)</td>
<td>3.283</td>
<td>0.194</td>
</tr>
<tr>
<td></td>
<td>71-80</td>
<td>10 (16.13)</td>
<td>17 (29.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 80</td>
<td>4 (6.45)</td>
<td>2 (3.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>Farmer</td>
<td>48 (77.42)</td>
<td>45 (77.59)</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Non-farmer</td>
<td>14 (22.58)</td>
<td>13 (22.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resident area</td>
<td>Rural</td>
<td>41 (66.13)</td>
<td>38 (65.52)</td>
<td>0.005</td>
<td>0.944</td>
</tr>
<tr>
<td></td>
<td>Urban</td>
<td>21 (33.87)</td>
<td>20 (34.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset time</td>
<td></td>
<td>6.32 (4.94, 16.02)</td>
<td>3.73 (2.37, 8.52)</td>
<td>-3.899</td>
<td>0.000p</td>
</tr>
</tbody>
</table>

Data presented as n (%) or as median (first quartile, third quartile).

*P* < 0.01.

**Clinical features of patients in the two groups**

We further compared the clinical features of patients in the two groups, including clinical manifestations, presence of extracellular TB, and other concurrent diseases. Cough with expectoration were the most common symptoms in both groups; there was no significant between-group difference in this respect ($P > 0.05, \text{Table 2}$). The two groups were also comparable in terms of the incidence of other less common symptoms including hemoptysis, breathlessness, or fever ($P > 0.05, \text{Table 2}$). The presence of extrapulmonary TB ($n = 11, 9.17\%$) was rare in our study cohort; 3 patients had cervical lymphatic TB, five had laryngeal TB, one had bone TB, and one had tuberculous meningitis. No significant between-group difference was observed with respect to the incidence of extrapulmonary TB ($P > 0.05, \text{Table 2}$). Half of the study population had concurrent chronic diseases ($n = 61, 50.8\%$); of these, 10 patients ($8.33\%$) had more than 3 types of concurrent diseases other than TBTB. We did not observe any significant between-group difference with respect to the prevalence of concurrent chronic diseases ($P > 0.05, \text{Table 2}$).

**Comparison of imaging findings**

We presumed that implementation of chest computed tomography (CT) scan and the correct interpretation of CT findings play an important role in the diagnosis of TBTB. We compared the pre-admission CT scan data between the two groups. Almost all the patients ($n = 57, 98.28\%$) in the diagnosed group had undergone chest CT scan prior to admission; however, only 43 out of 62 patients ($69.35\%$) in the misdiagnosed group had undergone CT scan prior to admission ($P < 0.001, \text{Table 3}$). Among the patients for whom prior CT scan data was available, cases with reported signs of TBTB, like segmental atelectasis, airway stricture, or stenosis, were significantly lower in the misdiagnosed group as compared to that in the diagnosed group ($P < 0.05, \text{Table 3}$). A similar finding was observed with respect to the percentage of positive CT results (CT findings indicative of TBTB) ($P = 0.021, \text{Table 4}$).

Some patients with TBTB may have completely normal chest CT scan, but can only be diagnosed by bronchoscopy and bronchoscopic biopsy (as shown in Figure 1). Therefore, we also compared the implementation of bronchoscopy prior to admission in the two groups and evaluated the bronchoscopic findings. The percentage of patients who had undergone bronchoscopy prior to admission in the misdiagnosed group ($21/62, 33.9\%$) was significantly lower than that in the diagnosed group ($51/58, 87.9\%$) ($P < 0.001, \text{Table 5}$). Among all patients who had undergone bronchoscopy prior to admission, the endoscopic findings of patients in the two groups were similar in terms of subtype classification ($P = 0.369$) and range of lesion involvement ($P = 0.855$) (Table 5).
Tang F et al. Key determinants of TBTB diagnosis

### Table 2 Comparison of clinical features in the two groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Categories</th>
<th>Misdiagnosed group, n = 62</th>
<th>Diagnosed group, n = 58</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical manifestations, n (%)</td>
<td>Cough</td>
<td>53 (85.48)</td>
<td>49 (84.48)</td>
<td>0.024</td>
<td>0.878</td>
</tr>
<tr>
<td></td>
<td>Expectoration</td>
<td>38 (61.29)</td>
<td>40 (68.97)</td>
<td>0.776</td>
<td>0.378</td>
</tr>
<tr>
<td></td>
<td>Hemoptysis</td>
<td>11 (17.74)</td>
<td>14 (24.14)</td>
<td>0.743</td>
<td>0.389</td>
</tr>
<tr>
<td></td>
<td>Breathlessness</td>
<td>23 (37.10)</td>
<td>18 (31.03)</td>
<td>0.49</td>
<td>0.484</td>
</tr>
<tr>
<td></td>
<td>Fever (≥ 37.3 °C)</td>
<td>19 (30.65)</td>
<td>10 (17.24)</td>
<td>2.938</td>
<td>0.087</td>
</tr>
<tr>
<td></td>
<td>Other systemic symptoms</td>
<td>14 (22.58)</td>
<td>11 (18.97)</td>
<td>0.237</td>
<td>0.626</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis, n (%)</td>
<td>Cervical lymphatic tuberculosis</td>
<td>2 (3.23)</td>
<td>1 (1.72)</td>
<td>-</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Bone tuberculosis</td>
<td>1 (1.61)</td>
<td>1 (1.72)</td>
<td>-</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Laryngeal tuberculosis</td>
<td>2 (3.23)</td>
<td>3 (5.17)</td>
<td>-</td>
<td>0.672</td>
</tr>
<tr>
<td></td>
<td>Tuberculous meningitis</td>
<td>1 (1.61)</td>
<td>0 (0.00)</td>
<td>-</td>
<td>1.000</td>
</tr>
<tr>
<td>Chronic diseases, n (%)</td>
<td>1</td>
<td>15 (24.19)</td>
<td>7 (12.07)</td>
<td>2.942</td>
<td>0.086</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>18 (29.03)</td>
<td>11 (18.97)</td>
<td>1.657</td>
<td>0.198</td>
</tr>
<tr>
<td></td>
<td>≥ 3</td>
<td>7 (11.29)</td>
<td>3 (5.17)</td>
<td>1.468</td>
<td>0.226</td>
</tr>
</tbody>
</table>

Data presented as n (%).  
*P < 0.05.  
**P < 0.01.

### Table 3 Comparison of computed tomography findings in the two groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Categories</th>
<th>Misdiagnosed group, n = 62</th>
<th>Diagnosed group, n = 58</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT scan</td>
<td>Yes</td>
<td>43 (69.35)</td>
<td>57 (98.28)</td>
<td>18.047</td>
<td>0.000*</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>19 (30.65)</td>
<td>1 (1.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT findings</td>
<td>Segmental atelectasis</td>
<td>21 (33.87)</td>
<td>30 (51.72)</td>
<td>3.909</td>
<td>0.048*</td>
</tr>
<tr>
<td></td>
<td>Airway stricture/stenosis</td>
<td>15 (24.19)</td>
<td>23 (39.66)</td>
<td>3.311</td>
<td>0.069</td>
</tr>
<tr>
<td></td>
<td>Mediastinal/hilar lymphadenectomy</td>
<td>6 (9.68)</td>
<td>3 (5.17)</td>
<td>-</td>
<td>0.495</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>1 (1.61)</td>
<td>1 (1.72)</td>
<td>-</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Data presented as n (%).  
*P < 0.05.  
**P < 0.01.

### Table 4 Comparison of computed tomography scan interpretation between the two groups

<table>
<thead>
<tr>
<th>CT interpretation</th>
<th>Misdiagnosed group, n = 43</th>
<th>Diagnosed group, n = 57</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>12 (27.91)</td>
<td>29 (50.00)</td>
<td>5.346</td>
<td>0.021*</td>
</tr>
<tr>
<td>Negative</td>
<td>31 (72.09)</td>
<td>28 (49.12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as n (%).  
*P < 0.05.

**DISCUSSION**

PTB is highly prevalent across the world, especially in developing countries; TBTB accounts for 10%-40% of all cases of PTB[9]. The diagnosis of TBTB is challenging, as the bronchial lesions are usually not detectable on X-ray and the symptoms are non-specific and insidious at onset; this is especially so in senile patients in whom the
Table 5 Comparison of endoscopic features and classification of tracheobronchial tuberculosis in the two groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Categories</th>
<th>Misdiagnosed group, n = 62</th>
<th>Diagnosed group, n = 58</th>
<th>$\chi^2$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoscopy before admission</td>
<td></td>
<td>21 (33.87)</td>
<td>51 (87.93)</td>
<td>36.491</td>
<td>0.000b</td>
</tr>
<tr>
<td>Classification of TBTB</td>
<td>I</td>
<td>2 (3.23)</td>
<td>4 (6.9)</td>
<td>-</td>
<td>0.369</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>17 (27.42)</td>
<td>19 (32.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>6 (9.68)</td>
<td>2 (3.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>27 (43.55)</td>
<td>20 (34.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>V</td>
<td>1 (1.61)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VI</td>
<td>9 (14.52)</td>
<td>13 (22.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range of lesion involvement</td>
<td>Trachea</td>
<td>3 (4.84)</td>
<td>7 (12.07)</td>
<td>-</td>
<td>0.855</td>
</tr>
<tr>
<td></td>
<td>left principal bronchus</td>
<td>6 (9.68)</td>
<td>8 (13.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>left upper bronchus</td>
<td>16 (25.81)</td>
<td>13 (22.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>left lower bronchus</td>
<td>7 (11.29)</td>
<td>6 (10.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right principal bronchus</td>
<td>15 (24.19)</td>
<td>12 (20.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right upper bronchus</td>
<td>4 (6.45)</td>
<td>3 (5.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right middle bronchus</td>
<td>11 (17.74)</td>
<td>9 (15.52)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as n (%).

bP < 0.01.

manifestations can be obscured by co-existing pulmonary diseases[10]. Early diagnosis of senile TBTB is a key imperative owing to the extremely high mortality rate. In the present study, we sought to identify means to improve the diagnostic accuracy in senile patients with TBTB. Our study revealed that senile TBTB is commonly omitted or misdiagnosed as other pulmonary diseases. We found no significant difference between misdiagnosed patients and those who were correctly diagnosed in terms of demographic characteristics, clinical manifestations, or concomitant diseases. However, a significantly lesser percentage of patients received chest CT scan and bronchoscopy in the misdiagnosed group as compared to that in the correctly-diagnosed group. Our findings indicate that the lack of CT scan or bronchoscopy examination is the major factor that hinders the diagnosis of TBTB in senile patients.

TBTB is a specific subtype of PTB in which the tuberculous lesions are primarily located in the wall of airway, and are not necessarily accompanied by involvement of pulmonary parenchyma[9,11]. Pathological changes in the airway wall can lead to airway stenosis in up to 90% of TBTB patients, especially in the late stage of disease; this is a major cause of mortality in these patients[7,12]. Early diagnosis and treatment is the key strategy to stop the progression of airway stenosis. However, misdiagnosis or delayed diagnosis of TBTB is a common phenomenon, resulting in increased likelihood of progression to fibro-stenosis[5]. More than half of all TBTB patients in the present study were initially misdiagnosed, usually as PTB, pneumonia, or chronic obstructive pulmonary disease. Although the diagnosis of PTB would not delay the initiation of antitubercular treatment, TBTB is the most aggressive subtype of PTB, which requires more intensive therapeutic strategy to prevent the occurrence or progression of airway ulceration, necrosis, and fibrostenosis. Therefore, identification of TBTB at an early stage is a key imperative. As expected, misdiagnosis significantly prolonged the disease onset time (time elapsed between disease onset and confirmation of diagnosis) and delayed the start of treatment.

Several factors contribute to the delayed diagnosis of TBTB in clinical practice. Firstly, the typically insidious disease onset and the non-specific clinical presentation tends to hinder the diagnosis, especially in the early stages[9]. A high index of clinical suspicion supported by evidence from radiological and bronchoscopic detection is key for early diagnosis[10]. Secondly, identification of TBTB relies on evidence of pathological changes in airway tissues; however, these changes are usually undetectable on X-ray until the development of severe tracheobronchial stenosis at late stage[13]. Even when the concomitant parenchymal changes are detectable on general radiography, it tends to obscure the presence of airway involvement and lead to
misdiagnosis of parenchymal disease[9]. The lack of specific diagnostic approach is the major obstacle for early diagnosis of TBTB. Lastly, senile patients with underlying conditions are most vulnerable to TBTB; these patients tend to have underlying pulmonary diseases, such as chronic obstructive pulmonary disease, parenchymal TB, and pneumonia. These preexisting diseases can also induce respiratory symptoms like cough, hemoptysis, breathlessness, and fever; this tends to obscure the concurrent TBTB[6,7]. All these factors make the early detection of TBTB extremely challenging, especially among senile patients.

In the present study, we first assessed whether the delayed diagnosis of TBTB was due to atypical clinical presentation or the presence of comorbid conditions. Unexpectedly, we did not observe any significant between-group difference in terms of clinical manifestations, concomitant chronic diseases or demographic features. This implies that the insidious manifestations and concomitant diseases were not the major causes of TBTB misdiagnosis in clinical practice.

As mentioned above, the lack of specific diagnostic modalities hinder the early identification of TBTB. The gold standard for diagnosis of PTB is the positive culture of tubercular bacilli from sputum or bronchoalveolar lavage fluid; this is a time-consuming method and is associated with a low sensitivity[14]. The development of TB antibodies/RNA/DNA detection, Interferon-Gamma Release Assays (IGRAs), and Gene Xpert MTB/RIF have helped improve the diagnostic yield; however, the early diagnosis of PTB remains a challenge[15,16]. The diagnosis of TBTB requires evidence of airway involvement in addition to the detection of tubercular bacilli; this makes the diagnosis of TBTB even more challenging. X-ray has a poor sensitivity for the detection of tracheobronchial lesions; however, CT scan (especially 64-slice spiral CT) has been shown to efficiently detect the TBTB lesions[17-19]. CT imaging can clearly delineate the extent of bronchial or parenchymal involvement and determine the stage of disease progression[9]. Bronchoscopic examination is another highly recommended modality for detection of TBTB. Bronchoscopy can detect morphological features (e.g., edematous, fibrostenotic, granular or ulcerative lesions) of the airway lesions, which provides critical information for the staging of TBTB[20]. Moreover, it is a convenient method for obtaining biopsy tissue for pathological examination[21,22]. Specifically,
for TBTB progressing to fibro-stenosis stage, when tuberculous bacilli are undetectable, bronchoscopic evidence of chronic fibrosis and granular changes can support the diagnosis of TBTB[20,22]. Given the critical role of CT scan and bronchoscopy in the diagnosis of TBTB, we assessed whether the lack of implementation of these examinations contributed to the delayed diagnosis of TBTB. Our results showed that the percentage of patients who did not receive CT scan or bronchoscopy examination before admission in the misdiagnosed group was significantly greater than that in the correctly-diagnosed group. A large proportion of TBTB patients did not receive CT scan or bronchoscopy during diagnostic workup; this indicates the need for greater awareness among physicians about this disease. Our findings highlight the importance of a high suspicion index for TBTB along with early implementation and accurate interpretation of chest CT scan and bronchoscopy for the diagnosis of TBTB. Detailed medical history and meticulous physical examination also play a role in the early identification of TBTB. For patients with signs or symptoms suggestive of TBTB, CT scan and bronchoscopy should be considered especially in senile patients.

To the best of our knowledge, this is the first study to identify factors associated with misdiagnosis of senile TBTB in contemporary clinical practice. However, some limitations of our study should be considered while interpreting the results. First, the sample size in this study was relatively small; larger studies are required to obtain more definitive evidence. Moreover, most of the medical data analyzed was obtained from other institutions. The analysis did not take into account the level of care and diagnostic competence of these medical institutions. Finally, we only included cases who were admitted at our center; our conclusions need to be verified in a multi-center study.

CONCLUSION
To conclude, our study identified factors that may contribute to the misdiagnosis of TBTB in contemporary clinical practice. Early implementation and accurate interpretation of chest CT scan and bronchoscopy would facilitate early diagnosis and minimize misdiagnosis of TBTB in senile patients.

ARTICLE HIGHLIGHTS

Research background
Tracheobronchial tuberculosis (TBTB) is commonly misdiagnosed in clinical practice, especially among senile patients.

Research motivation
To characterize senile patients with TBTB and to identify the potential causes of misdiagnosis.

Research objectives
One hundred twenty patients with senile TBTB who were admitted to the Anhui Chest hospital between May 2017 and May 2019 were retrospectively analyzed.

Research methods
Patients were classified as diagnosed group (n = 58) and misdiagnosed group (n = 62). Clinical manifestations, laboratory results, radiographic data, and endoscopic findings were compared between the two groups to identify the major factors that contribute to the misdiagnosis or delayed diagnosis of the disease.

Research results
Patients in the misdiagnosed group were most commonly diagnosed as pulmonary tuberculosis (non-TBTB, 29/62, 46.8%), general pneumonia (9/62, 14.5%), chronic obstructive pulmonary disease (8/62, 12.9%), and tracheobronchial carcinoma (7/62, 11.3%). The misdiagnosed group had lower proportion of patients who underwent bronchoscopy [33.87% (21/62) vs 87.93% (51/58)], chest CT scan [69.35% (43/62) vs 98.28% (57/58)], and those who showed CT signs of tuberculosis [27.91% (12/62) vs 50% (29/58)] as compared to that in the diagnosed group (P < 0.05).
**Research conclusions**

Insufficient or inaccurate radiographic or bronchoscopic assessment was the major cause of delayed diagnosis of TBTB.

**Research perspectives**

Increased implementation and better interpretation of CT scan and early implementation of bronchoscopy can help reduce misdiagnosis of senile TBTB.

**REFERENCES**


8. Ding WM. Guidelines for the diagnosis and treatment of tracheobronchial tuberculosis. The 2012 Annual Academic Conference and Professional Group Establishment Conference of the Clinical Professional Committee of the Chinese Tuberculosis Association; 2012 August 10; Changechun, Jilin, China


Retrospective Study

Long-term outcome of pancreatic function following oncological surgery in children: Institutional experience and review of the literature

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Author contributions: All authors participated in the production of the work; all authors have read and approved the final manuscript.

Institutional review board statement: The Ethical Committee of “Bambino Gesù” Children’s Hospital in Rome approved this study. Our Hospital is an Institute authorized by the Ministry of Health Care for research and clinical study. Therefore, to enroll patients in clinical studies all the parents or tutors give their consent by signature of a specific document when the children are admitted to our Hospital. In this way, we have the consent in line with the indications of our Ethical Committee when the patients are admitted to the hospital.

Informed consent statement: All

Abstract

BACKGROUND
Pancreatic neoplasms are uncommon in children and in most cases they are benign or have low malignant potential. Pancreatoblastoma and solid pseudo-papillary tumor are the most frequent types in early and late childhood, respectively. Complete resection, although burdened by severe complications, is the only curative treatment for these diseases. Pancreatic surgery may result in impaired exocrine and endocrine pancreatic function. However, limited data are available on the long-term pediatric pancreatic function following surgical resection.

AIM
To investigate endocrine and exocrine pancreatic function and growth after oncological pancreatic surgery in a pediatric series.

METHODS
Pancreatic neoplasms are uncommon in childhood with an incidence rate, as reported in the United States, of 0.018 cases per 100000 people[1]; in most cases they are benign or have low malignant potential[2]. Pancreatoblastoma and solid pseudopapillary tumor (SPT) are the most common histologies in early and late childhood, respectively[1,5,4]. Endocrine tumors, adenocarcinoma, sarcoma, lymphoma and neuroblastoma rarely occur in children. Prognosis, although better than in adults, is strongly influenced by tumor histology, with excellent survival for SPTs (95%) and lower for neuroendocrine tumors (51%), sarcomas (43%) and acinar cell carcinomas (34%)[5]. Complete surgical resection provides the only curative treatment for patients with pancreatic neoplasms, except for lymphoma[6]. Distal pancreatectomy is the preferred
surgical approach for body/tail neoplasms and pancreatoduodenectomy (PD) for head neoplasms[7-9]. PD, also known as Whipple procedure, is the treatment of choice for pancreatic neoplasms involving the head of the pancreas and the periampullary tract[10-13]. It is, however, a very complex surgery with many complications and a high mortality rate, even in adults[14-17]. Pancreatic resections may result in impaired pancreatic, endocrine and exocrine function[7-9,18-22]. Given the great relevance of pancreatic function on nutritional status and growth in childhood, we planned the present study to assess the long-term outcome of exocrine and endocrine pancreatic function, growth and vitamin status following pancreatic resection for neoplasms in our Institution.

**MATERIALS AND METHODS**

**Study design**

All consecutive patients, 18 years old or younger, affected by pancreatic neoplasms and who had undergone pancreatic surgery between January 31, 2002 to the present were retrospectively reviewed from our Institutional database. Patients with pancreatic neoplasms had been followed since 2002 by a structured multidisciplinary team consisting of pediatric surgeons, pediatric gastroenterologists, oncologists, endocrinologists, radiologists and dietitians.

All patients with pancreatic neoplasms who had undergone pancreatic surgery were considered eligible.

The following outcomes were selected: (1) Rate of exocrine insufficiency, defined as steatorrhea associated with fecal elastase-1 < 200 µg/g stool[23]; (2) Rate of endocrine insufficiency defined as fasting blood glucose ≥ 126 mg/dL (≥ 7.0 mmol/L) or glycated hemoglobin ≥ 6.5% (≥ 48 mmol/L) for the diagnosis of diabetes and fasting blood glucose 100-125 mg/dL (5.6-6.9 mmol/L) or glycated hemoglobin 5.7%-6.4% (39-47 mmol/mol) for the diagnosis of impaired glucose tolerance (IGT)[24]; (3) Growth based on the body mass index (BMI) z-score trend; the growth charts from the CDC (Centers for Disease Control)[25] were used as a reference; and (4) Rate of fat-soluble vitamin deficiency (A, E, D, clotting test).

Our scheduled follow-up after oncological pancreatic surgery is reported in Table 1. Generally, steatorrhea was assessed before discharge and at every follow-up visit; we employed only fecal elastase to follow the trend of exocrine failure.

Data relating to the study variables were extracted from medical records.

**Statistical analysis**

Categorical variables were summarized as percentage and continuous variables as mean ± SD. The Mann-Whitney U test was used to compare continuous variables and Fisher’s exact test was used to compare frequencies between groups. A P value of < 0.05 was considered to indicate statistical significance. Statistical evaluation and figures were performed using Graph Pad 6 for Windows.

**Ethics**

The Ethical Committee of “Bambino Gesù” Children’s Hospital in Rome approved this study. Our Hospital is an Institute authorized by the Ministry of Health Care for research and clinical study. Therefore, to enroll patients in clinical studies all the parents or tutors give their consent by signature of a specific document when the children are admitted to our Hospital. In this way we have the consent in line with the indications of our Ethical Committee when the patients are admitted to the hospital.

**RESULTS**

Sixteen patients, twelve girls (75%) and four boys (25%) (P = 0.0121), all surviving, fulfilled the study inclusion criteria. Mean age at diagnosis and at the last evaluation were 10.7 ± 5.3 years and 16.6 ± 5.2 years, respectively. Mean follow-up was 5.7 ± 4.3 years. Nine of 16 patients (56%) had a neoplasm in the head of the pancreas (P = NS), and of the remaining 7 patients, 4 had a tumor in the body/tail, 2 in the tail and 1 in the body. Histologies were as follows: SPT in 10 patients (62.5%) (P = NS); the remaining histopathological diagnoses were: Insulinoma in 2 patients, neuroendocrine tumor in 2 and acinar cell carcinoma in the remaining two patients. Mean age at diagnosis was significantly higher in patients with SPT (13.5 ± 2.4 years) than in the
Table 1 Our scheduled follow-up for pancreatic neoplasms after surgery in children

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination (physical examination, symptoms, weight, height, BMI)</td>
<td>Every 4 mo</td>
<td>Every 6 mo</td>
<td>Once a year</td>
</tr>
<tr>
<td>Routine lab tests (CBC, liver and kidney function tests, amylase, lipase, bilirubin, albumin, etc.)</td>
<td>Every 4 mo</td>
<td>Every 6 mo</td>
<td>Once a year</td>
</tr>
<tr>
<td>Vitamin dosage (A, D, E, clotting test)</td>
<td>Every 4 mo</td>
<td>Every 6 mo</td>
<td>Once a year</td>
</tr>
<tr>
<td>Serological markers (according to the underlying histology) (alpha-FP, Chromogranin-A)</td>
<td>Every 4 mo</td>
<td>Every 6 mo</td>
<td>Once a year</td>
</tr>
<tr>
<td>Assessment of exocrine pancreatic function (fecal elastase)</td>
<td>Every 4 mo</td>
<td>Every 6 mo</td>
<td>Once a year</td>
</tr>
<tr>
<td>Assessment of endocrine pancreatic function (fasting blood glucose, glycated hemoglobin, C-peptide)</td>
<td>Every 4 mo</td>
<td>Every 6 mo</td>
<td>Once a year</td>
</tr>
<tr>
<td>Imaging (abdominal US)</td>
<td>Every 4 mo</td>
<td>Every 6 mo</td>
<td>Once a year</td>
</tr>
<tr>
<td>Surgical, diabetological and oncological consulting</td>
<td>Every 4 mo</td>
<td>Every 6 mo</td>
<td>Once a year</td>
</tr>
<tr>
<td>Nutritional assessment (3-d recall dietary assessment and diet optimization by dietitians)</td>
<td>Every 4 mo</td>
<td>Every 6 mo</td>
<td>Once a year</td>
</tr>
</tbody>
</table>

T1: First year after diagnosis; T2: Second year after diagnosis; T3: Third year to 10 yr after diagnosis (end of follow-up); BMI: Body mass index; CBC: Complete blood count; alpha-FP: alpha-Fetoprotein; US: Ultrasound.

other (6.2 ± 5.8 years) (P = 0.0167). Abdominal pain was the most frequent presenting symptom (43.7%). PD was the main surgery performed (50% of patients). Exocrine and endocrine insufficiency occurred in 4 (25%) and in 2 (12.5%) of 16 patients, respectively. Two patients developed both exocrine and endocrine insufficiency and 2 only exocrine insufficiency. All patients with exocrine pancreatic failure required supplementation with pancrelipase, which is still ongoing, while 2 patients showed IGT not requiring insulin therapy. All these patients had pancreatic head tumors treated by PD. Interestingly, exocrine insufficiency occurred within the first 6 mo after surgery, while endocrine insufficiency occurred later (8 and 10 years after surgery). With regard to the growth trend, mean BMI z-score at diagnosis was 0.36 ± 1.1 and at the last follow-up was 0.27 ± 0.95 (P = NS) (see also Figure 1 for details). Vitamins A and E and clotting tests were in the normal ranges in all patients. Vitamin D was found to be insufficient (< 30 ng/mL) at some follow-up visits in 8 of the 16 patients. The main characteristics of our patients are detailed in Table 2.

**DISCUSSION**

Pancreatic neoplasms are rare in childhood and the main treatment, regardless of tumor type, is radical resection[21]. The extent of surgical resection needed for complete debulking is related to the neoplasm site. Whenever possible, less extensive resection is advocated; however, a minority of patients will require resection of the pancreatic head and hepatobiliary reconstruction. Proper discussion of the risks and benefits is particularly difficult due to the lack of literature. In particular, few data are available on the long-term outcome of exocrine and endocrine insufficiency, following surgery. Due to the high relevance of normal absorption in children to guarantee the expected growth course, we investigated, in a series of 16 children with pancreatic tumors who had undergone surgery in the last 19 years, the long-term outcome of exocrine/endocrine function, growth and development of fat-soluble vitamin deficiency. Overall, 25% of patients in the present series developed exocrine failure. In adults, the rate of pancreatic exocrine insufficiency after partial pancreatectomy seems to be higher (about 35%)[19]. In Tables 3 and 4 we summarize the main characteristics of the studies that focused on long-term outcome of pancreatic functions following oncological surgery in children[26-37]. The data showed that the prevalence of exocrine insufficiency in pediatric patients ranged from 0%[29] to 83.3%[33]. Vasudevan et al[27] found exocrine failure rate similar to our finding (23%), while Cheng et al[26] found a much lower rate (8.6%). Park et al[34] reported that six of 8 patients experienced mild steatorrhea.
Table 2 Main demographic and clinical characteristics of our patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Histology</th>
<th>Symptoms</th>
<th>Tumor site</th>
<th>Type of surgery</th>
<th>Length of follow-up</th>
<th>Exocrine pancreatic failure</th>
<th>Endocrine pancreatic failure</th>
<th>Vitamin D insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>12</td>
<td>SPT</td>
<td>Weight loss</td>
<td>HEAD</td>
<td>PPPD</td>
<td>10.4 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>9.8</td>
<td>SPT</td>
<td>Occasional diagnosis</td>
<td>BODY</td>
<td>Distal Pancreatectomy</td>
<td>6.4 yr</td>
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<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>17.3</td>
<td>SPT</td>
<td>AP</td>
<td>HEAD</td>
<td>PPPD</td>
<td>3.9 yr</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>15.5</td>
<td>Neuroendocrine tumor</td>
<td>AP</td>
<td>HEAD</td>
<td>PPPD</td>
<td>2.3 yr</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>6.6</td>
<td>Acinar cell carcinoma</td>
<td>AP* weight loss</td>
<td>HEAD</td>
<td>PPPD</td>
<td>11.5 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>4.11</td>
<td>Acinar cell carcinoma</td>
<td>Not available</td>
<td>HEAD</td>
<td>PD</td>
<td>12.3 yr</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>14.3</td>
<td>SPT</td>
<td>Weight loss</td>
<td>TAIL</td>
<td>Distal Pancreatectomy</td>
<td>2 yr</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>13.2</td>
<td>SPT</td>
<td>AP</td>
<td>HEAD</td>
<td>PPPD</td>
<td>9 mo</td>
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<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>3</td>
<td>Insulinoma</td>
<td>Hypoglycemia</td>
<td>HEAD</td>
<td>Cephalic Pancreatectomy</td>
<td>11 yr</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>11</td>
<td>SPT</td>
<td>AP</td>
<td>BODY/TAIL</td>
<td>Distal Splenopancreatectomy</td>
<td>2 yr</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>10</td>
<td>Neuroendocrine tumor</td>
<td>Screening in TuberousSclerosis</td>
<td>BODY/TAIL</td>
<td>Distal Pancreatectomy</td>
<td>9 yr</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>15.5</td>
<td>SPT</td>
<td>No symptoms</td>
<td>BODY/TAIL</td>
<td>Distal Splenopancreatectomy</td>
<td>2.5 yr</td>
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<td>No</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>13.8</td>
<td>SPT</td>
<td>AP</td>
<td>HEAD</td>
<td>PPPD</td>
<td>10 yr</td>
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<td>No</td>
<td>No</td>
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<tr>
<td>14</td>
<td>F</td>
<td>11.6</td>
<td>SPT</td>
<td>No symptoms</td>
<td>BODY/TAIL</td>
<td>Distal Splenopancreatectomy</td>
<td>3.4 yr</td>
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<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>16.2</td>
<td>SPT</td>
<td>AP* weight loss</td>
<td>TAIL</td>
<td>Distal Pancreatectomy</td>
<td>3.8 yr</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>7</td>
<td>Insulinoma</td>
<td>Hypoglycemia</td>
<td>HEAD</td>
<td>PPPD</td>
<td>1 mo</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

F: Female; M: Male; Age: Years at diagnosis; SPT: Solid pseudopapillary tumor; AP: Abdominal pain; PD: Pancreatectomyduodenectomy; PPPD: Pylorus preserving pancreaticoduodenectomy; Vitamin D insufficiency: < 30 ng/mL.

In contrast, endocrine insufficiency, described in 40% of adult patients after partial pancreatectomy[19], was observed only in few pediatric patients. We found endocrine failure in 12.5% and Vasudevan et al[27] found endocrine failure in 3%. No patients with endocrine insufficiency were found in seven surveys[28,29,31,33,35-37]. Cheng et al[26] reported that only one patient developed endocrine insufficiency in 104 and Park et al[34] found one in 8 patients. This finding might reflect the larger functional reserve of the endocrine pancreas in young patients[32]. It is possible that the functional reserve could become insufficient many years after pancreatic resection, as confirmed by our two cases who developed endocrine failure after 8 and 10 years after surgery. The two patients who showed IGT not requiring insulin therapy, did not develop islet cell autoantibodies, so we could exclude the diagnosis of latent autoimmune diabetes in adults[38]. This finding suggests that long-term follow-up is crucial to identify endocrine pancreatic failure.

According to our results, previous studies showed that pancreatic exocrine function can occur early (within 2 mo after surgery) following PD but that it may later revert (from 6 mo to 12 mo)[21,22]. Glucose metabolism tends to remain normal for 1 year after PD, but it can worsen after many years[20,22,39].

The magnitude of the pancreatic resection is the main factor influencing the worsening of pancreatic function over the years. Divarcı et al[29], found no cases of exocrine and endocrine failure in patients who underwent tumor enucleation. Lindholm et al[33] found a rate of exocrine insufficiency closer to that reported in...
Table 3 Summary of the reports included in the literature review

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Country</th>
<th>Length of follow-up (yr)</th>
<th>n of cases/M/F (%)</th>
<th>Mean or median age (yr)</th>
<th>Exocrine insufficiency (%)</th>
<th>Endocrine insufficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>Italy</td>
<td>5.7</td>
<td>16 (25/75)</td>
<td>10.7</td>
<td>25</td>
<td>12.5</td>
</tr>
<tr>
<td>Cheng et al[26], 2020</td>
<td>China</td>
<td>3.1</td>
<td>104 (31/69)</td>
<td>9.9</td>
<td>8.6</td>
<td>1</td>
</tr>
<tr>
<td>Vasudevan et al[27], 2020</td>
<td>United States</td>
<td>2.8</td>
<td>65</td>
<td>13</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Mizuno et al[28], 2018</td>
<td>Japan</td>
<td>30</td>
<td>1 (M)</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Divarci et al[29], 2017</td>
<td>Turkey</td>
<td>3.6</td>
<td>5 (0/100)</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>d’Ambrosio et al[30], 2014</td>
<td>Italy</td>
<td>2.1</td>
<td>5 (40/60)</td>
<td>7</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Laje et al[31], 2013</td>
<td>United States</td>
<td>6.7</td>
<td>6 (17/83)</td>
<td>15</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Scandavini et al[32], 2018</td>
<td>Sweden</td>
<td>6.6</td>
<td>13 (23/77)</td>
<td>11.4</td>
<td>31</td>
<td>7.7</td>
</tr>
<tr>
<td>Lindholm et al[33], 2017</td>
<td>United States</td>
<td>4.7</td>
<td>12 (42/58)</td>
<td>9</td>
<td>83.3</td>
<td>0</td>
</tr>
<tr>
<td>Park et al[34], 2016</td>
<td>Korea</td>
<td>10.5</td>
<td>8 (25/75)</td>
<td>10.5</td>
<td>75</td>
<td>12.5</td>
</tr>
<tr>
<td>Muller et al[35], 2012</td>
<td>France</td>
<td>4.2</td>
<td>16 (44/56)</td>
<td>8.9</td>
<td>6.25</td>
<td>0</td>
</tr>
<tr>
<td>Speer et al[36], 2012</td>
<td>United States</td>
<td>1.4</td>
<td>11 (36/64)</td>
<td>14</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Yazbeck et al[37], 2010</td>
<td>Lebanon</td>
<td>-</td>
<td>1 (F)</td>
<td>13</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

1Two patients excluded due to pancreatic trauma.
2Two patients excluded due to congenital pancreatic malformation and calcifying pancreatitis.
F: Female; M: Male.

Table 4 Overall main characteristics of the reviewed studies

<table>
<thead>
<tr>
<th>Onset symptoms (%)</th>
<th>Histology (%)</th>
<th>Type of surgery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain (50)</td>
<td>SPT (64)</td>
<td>PD (61)</td>
</tr>
<tr>
<td>Palpable mass (17)</td>
<td>Pancreatoblastoma (13)</td>
<td>Distal/central pancreatectomy (30)</td>
</tr>
<tr>
<td>Nausea/emesis (16)</td>
<td>Neuroendocrine tumors (7)</td>
<td>Tumor enucleation (9)</td>
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<tr>
<td>Occasional diagnosis (8)</td>
<td>Neuroblastoma (4)</td>
<td></td>
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<tr>
<td>Jaundice (8)</td>
<td>Rhabdomyosarcoma/sarcoma (4)</td>
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</tr>
<tr>
<td>Diarrhea (1)</td>
<td>Acinar cell carcinoma (4)</td>
<td></td>
</tr>
<tr>
<td>Other (3)</td>
<td>Pancreatic islet cells cancer (1)</td>
<td></td>
</tr>
</tbody>
</table>

SPT: Solid pseudopapillary tumor; PD: Pancreatectomy.

adults; interestingly this study included only patients who had undergone PD, as occurred in adults; pylorus-sparing PD can indeed worsen pancreatic function due to insufficient pylorus contraction with consequent stasis within the pancreatic duct and parenchyma destruction[40,41].

Table 5 shows available data in the literature, including data from the present report, to assess associations between exocrine and endocrine insufficiency with tumor site and type of surgery. It can be seen that 93% of all cases of exocrine insufficiency is associated with PD, confirming the results of Lindholm et al[33].
Table 5 Pancreatic function and neoplasm site/surgery

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Head (%)</th>
<th>Body/tail (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exocrine insufficiency</td>
<td>235</td>
<td>149 (63)</td>
<td>106 (37)</td>
</tr>
<tr>
<td>Endocrine insufficiency</td>
<td>5</td>
<td>4 (80)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>PD (%)</th>
<th>Other surgery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exocrine insufficiency</td>
<td>30</td>
<td>28 (93)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Endocrine insufficiency</td>
<td>5</td>
<td>4 (80)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

PD: Pancreaticoduodenectomy.

Surgery did not impact on growth course in our patients according to the finding of a previous study[34]. We can argue that the early identification of pancreatic insufficiency and prompt treatment with enzymes is the main strategy to avoid nutritional deficiency and to ensure adequate growth. Early identification of exocrine insufficiency may also prevent the development of fat-soluble vitamin deficiency. Some patients developed vitamin D insufficiency while vitamin A, E and clotting tests remained in the normal ranges in all patients. It can be argued that the low levels of vitamin D may not be exclusively related to exocrine pancreatic insufficiency, in view of the high prevalence of vitamin D insufficiency in the healthy population[42].

CONCLUSION

In conclusion, despite the important limitation of the retrospective design of this study that could have led to missed data, these findings highlight digestive and nutritional issues in a context in which they are frequently disregarded. Careful and long-term monitoring should follow any pancreatic surgery in children. The loss of exocrine function can occur early but it seems to have no impact on the growth course if it is promptly treated. The impairment of endocrine function is less frequent and may take many years to develop.
ARTICLE HIGHLIGHTS

Research background
Pancreatic neoplasms are very rare in children and available data in this field are limited. Surgery allows the long-term survival of these patients, even if it could lead to complications such as pancreatic insufficiency. Currently there is little evidence on the onset of pancreatic failure and growth trend in children after pancreatic surgery.

Research motivation
We would like to increase knowledge regarding the evolution of pancreatic function after surgical resection in children with pancreatic neoplasms. Currently there is no scheduled follow-up to monitor the long-term complications of pancreatic surgery and in pediatric age it is essential to immediately diagnose the possible onset of pancreatic insufficiency to ensure adequate growth.

Research objectives
The aim of this study was to evaluate the long-term outcome of pancreatic function after pancreatic surgery in children, identify the incidence of endocrine and exocrine pancreatic insufficiency, fat-soluble vitamin deficiency and failure to thrive.

Research methods
We retrospectively analyzed all consecutive pediatric patients diagnosed with pancreatic neoplasms who underwent pancreatic surgery in our institution between January 31, 2002 and the present. Patients were followed by a multidisciplinary team that assessed auxological parameters, clinical symptoms, laboratory and radiological tests at each follow-up visit.

Research results
Sixteen patients (12 girls and 4 boys, mean age 10.7 ± 5.3 years), were included. The most frequent surgery was pancreaticoduodenectomy (50%). Exocrine failure occurred in 4 patients (25%) within 6 mo after surgery, while endocrine failure occurred in 2 patients (12.5%) 8 and 10 years after surgery, respectively. No statistically significant differences were found in BMI z-score at diagnosis and at the last follow-up. Vitamin D was insufficient (< 30 ng/mL) in 8 of the 16 patients while vitamins A, E and clotting test were into the normal ranges in all patients.

Research conclusions
Our study highlights that the development of exocrine and endocrine pancreatic insufficiency after pancreatic surgery is not rare; these potential complications must be adequately identified and treated, as pancreatic enzyme replacement therapy prevents malabsorption and consequent growth failure.

Research perspectives
It is essential to identify and establish a standardized follow-up in pediatric patients, organized by a multidisciplinary team including a surgeon, oncologist, gastroenterologist, endocrinologist, radiologist and dietician.

ACKNOWLEDGEMENTS
We thank Guglielmi L for editing and reviewing the English language and for biostatistical analysis.

REFERENCES


Retrospective Study

Efficacy of arbidol in COVID-19 patients: A retrospective study

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Informed consent statement: The ethics committee waived the requirement for written informed patient consent, because this was a retrospective study based on the assessment of medical records.

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

Data sharing statement: No additional data are available.

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Abstract

BACKGROUND

To date, no treatment has proven to be absolutely effective for coronavirus disease 2019 (COVID-19) patients, and further research is necessary. As a traditional antiviral drug, arbidol was widely used in Wuhan at the beginning of the COVID-19 epidemic and is of increasing interest for treating COVID-19 based on in vitro data suggesting activity against severe acute respiratory syndrome (SARS). Although arbidol has been widely used in China to treat COVID-19 patients, clinical trials to date have not clearly substantiated this approach.

AIM

To evaluate the efficacy of arbidol for COVID-19.

METHODS

A retrospective study was conducted on 132 moderate and severe COVID-19 patients admitted to Jinyintan Hospital and Huoshenshan Hospital (officially designated for COVID-19 treatment) from February to March 2020 in Wuhan, China. This study mainly evaluated the efficacy of arbidol in patients with COVID-19 in the early stage of the SARS coronavirus 2 epidemic. Arbidol was administered at a dose of 200 mg, three times a day, with a 10-d course to adults not receiving any other drugs. Due to the shortage of beds at the time, not every patient could be admitted immediately. We looked for the early stages of the sudden outbreak, places of limited medical resources, limited ward beds, and delayed admission; thus, some patients naturally fit into the control group who did not receive any antiviral drugs. Out of the 132 patients, 72 received arbidol treatment, and 60 did not. We compared the disease course of the two groups and explored the predictors of extended disease duration.
**RESULTS**

Seventy-two patients commenced arbidol, and 60 patients did not receive arbidol treatment. The disease duration in the former group was shorter (23.42 ± 6.92 vs 29.60 ± 6.49, P < 0.001). Multivariate regression analysis showed that the risk of a prolonged course of disease increased by 7.158 times in the non-arbidol treatment group. Ferritin > 483.0 ng/mL and lactate dehydrogenase (LDH) > 237.5 U/L were found to be independent risk factors for protracted cases, with the risk of an extended disease duration increasing to 2.852 times and 5.946 times, respectively.

**CONCLUSION**

The duration course of moderate and severe COVID-19 patients is reduced by 6.183 d when arbidol is administered. Ferritin > 486.5 ng/mL and LDH > 239.5 U/L are independent risk factors for delayed recovery from COVID-19. Early oral administration of arbidol 200 mg t.i.d. with a 10-d course of treatment may be an effective management strategy in COVID-19 patients, particularly those with increased serum ferritin or elevated LDH.

**Key Words:** COVID-19; SARS-CoV-2; Arbidol; Treatment; Antiviral

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**Core Tip:** This study indicated that the duration course of moderate and severe coronavirus disease 2019 (COVID-19) patients is reduced by 6.183 d when arbidol is administered. Ferritin > 486.5 ng/mL and lactate dehydrogenase (LDH) > 239.5 U/L are independent risk factors for delayed recovery from COVID-19. Early oral administration of arbidol 200 mg t.i.d. with a 10-d course of treatment may be an effective management strategy in COVID-19 patients, particularly those with increased serum ferritin or elevated LDH.

**INTRODUCTION**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019 and rapidly spread worldwide. The evidence gathered from the collective battle to prevent and contain the coronavirus disease 2019 (COVID-19) pandemic for more than a year has shown that most COVID-19 infections clinically manifest with headache, loss of sense of smell, nasal congestion, and malaise. Hospitalization is generally not required unless there is fever or abnormal findings on clinical imaging[1,2]. Approximately 1/5 to 1/10 of patients with old age or an underlying condition will require inpatient admission[3,4]. The intensive care unit (ICU) admission rate is 5% to 32%, and the mortality rate is 26%. Independent risk factors for mortality include old age, male sex, chronic comorbidities, and obesity[3,5]. Currently, there is no effective treatment for COVID-19. The commonly used drugs and efficacy of antiviral therapy remain controversial[6]. Arbidol is a promising repurposed antiviral agent, with a unique mechanism of action targeting the S protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope[7]. Arbidol can be easily administered orally at home with few noted side effects and costs only US $50 for 10 d of treatment. The agent is currently approved in Russia and China for the treatment and prophylaxis of influenza and is of increasing interest for treating COVID-19 based on *in vitro* data suggesting activity against SARS[8]. Although arbidol has been widely used in China to treat COVID-19 patients, clinical trials to date have not clearly substantiated this approach[9].

Therefore, this study collected data on the efficacy of arbidol treatment in 132 moderate and severe COVID-19 patients from Jinyintan Hospital and Huoshenshan Hospital in Wuhan, China. As the pandemic in China was brought effectively under
Wei S et al. Efficacy of arbidol in COVID-19 patients

control in April 2020 with a significant decline in new cases, a retrospective study was conducted from February to March 2020 on the treatment of COVID-19 using arbidol.

MATERIALS AND METHODS

Case definition

Diagnostic criteria: Reverse transcriptase-polymerase chain reaction (RT-PCR) was used for testing SARS-CoV-2 positivity. Clinical classifications were as follows: Mild clinical forms had no evidence of pneumonia on computed tomography (CT) imaging; moderate clinical forms, including fever, respiratory symptoms, and pneumonia lesions, could be found on radiology imaging. The inclusion criteria for severe adult patients were: (1) Shortness of breath and respiration rate ≥ 30 times/min; (2) oxygen saturation (SPO$_2$) ≤ 93% at rest; and (3) arterial blood oxygen partial pressure (PaO$_2$)/oxygen concentration (FiO$_2$) ≤ 300 mmHg (1 mmHg = 0.133 kPa), and pulmonary imaging showed marked lesion progression > 50% within 24-48 h. Critically ill patients must meet one of the following conditions: (1) Onset of respiratory failure and requiring mechanical ventilation; (2) shock symptoms; and (3) multiple organ failure requiring ICU monitoring and management.

Participants

Patients from Jinyintan Hospital and Huoshenshan Hospital, two infectious disease hospitals in Wuhan, China, were recruited for the study. Overall, 132 patients above 18 years old who met the diagnostic criteria for moderate to severe presentation of COVID-19 and the arbidol treatment program were included[9]. Mild clinical forms and critically ill patients were excluded.

Data collection

The study included demographics, chest CT, blood test results, time to commence arbidol treatment during the disease, and duration of the disease. All patients received treatment in isolation wards. Vital signs, oxygen saturation, biochemistry, full blood count, C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), ferritin, serum amyloid A, and other blood tests and chest imaging were closely monitored. The course of the disease was defined as the number of days since the onset of illness as per the patient’s chief complaint plus the number of days for admission.

RT-PCR assay

RT-PCR was used for virus detection from nasopharyngeal swabs, sputum or other lower respiratory tract secretions, blood, and feces.

Ethics statement

The institutional ethics board of Jinyintan Hospital approved this study. Due to the nature of retrospective chart review, the need for informed consent from individual patients was waived (No. KY-2020-71.01).

Treatment plan

The treatment plan was determined by the doctor on duty, and the directions for arbidol use were 200 mg for adults, three times a day, with a 10-d course of treatment and not receiving any other antiviral drugs. We compared the disease course of the two groups and explored the predictors of long disease duration.

Discharge criteria

Patients who met the following conditions were discharged: (1) Body temperature returned to normal for more than 3 d; (2) significant reduction of respiratory symptoms; and (3) pulmonary imaging showed significant improvement in acute exudative lesions and two consecutive sputum and NP swabs and other respiratory specimens tested negative for nucleic acid (with an interval of 24 h+).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (version 23.0) to compare the baseline data of the two groups and the disease course. Various factors of long and short disease duration were compared. An independent sample $t$ test was used to compare the normally distributed continuous variables (mean ± SD), and
continuous variables not fully conforming to a normal distribution (median, IQR) were compared using the Mann-Whitney U test. Categorical variables are expressed as numbers (%) and were compared by χ² test or Fisher’s exact test.

The receiver operating characteristic (ROC) curve was used to calculate the cutoff points of various chance factors in long disease duration cases. We used single and multifactor analyses to study the independent risk factors that affect the course and duration of disease. A two-tailed α of less than 0.05 was considered statistically significant.

RESULTS

Effects of using arbidol

To analyze the effects of arbidol, we formed two study groups: An intervention group (72 patients who used arbidol) and a control group (60 patients who did not receive any antiviral drugs). The mean duration of the disease course was 25.73 ± 7.45 d. The patients in the arbidol group had a shorter course of disease than the patients in the non-antiviral treatment group (23.42 ± 6.92 vs 29.60 ± 6.49, P < 0.001). It took less time for two nucleic acid testing results to turn negative (21.61 ± 6.95 vs 27.59 ± 6.39, P < 0.001) and for chest CT improvement in the intervention group (18.33 ± 5.94 vs 24.28 ± 5.35, P < 0.001) (Table 1).

Demographic characteristics

The baseline characteristics of patients in the intervention group and the non-antiviral treatment group were similar. No significant differences were found in the moderate/severe ratio, age, sex, underlying disease, comorbidities (abnormal heart and liver function, abnormal creatinine), LDH, white blood cell count, lymphocyte count, CRP, ESR, ferritin, IL-6, PCT, or serum amyloid A (P > 0.05) (Table 2).

Independent risk factors for long course of disease

The mean duration of the disease course was 25.73 ± 7.45 d, and using this value as the cutoff, the groups were further divided into a short disease duration group [74 (56.1%) patients with disease duration < 25.7 d] and a long disease duration group [58 (43.9%) patients with disease duration > 25.7 d].

Taking into consideration the characteristics of various factors shown in the long disease duration ROC curve, we found that the LDH cutoff value of the long duration group was 239.5 U/L, the area under the ROC curve was 0.707, (0.595-0.820, P = 0.001), the sensitivity was 75%, and the specificity was 67.4%; the corresponding values of ferritin were 486.5 ng/mL, 0.708 (0.599-0.816, P = 0.001), 80%, and 56.5%. P-values of several other factors were greater than 0.05, offering little value in ascertaining the duration of the disease (Figure 1, Table 3).

After evaluating variables by single-factor analysis of variance, we found that high LDH, high ferritin, and no arbidol treatment were risk factors for a long course of disease. Further multifactor analysis of variance confirmed that intervention, ferritin > 486.5 ng/mL, and LDH > 239.5 U/L were independent risk factors for a long course of disease (Table 4).

DISCUSSION

All positive-strand RNA viruses of eukaryotes recombine the inner cell membrane to produce specific viral replication organelles. The broad-spectrum antiviral activity of arbidol indicates that it weakens the viral replication binding protein in the inner cell membrane[10]. In addition, a study indicated that SARS-CoV-2 executes the fusion of ACE2 on the surface of the cell membrane through the envelope spike protein. Molecular dynamics and structural studies have confirmed that the spike glycoprotein of SARS-CoV-2 is the drug target of arbidol. This shows that arbidol prevents the trimerization of the spike protein and inhibits host cell adhesion, making arbidol a potential repurposed drug[11].

Therefore, arbidol was widely used as an antiviral agent in the treatment of COVID-19 patients during the early epidemic in China[12]. However, there is no evidence that arbidol treatment is associated with improved outcomes, but some studies suggest that it tends to shorten the duration of positive RNA tests and increase the negative conversion rate[13]. Therefore, the role of arbidol in the treatment of COVID-19 is
### Table 1 Comparison of recovery time of various indicators between arbidol therapy group and non–antiviral treatment control group

<table>
<thead>
<tr>
<th></th>
<th>Arbidol treatment (n = 72)</th>
<th>None-antiviral treatment (n = 60)</th>
<th>P value</th>
<th>Difference (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (d)(^1)</td>
<td>23.42 ± 6.92</td>
<td>29.60 ± 6.49</td>
<td>&lt; 0.001</td>
<td>6.183</td>
</tr>
<tr>
<td>Days before 2 NAT negative results(^1)</td>
<td>21.61 ± 6.95</td>
<td>27.59 ± 6.39</td>
<td>&lt; 0.001</td>
<td>5.983</td>
</tr>
<tr>
<td>Days before significantly improved chest CT outcome(^1)</td>
<td>18.33 ± 5.94</td>
<td>24.28 ± 5.35</td>
<td>&lt; 0.001</td>
<td>5.949</td>
</tr>
</tbody>
</table>

\(^1\) t test. NAT: Nucleic acid testing; CT: Computed tomography.

### Table 2 Baseline data of patients, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Arbidol treatment (n = 72)</th>
<th>No antiviral treatment (n = 60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58.5 (45-65.8)</td>
<td>58.5 (52-66)</td>
<td>0.459</td>
</tr>
<tr>
<td>Male gender(^2)</td>
<td>46 (63.9)</td>
<td>35 (58.3)</td>
<td>0.514</td>
</tr>
<tr>
<td>Underlying illnesses(^2)</td>
<td>23 (31.9)</td>
<td>17 (28.3)</td>
<td>0.653</td>
</tr>
<tr>
<td>Abnormal liver function(^2)</td>
<td>29 (40.3)</td>
<td>22 (33.7)</td>
<td>0.671</td>
</tr>
<tr>
<td>Abnormal heart function(^1)</td>
<td>3 (4.2)</td>
<td>3 (5)</td>
<td>0.819</td>
</tr>
<tr>
<td>Abnormal creatinine(^1)</td>
<td>1 (1.4)</td>
<td>1 (1.7)</td>
<td>0.896</td>
</tr>
<tr>
<td>Lactate dehydrogenase(^1)</td>
<td>202.5 (159-263)</td>
<td>255 (191-265)</td>
<td>0.054</td>
</tr>
<tr>
<td>Leukocyte count(^1)</td>
<td>4.90 (4.36-6.13)</td>
<td>5.16 (4.10-6.88)</td>
<td>0.654</td>
</tr>
<tr>
<td>Lymphocyte count(^1)</td>
<td>1.24 (1.14-1.33)</td>
<td>1.135 (0.86-1.55)</td>
<td>0.076</td>
</tr>
<tr>
<td>C-reactive protein(^1)</td>
<td>8.65 (3.175-63.3)</td>
<td>14.4 (3-67.7)</td>
<td>0.805</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate(^1)</td>
<td>35 (8-57)</td>
<td>32 (6-58)</td>
<td>0.076</td>
</tr>
<tr>
<td>Ferritin(^1)</td>
<td>508 (320-672)</td>
<td>605.5 (380-935.5)</td>
<td>0.092</td>
</tr>
<tr>
<td>Interleukin-6(^1)</td>
<td>8 (5.71-12)</td>
<td>7.18 (6-8.62)</td>
<td>0.337</td>
</tr>
<tr>
<td>Procalcitonin (abnormal/normal)(^3)</td>
<td>1 (2.7)</td>
<td>0 (0)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Serum amyloid A(^3)</td>
<td>51.81 (18.33-218)</td>
<td>65 (7.75-169.13)</td>
<td>0.443</td>
</tr>
<tr>
<td>Moderate cases(^2)</td>
<td>51 (70.8)</td>
<td>42 (70.0)</td>
<td>0.917</td>
</tr>
<tr>
<td>Severe cases(^2)</td>
<td>21 (29.2)</td>
<td>18 (30.0)</td>
<td>0.917</td>
</tr>
</tbody>
</table>

\(^1\) Mann–Whitney U test.
\(^2\) Chi-square test.
\(^3\) Fisher’s exact test. Normal range of indicators: Lactate dehydrogenase 120-250 U/L, Leukocyte count 3.5-9.5 × 10^9/L, Lymphocyte count 1.1-3.2 × 10^9/L, procalcitonin < 0.5 ng/mL, serum amyloid A 0-10 mg/L, erythrocyte sedimentation rate 0-20 mm/h, C-reactive protein 0-5 mg/L, ferritin 4.63-204 ng/mL, and interleukin-6 0-7 pg/mL. Abnormal liver function: Alanine amiotransferase or aspartate aminotransferase is higher than the normal range. Abnormal cardiac function: Creatine kinase-MB, troponin I, or brain natriuretic peptide is above the normal range or combined with shortness of breath, oliguria, and edema. Abnormal renal function: Creatinine is higher than normal.

This was a retrospective study of clinical data gathered from 132 patients diagnosed with COVID-19, including moderate to severe cases. The research data were collected by doctors on aid missions to Hubei province during the Wuhan lockdown. This data analysis represents the first batch of COVID-19 patients amidst the later global outbreak, as doctors from all over the country were called upon to leave Wuhan for their own provinces in order to achieve effective control; thus, only 2 to 3 mo of data were collected. Although the sample size of this study was relatively small, it contains real data on the actual effect of the use of arbidol against COVID-19 worldwide. Due to the shortage of beds at the time, not every patient could be admitted immediately. Of the 132 patients, 72 received arbidol treatment, and 60 did not. The results of this study suggest that the duration course of COVID-19 was reduced by 6.183 days when arbidol was administered. This indicates the vital importance of the timing of administration for antiviral therapy. Since China exerted strict control over the pandemic, it was impossible to artificially set a control group for COVID-19.
Table 3 Indicators in receiver operating characteristic curve

<table>
<thead>
<tr>
<th>Test variable</th>
<th>AUC</th>
<th>95% CI</th>
<th>Cut-off</th>
<th>P value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden's index</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC</td>
<td>0.424</td>
<td>0.294</td>
<td>0.555</td>
<td>1.735</td>
<td>0.227</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>0.517</td>
<td>0.384</td>
<td>0.649</td>
<td>66.95</td>
<td>0.792</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>0.416</td>
<td>0.292</td>
<td>0.540</td>
<td>77.65</td>
<td>0.180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>0.708</td>
<td>0.599</td>
<td>0.816</td>
<td>486.5</td>
<td>0.001</td>
<td>80%</td>
<td>56.5%</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.597</td>
<td>0.476</td>
<td>0.718</td>
<td>5.935</td>
<td>0.123</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>0.707</td>
<td>0.595</td>
<td>0.820</td>
<td>239.5</td>
<td>0.001</td>
<td>75%</td>
<td>67.4%</td>
</tr>
<tr>
<td>Serum amyloid A</td>
<td>0.533</td>
<td>0.409</td>
<td>0.658</td>
<td>45.10</td>
<td>0.001</td>
<td>80%</td>
<td>56.5%</td>
</tr>
</tbody>
</table>

AUC: Area under curve; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase.

Table 4 Single and multifactor analyses of variance identify high lactate dehydrogenase, ferritin, and no arbidol treatment as independent risk factors for long disease duration

<table>
<thead>
<tr>
<th></th>
<th>Single factor</th>
<th>Multi factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Nontreatment</td>
<td>8.167 (3.731-17.874)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ferritin (&gt; 486.5 ng/mL)</td>
<td>4.368 (1.895-10.066)</td>
<td>0.001</td>
</tr>
<tr>
<td>LDH (&gt; 239.5 U/L)</td>
<td>8.167 (3.731-17.874)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (&gt; 60 yr)</td>
<td>0.699 (0.334-1.338)</td>
<td>0.255</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.628 (0.310-1.273)</td>
<td>0.197</td>
</tr>
<tr>
<td>Underlying disease (yes vs none)</td>
<td>1.421 (0.674-2.996)</td>
<td>0.356</td>
</tr>
<tr>
<td>Abnormal liver function(^1) (yes vs none)</td>
<td>1.229 (0.607-2.487)</td>
<td>0.567</td>
</tr>
<tr>
<td>Abnormal heart function(^2) (yes vs none)</td>
<td>0.242 (0.027-2.132)</td>
<td>0.201</td>
</tr>
<tr>
<td>Abnormal creatinine(^2) (yes vs none)</td>
<td>1.281 (0.078-20.922)</td>
<td>0.862</td>
</tr>
</tbody>
</table>

\(^1\)Chi-square test.  
\(^2\)Fisher’s exact test.  
LDH: Lactate dehydrogenase; OR: Odds ratio.

Patients who opted not to have any antiviral treatment after they were admitted to the hospital. Therefore, we looked for the early stages of the outbreak of the epidemic, places of limited medical resources, limited ward beds, and delayed admission. As such, we were able to identify some patients who naturally fit into the control group because they did not receive any antiviral drugs. The results of the study show that not using arbidol could increase the risk of prolonging the course of COVID-19 to 7.158 times. This suggests that patients may benefit from treatment with arbidol. None of the 72 patients in this study developed any side effects following arbidol use, suggesting that high drug safety may make arbidol a suitable drug for at home use by patients.

In our study, the mean disease duration of COVID-19 was 25.73 ± 7.45 d. According to the characteristics of long disease duration in the ROC curve, ferritin > 486.5 ng/mL and LDH > 239.5 U/L were independent risk factors for a long course of disease. The risks for long duration increased to 2.582 times and 5.946 times, respectively.

In addition, a randomized controlled study of 100 COVID-19 patients included 50 patients in the hydroxychloroquine followed by KALETRA (lopinavir/ritonavir) group and 50 patients in the hydroxychloroquine followed by arbidol group. The length of hospital stay in the arbidol group was significantly less than that in the KALETRA group (7.2 d vs 9.6 d, \( P = 0.02 \)). The results of the relevant parts of this report are quite similar\(^12\).
CONCLUSION

This study indicates that the duration course of COVID-19 patients with moderate and severe cases is reduced by 6.183 d when arbidol is administered. Ferritin > 486.5 ng/mL and LDH > 239.5 U/L are independent risk factors for a long course of disease. Oral administration of arbidol 200 mg t.i.d. with a 10-d course of treatment is recommended for COVID-19 patients, particularly those with elevated ferritin and LDH. Nevertheless, future randomized controlled trials are desperately needed to confirm these findings and further study the mid- and long-term outcomes after discharge.

ARTICLE HIGHLIGHTS

Research background
To date, no treatment has proven to be effective for coronavirus disease 2019 (COVID-19) patients, and further research is necessary. Although arbidol has been widely used in China to treat COVID-19 patients, clinical trials to date have not clearly substantiated this approach.

Research motivation
This study mainly evaluated the efficacy of arbidol in patients with COVID-19 in the early stage of the severe acute respiratory syndrome coronavirus 2 epidemic.

Research objectives
This study aimed to evaluate the efficacy of arbidol in COVID-19 patients.

Research methods
Out of the 132 patients, 72 received arbidol treatment, and 60 did not. The disease course of the two groups was compared, and the predictors of extended disease duration were identified.

Research results
The disease duration in the arbidol treatment group was shorter. The risk of a prolonged course of disease increased by 7.158 times in the non-arbidol treatment group. Ferritin > 483.0 ng/mL and lactate dehydrogenase (LDH) > 237.5 U/L were found to be independent risk factors for protracted cases, with the risk of an extended disease duration increasing to 2.852 times and 5.946 times, respectively.

Research conclusions
Abidol can shorten the course of COVID-19 in moderate and severe patients. Ferritin > 486.5 ng/mL and LDH > 239.5 U/L are independent risk factors for delayed recovery from COVID-19.
Early administration of arbidol may be an effective management strategy in some COVID-19 patients, particularly those with increased serum ferritin or elevated LDH.

REFERENCES


Retrospective Study

Characteristic analysis of clinical coronary heart disease and coronary artery disease concerning young and middle-aged male patients

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Author contributions: Peng KG designed the experiment; Yu HL drafted the work; Peng KG collected the data; Yu HL analyzed and interpreted data; Peng KG and Yu HL wrote the article.

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Abstract

BACKGROUND
Coronary heart disease (CHD) is a type of coronary atherosclerotic heart disease. In recent years, the incidence of CHD has been increasing annually, with an increasing number of young patients. Severe CHD may cause severe myocardial ischemia or myocardial necrosis, which in turn may cause myocardial infarction and related complications that seriously affect the life and health of the patient.

AIM
To examine the coronary arteries and clinical features of young and middle-aged male patients with CHD.

METHODS
From February 2019 to January 2020, 110 male CHD patients admitted to our hospital were selected as research subjects and were divided into two groups by age: middle-aged group (n = 55) and young group (n = 55). The coronary arteries and clinical features of the patients were compared.

RESULTS
There were no significant differences in dyslipidemia, stroke history, high-density lipoprotein cholesterol, or triacylglycerol (P > 0.05) between the two groups. In the young group, age, diabetes, hypertension, smoking history, body mass index, family history of CHD, drinking history, fibrinogen, low-density lipoprotein cholesterol, total cholesterol, and single-vessel disease were higher than those in the middle-aged group. Correspondingly, serum uric acid, hyperuricemia, myocardial infarction, Gensini score > 50, collateral circulation, multivessel disease, double vessel disease, involvement of the right coronary artery, and involvement of the left main coronary artery were lower in the young group than
in the middle-aged group. The middle-aged group mainly suffered from a high Gensini score, implicating multiple arteries, whereas the young group was mainly affected by single-vessel disease. The between-group difference was significant ($P < 0.05$).

**CONCLUSION**

In CHD attacks, multiple coronary arteries are implicated in middle-aged male patients and single-vessel disease in young male patients.

**Key Words:** Coronary heart disease; Coronary artery disease; Coronary artery features; Myocardial ischemia; Risk factors

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**Core Tip:** Retrospective studies have confirmed the involvement of multiple coronary arteries in the onset of coronary heart disease (CHD) in middle-aged and elderly male patients and in single-vessel disease in young male patients. This study included 110 male CHD patients as research cases to examine the coronary arteries and clinical features of young and middle-aged male CHD patients.

**Citation:** Peng KG, Yu HL. Characteristic analysis of clinical coronary heart disease and coronary artery disease concerning young and middle-aged male patients. *World J Clin Cases* 2021; 9(25): 7358-7364


**DOI:** [https://dx.doi.org/10.12998/wjcc.v9.i25.7358](https://dx.doi.org/10.12998/wjcc.v9.i25.7358)

**INTRODUCTION**

Coronary heart disease (CHD) is a type of coronary atherosclerotic heart disease. Due to pressure exerted at work, irregular daily schedules and diets, accelerated pace of life, and other factors, the incidence of CHD increases annually and is more prevalent in younger people[^1-7]. In more severe cases, coronary artery stenosis or occlusion occurs, and the myocardial blood supply continuously decreases and can even terminate. This can result in severe myocardial ischemia or myocardial necrosis that leads to myocardial infarction and related complications, which have a serious impact on the life and health of patients[^5,9]. As CHD tends to occur in younger people, the after-illness impact on reduced quality of life, labor loss, and prognosis in young patients is far greater than those on middle-aged patients. The clinical features and risk factors of young patients after onset have been characterized[^10].

This study aimed to examine the coronary arteries and clinical features of young and middle-aged male CHD patients.

**MATERIALS AND METHODS**

**Clinical data**

A total of 110 male CHD patients admitted in our hospital from February 2019 to January 2020 were included and then evenly divided into two groups according to age: middle-aged group (55 patients) and young group (55 patients). The inclusion criteria were as follows: CHD patients diagnosed by coronary arteriography (there was more than one coronary artery with > 50% diameter reduction through coronary arteriography, and a clinical diagnosis of myocardial infarction); first-episode patient; patient had complete general data; and the patient understood the whole process of the research and had signed an informed consent form. The exclusion criteria were as follows: patients with malignant tumors or immune system diseases; patients suffering from polyarteritis, CHD, and congenital coronary artery malformation; and patients suffering from aortic dissection, acute pericarditis, cardiomyopathy, myocarditis, and malformed pulmonary embolism. The patients' ages ranged from 33 to 77 (60.63 ±
5.48) years. The research was approved by the Ethics Committee.

**Method**

Applied coronary arteriography was performed on all patients. The patients’ basic clinical data, including past medical history, age, coronary arteriography results, and so forth, was collected.

**Observational index**

A comparative observation of the clinical data, coronary artery lesion features, and related blood lipid index factors was carried out. Clinical data included age, diabetes, hypertension, smoking history, body mass index, family history of CHD, hyperuricemia, dyslipidemia, myocardial infarction, drinking history, and stroke history. The number of vascular involvements included multivessel disease, double vessel disease, and single-vessel disease (SVD), and the site of vascular involvement included the right coronary artery and left main coronary artery, evaluating the stenosis degree of vascular disease by means of the Gensini score system. The AU5800 fully automatic biochemical analyzer was used to detect related blood lipid indices, including serum uric acid, fibrinogen, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triacylglycerol, and total cholesterol.

**Data processing**

The collected survey data were processed and analyzed using SPSS 22.0. The mean ± SD was used to describe blood lipid related index factors in patients, which were analyzed with the Student’s t-test. Basic clinical data were described using number (%) and then analyzed with the χ² test. A P < 0.05 indicated that the research data was significant.

**RESULTS**

**Analysis of the basic clinical data between the patient groups**

The between-group dyslipidemia and stroke history differences were not statistically significant (P > 0.05). In the young group, age, diabetes, hypertension, smoking history, body mass index, family history of CHD, and drinking history were higher than in the middle-aged group. In addition, the incidence of hyperuricemia and myocardial infarction were lower in the young group than in the middle-aged group. The between-group data difference was found to be statistically significant (P < 0.05), as shown in Table 1.

**Analysis of coronary artery lesion characteristics between the patient groups**

When the Gensini score was over 50, the middle-aged group collateral circulation, multivessel disease, double vessel disease, and involvement of the right coronary artery and left main coronary artery were higher than in the young group. In addition, the SVD in the middle-aged group was lower than in the young group. The between-group difference was found to be statistically significant (P < 0.05), as shown in Table 2.

**Factor analysis of blood lipid related index between the patient groups**

The between-group patient high-density lipoprotein cholesterol and triacylglycerol differences were not statistically significant (P > 0.05). The young group fibrinogen, low-density lipoprotein cholesterol, and total cholesterol levels were higher than those of the middle-aged group. Furthermore, the young group serum uric acid level was lower than the middle-aged group. The between-group data difference was statistically significant (P < 0.05), as shown in Table 3.

**DISCUSSION**

CHD is a common disease caused by functional and organic stenosis of the coronary arteries, resulting in decreased oxygenated blood in the heart[11]. CHD occurrence and development are closely related to daily life habits, individual differences in patients, and so on[12-17]. Along with plaque accumulation in the coronary arteries, coronary arteries in CHD patients are narrow, which easily causes angina and other complications. In addition, acute anterior cardiac pain commonly occurs in CHD and
Table 1 Analysis of the basic clinical data in between-group patients, mean ± SD or n (%)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Young group, n = 55</th>
<th>Middle-aged group, n = 55</th>
<th>t/X²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36.12 ± 4.25</td>
<td>71.36 ± 5.43</td>
<td>37.9012</td>
<td>0.0000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (14.54)</td>
<td>35 (63.63)</td>
<td>27.8341</td>
<td>0.0000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (16.36)</td>
<td>39 (70.90)</td>
<td>33.2661</td>
<td>0.0000</td>
</tr>
<tr>
<td>Smoking history</td>
<td>20 (36.36)</td>
<td>31 (56.36)</td>
<td>4.4234</td>
<td>0.0354</td>
</tr>
<tr>
<td>BMI in kg/m²²</td>
<td>27.35 ± 3.33</td>
<td>25.08 ± 2.19</td>
<td>4.2238</td>
<td>0.0001</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>4 (7.27)</td>
<td>12 (21.81)</td>
<td>4.6809</td>
<td>0.0305</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>3 (5.45)</td>
<td>23 (4.18)</td>
<td>20.1465</td>
<td>0.0000</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>20 (36.36)</td>
<td>22 (40.00)</td>
<td>0.1541</td>
<td>0.6946</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>17 (30.90)</td>
<td>30 (54.54)</td>
<td>6.2783</td>
<td>0.0122</td>
</tr>
<tr>
<td>Drinking history</td>
<td>19 (34.54)</td>
<td>7 (12.72)</td>
<td>7.2527</td>
<td>0.0070</td>
</tr>
<tr>
<td>Stroke history</td>
<td>2 (3.63)</td>
<td>6 (10.90)</td>
<td>2.1569</td>
<td>0.1419</td>
</tr>
</tbody>
</table>

CHD: Coronary heart disease; BMI: Body mass index.

Table 2 Analysis of coronary artery lesion characteristics in between-group patients, n (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Gensini score &gt; 50</th>
<th>Collateral circulation</th>
<th>MVD</th>
<th>DVD</th>
<th>SVD</th>
<th>Right coronary artery</th>
<th>Left main coronary artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young, n = 55</td>
<td>10 (18.18)</td>
<td>11 (20.00)</td>
<td>6 (10.90)</td>
<td>8 (14.54)</td>
<td>17 (30.90)</td>
<td>10 (18.18)</td>
<td>2 (3.63)</td>
</tr>
<tr>
<td>Middle-aged, n = 55</td>
<td>24 (43.63)</td>
<td>23 (41.81)</td>
<td>19 (34.54)</td>
<td>17 (30.90)</td>
<td>7 (12.72)</td>
<td>22 (40.00)</td>
<td>8 (14.54)</td>
</tr>
<tr>
<td>P value</td>
<td>0.0038</td>
<td>0.0132</td>
<td>0.0030</td>
<td>0.0405</td>
<td>0.0209</td>
<td>0.0117</td>
<td>0.0465</td>
</tr>
</tbody>
</table>

MVD: Multivessel disease; DVD: Double vessel disease; SVD: Single vessel disease.

Table 3 Factor analysis of blood lipid related index in between-group patients (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum uric acid, μmol/L</th>
<th>Fibrinogen, g/L</th>
<th>HDL-C, mmol/L</th>
<th>LDL-C, mmol/L</th>
<th>Triacylglycerol, mmol/L</th>
<th>Total cholesterol, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young, n = 55</td>
<td>285 ± 17</td>
<td>3.22 ± 0.95</td>
<td>1.12 ± 0.36</td>
<td>2.81 ± 0.46</td>
<td>2.13 ± 0.66</td>
<td>4.60 ± 0.57</td>
</tr>
<tr>
<td>Middle-aged, n = 55</td>
<td>386 ± 19</td>
<td>2.75 ± 0.71</td>
<td>1.02 ± 0.35</td>
<td>2.41 ± 0.23</td>
<td>1.97 ± 0.53</td>
<td>4.13 ± 0.41</td>
</tr>
<tr>
<td>X²</td>
<td>29.3796</td>
<td>2.9389</td>
<td>1.4770</td>
<td>5.7680</td>
<td>1.4018</td>
<td>4.9642</td>
</tr>
<tr>
<td>P value</td>
<td>0.0000</td>
<td>0.0040</td>
<td>0.1426</td>
<td>0.0000</td>
<td>0.1638</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.

angina patients, which result in myocardial infarction if not treated in a timely manner, seriously threatening the life and health of the patient. CHD is the most common cardiovascular disease causing disability or death [18-20]. The prevalence of CHD is currently trending toward younger individuals.

Young CHD patients are aged under 44 years and have myocardial damage triggered by the reduced blood supply to the myocardium caused by coronary artery occlusion or stenosis due to various factors. Compared to elderly patients, young patients have a certain degree of variability in their coronary arteries. This research showed that there were no significant differences between the patient groups with
respect to dyslipidemia and stroke history \((P > 0.05)\); in the middle-aged group, age, diabetes, hypertension, smoking history, body mass index, family history of CHD, and drinking history were lower than in the young group. The middle-aged group’s hyperuricemia and myocardial infarction were significantly lower than in the young group, and the between-group data difference was statistically significant \((P < 0.05)\). Moreover, there were no significant differences in the high-density lipoprotein cholesterol and triacylglycerol levels in the young and middle-aged groups \((P > 0.05)\). Fibrinogen, low-density lipoprotein cholesterol, and total cholesterol were higher in the young group than in the middle-aged group, and serum uric acid was lower in the young group than in the middle-aged group. The between-group data difference was statistically significant \((P < 0.05)\).

Moreover, there were no significant differences in the high-density lipoprotein cholesterol and triacylglycerol levels in the young and middle-aged groups \((P > 0.05)\).

Fibrinogen, low-density lipoprotein cholesterol, and total cholesterol were higher in the young group than in the middle-aged group, and serum uric acid was lower in the young group than in the middle-aged group. The between-group data difference was statistically significant \((P < 0.05)\).

When the Gensini score was over 50, the middle-aged group’s collateral circulation, multivessel disease, double vessel disease, and involvement of the right coronary artery and left main coronary artery were higher than in the young group. Furthermore, the middle-aged group’s SVD was lower; the difference between the groups was statistically significant \((P < 0.05)\).

The middle-aged group’s collateral circulation was higher than the young group because of the slower onset in the middle-aged group as well as the longer course of disease. The younger group had a shorter course of disease and a lack of build-up time for collateral circulation. This can be reasonably explained by the fact that middle-aged patients have a greater proportion of angina. However, morbidity of young patients is focused on myocardial infarction.

**CONCLUSION**

In conclusion, the morbidity of middle-aged male CHD patients involves multiple coronary arteries. In addition, young CHD patients are mostly focused on SVD with more risk factors.

**ARTICLE HIGHLIGHTS**

**Research background**

Coronary heart disease (CHD) is a type of coronary atherosclerotic heart disease. In recent years, the incidence of CHD has increased annually, and the age of onset has gradually decreased. Severe CHD may cause severe myocardial ischemia or myocardial necrosis, which in turn may cause myocardial infarction and related complications, with serious consequences.

**Research motivation**

Because CHD occurs in young people, the impact on the quality of life of young patients after the disease, labor loss, and prognosis are much greater than that of middle-aged patients. The clinical features and risk factors of young patients have been characterized, and we hope to explore this.

**Research objectives**

This study aimed to analyze the clinical characteristics of coronary artery disease in young and middle-aged men with CHD.

**Research methods**

A total of 110 male CHD patients were selected as research subjects and then divided into two groups by age: a middle-aged group \((n = 55)\) and a young group \((n = 55)\). The coronary arteries and clinical features of the patients were compared.

**Research results**

In the young group, age, diabetes, hypertension, smoking history, body mass index, family history of CHD, drinking history, fibrinogen, low-density lipoprotein cholesterol, total cholesterol, and single-vessel disease (SVD) were higher in the young group than in the middle-aged group. The middle-aged group mainly suffered from a high Gensini score, implicating multiple arteries, whereas the young group was mainly affected by SVD. The between-group differences were significant.
Research conclusions
In CHD attacks, multiple coronary arteries are implicated in middle-aged male patients, whereas SVD is implicated in young male patients.

Research perspectives
In middle-aged and elderly male patients, multiple coronary arteries are involved in CHD attacks, while in young male patients it is associated with SVD, which has certain hints for subsequent clinical diagnosis and treatment.

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Retrospective Study

Quantitative analysis of early diabetic retinopathy based on optical coherence tomography angiography biological image

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Author contributions: Shi Y and Lin PY design the study; Ruan YM and Lin CF drafted the work and collected the data; Hua SS and Li B analysed and interpreted data and wrote the article.

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

Conflict-of-interest statement: None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

Data sharing statement: No

Abstract

BACKGROUND

With the development of the economy and improvements in living standards, the incidences of diabetes mellitus (DM) and diabetic retinopathy (DR), which is a complication of DM, are on the rise.

AIM

To analyze early DR in patients with macular zone changes in biological images using optical coherence tomography angiography.

METHODS

A prospective case study was performed on 59 participants: 35 healthy eyes (control group), 35 eyes with diabetes but no DR group (no DR group), and 35 eyes with mild DR (NPDR group). All quantitative comparisons of parameters, including the fovea vascularity area, circularity index, and vascular complexity parameters, were performed using a biological image analysis software.

RESULTS

The foveal avascular zone (FAZ) area, FAZ circularity index, number of branches in the area, and the total of the single branches’ length in the area was 0.366 ± 0.031, 0.834 ± 0.037, 3241.8 ± 268.3, and 3.860 × 10\(^7\) ± 0.194 × 10\(^7\), and 0.421 ± 0.030, 0.739 ± 0.023, 2956.6 ± 476.4, and 3.177 × 10\(^7\) ± 0.161 × 10\(^7\) in the no DR group and the NPDR group, respectively, which were significantly different from the corresponding parameters of the control group (\(P < 0.05\)). Moreover, there were significant differences between these two groups (\(P < 0.05\)).

CONCLUSION

This study shows that early microcirculation changes in the macular area of the retina is associated with disease progression. Early changes in DR can be analyzed using optical coherence tomography angiography.
INTRODUCTION

Diabetic retinopathy (DR) occurs in 24.8% to 37.5% of patients with diabetes mellitus (DM) in China according to the latest epidemiological survey data from the International Diabetes Federation. With the development of the economy and improvements in living standards, the incidence of DM and DR, which is a complication of DM, are on the rise[1]. DR is characterized by lesions caused by microvascular retinal damage. Macular ischemia is a significant feature of DR and is thought to be caused by occlusion, loss, or degeneration of the capillary network in the macular area[2,3]. This condition is characterized by a reduction in the capillary network in the fovea. DR is the main cause of blindness in most developing countries[4]. Its early prevention and treatment are challenging and represent urgent public health problems.

Fluorescein angiography is used to visualize the vascular structures in DR for staging purposes. However, this is an invasive technique that only produces images of whole blood vessels and obscures the details of the individual layers of blood vessels. In recent years, noninvasive blood flow imaging technology, known as optical coherence tomography angiography (OCTA), has been developed. It has the advantage of being rapid, noninvasive, high-resolution, repeatable, and consistent. It can also be used as an early fundus screening method for patients with diabetes mellitus.

MATERIALS AND METHODS

Study design and participant selection

This was a prospective case study. There were 59 participants in this study. Thirty-eight patients with DM (70 eyes) underwent fundus fluorescein angiography (FFA) at Ningbo First Hospital from May 2019 to December 2019. The group included 18 male patients (35 eyes) and 20 female patients (35 eyes), aged 38-70 years (mean ± SD: 53.11 ± 6.21 years). There were 35 eyes that had no diabetic retinopathy (no DR) and 35 eyes that had non proliferative diabetic retinopathy (NPDR). Another 21 healthy subjects (35 eyes) with matched age participated as the control group and included 13 males (20 eyes) and 8 females (15 eyes), aged 36-63 years (mean ± SD: 53.11 ± 5.81 years).

Exclusion criteria were as follows: (1) Proliferative diabetic retinopathy observed on fundus examination after pupil dilatation; (2) Failure to cooperate with the required examination; (3) History of glaucoma and uveitis; (4) History of retinal photocoagulation, vitrectomy, and other intraocular surgery in any form; and (5) The refractive media was cloudy. In this study, all participants and their families were informed of the details of the study and signed an informed consent form. This study was approved by the Medical Ethics Committee of Ningbo First Hospital.

Key Words: Optical coherence tomography angiography; Quantitative analysis; Diabetic retinopathy

Citation: Shi Y, Lin PY, Ruan YM, Lin CF, Hua SS, Li B. Quantitative analysis of early diabetic retinopathy based on optical coherence tomography angiography biological image. World J Clin Cases 2021; 9(25): 7365-7371
DOI: https://dx.doi.org/10.12998/wjcc.v9.i25.7365
**Methods**

All selected participants underwent examination for best-corrected visual acuity and intraocular pressure (IOP), optometry, slit lamp examination, fundus examination, FFA, and OCTA (Heidelberg Engineering, Germany). Both FFA and OCTA were performed on the same day by the same ophthalmologist. DR staging was confirmed by FFA and confirmed by another ophthalmologist. Before OCTA, the participants’ pupils were dilated with compound tropicamide eye drops for about 30 min, with the pupils dilated to at least 5 mm. Participants were asked to sit in front of the OCTA instrument, and a series of OCTA images were collected.

**Image analysis and observation**

The software used was ImageJ analysis (version 1.52 p, [http://imagej.nih.gov/ij/](http://imagej.nih.gov/ij/); Provided in the public Domain by the National Institutes of Health, Bethesda, MD, United States)[6]. The superficial plexus (SCP) indexes were used in this study because the foveal avascular zone (FAZ) is more superficial and more abstract. SCP imaging and selection tool were used to draw the outline of the FAZ manually, and the circumference and area of FAZ were calculated automatically by this software. Then the circularity index (CI) of FAZ was measured using the following formula: FAZ CI = (4π x area)/(circumference)². CI is the expression of shape regularity, and the closer its value is to 1, the more similar its shape is[7]. The images were converted to 8-bit, subjected to binarization, and skeletonized for image skeletal analysis, focusing on two parameters: number of branches in the area (NoB) and total of the single branches’ length in the area (tBL)[8].

**Statistical methods**

All data were analyzed using SPSS 25.0, and variable data are presented as mean ± SD. A one-way ANOVA was used for each variable, and a Scheffe test was used for comparison among groups. Statistical significance was set at $P < 0.05$.

**RESULTS**

**General information**

There were no statistically significant differences in age, sex, IOP, or visual acuity between the groups ($P > 0.05$).

**Macular area parameter data**

All parameters of the no DR group and the NPDR group were significantly different from those of the control group ($F = 136.94, 105.41, 74.96, 130.22, P = 0.000, 0.000; P = 0.035, 0.000; P = 0.000, 0.000; P = 0.033, 0.000$), and there were significant differences in parameters between the no DR and NPDR groups ($P = 0.000, 0.000, and 0.002$; Table 1).

The box diagrams in Figures 1-4 indicate that the FAZ area gradually increased with the development of DR, while FAZ CI, NoB, and tBL gradually decreased with the development of DR.

**DISCUSSION**

OCTA is a newly introduced clinical method that can provide a detailed image of the retinal microvascular system by segmenting the retinal vascular layers. It is a non-invasive imaging technique that measures the related and phase characteristics of the signal strength in seconds to generate high-resolution angiographic images of retinal blood flow. Images of the retina and choroid microvasculature can be compared by calculating the position of the retina during repeated scanning movements. OCTA is advantageous for the examination of non-perfused areas in DR microcirculation assessment.

Recently, Gildea[9] published a review of the diagnostic value of OCTA in evaluating multiple microvascular parameters in patients with DM, highlighting the role of OCTA in the identification and location of small aneurysms, preoperative neovascularization and capillary non-perfusion visualization, detection of FAZ amplification, and the reconstruction and quantification of vascular perfusion and branching complexity. Several studies have used OCTA to focus on FAZ measurements as markers of microvascular injury, demonstrating that the FAZ region is larger in patients with DM than in healthy controls[10-14]. The following data are shown in our study of OCTA.
Table 1 Parameters and data of macular area

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group</th>
<th>No DR group</th>
<th>NPDR group</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAZ</td>
<td>0.312 ± 0.019</td>
<td>0.366 ± 0.031&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.421 ± 0.030&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
<tr>
<td>FAZ CI SCP</td>
<td>0.857 ± 0.044</td>
<td>0.834 ± 0.037&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.739 ± 0.022&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
<tr>
<td>NoB SCP</td>
<td>3896.4 ± 162.2</td>
<td>3241.8 ± 268.3&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>2956.6 ± 476.4&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
<tr>
<td>tBL SCP</td>
<td>4.006 × 10&lt;sup&gt;7&lt;/sup&gt; ± 0.307 × 10&lt;sup&gt;7&lt;/sup&gt;</td>
<td>3.860 × 10&lt;sup&gt;7&lt;/sup&gt; ± 0.194 × 10&lt;sup&gt;7&lt;/sup&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.177 × 10&lt;sup&gt;7&lt;/sup&gt; ± 0.161 × 10&lt;sup&gt;7&lt;/sup&gt;&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup><sup>P</sup> < 0.05 (comparison with control group).

<sup>b</sup><sup>P</sup> < 0.01 (comparison with control group).

<sup>c</sup><sup>P</sup> < 0.01 (comparison between the two groups).

FAZ: The foveal avascular zone; CI: Circularity index; SCP: Superficial plexus; NoB: Number of branches in the area; tBL: Total of the single branches’ length in the area.

Figure 1 Foveal avascular zone area changes with diabetic retinopathy progress. FAZ: Foveal avascular zone; DR: Diabetic retinopathy; NPDR: Non proliferative diabetic retinopathy.

Figure 2 Foveal avascular zone circularity index changes with diabetic retinopathy progress. FAZ: Foveal avascular zone; DR: Diabetic retinopathy; NPDR: Non proliferative diabetic retinopathy; CI: Circularity index.

measurement: The FAZ area was significantly larger in the no DR and NPDR groups than in the control group. For patients with no DR, although the fundus examination showed no obvious pathological changes, the FAZ area expansion indicated that macular occlusion and a nonperfusion status had started. Additionally, we found that the FAZ area in the early period of DM was significantly different between patients without DR and patients with NPDR. As retinopathy progressed, the FAZ area increased, suggesting that macular retinal capillary occlusion and nonperfusion increased in severity.
Recently, different quantitative methods for the evaluation of roundness of the FAZ in patients with DM have been proposed\[15,16\]. In this study, CI was an early parameter for FAZ variation in the SCP. From the control group to the no DR and DR groups, there was a significant downward trend in CI, indicating that with the progression of retinal microvascular injury caused by diabetes, the regularity of the FAZ gradually changed significantly in patients with DM compared with that in the control participants.

In this study, we found that compared with the values in the control group, NoB and tBL in the macular area in the NPDR group were significantly decreased. The findings were consistent with the conclusion of Stela V\[17\], where the same method was used to study the area around the optic disc in patients with DM. They found that patients with DM without clinical DR symptoms had a significant reduction in the area around the optic discs compared with that in healthy participants. Therefore, we believe that the decrease in NoB and tBL may be due to the loss of small branch vessels, which leads to a reduction in retinal branch complexity\[18\]. Additionally, these findings support the hypothesis that the complexity of the microvascular network decreases gradually as DR severity increases\[18\].

This study had some limitations. OCTA cannot be applied to all patients with DR, as patients need to have a clear refractive media and good vision. Thus, it is challenging to perform in patients with poor vision, such as those with PDR. A larger sample size is also needed to understand better the exact extent of microvascular damage in the early stages of DR.
CONCLUSION

In summary, this study shows that in patients with DM, fundus lesions with vascular parameters were visible through quantitative OCTA analysis before microcirculation changes in the macular area. OCTA is a new screening tool for patients with DM, and timely monitoring of clinical fundus changes before disease progression might allow for early diagnosis and treatment of DR.

ARTICLE HIGHLIGHTS

Research background
According to the latest epidemiological survey data from the International Diabetes Federation, diabetic retinopathy (DR) occurs in 24.8% to 37.5% of patients with diabetes mellitus (DM) in China.

Research motivation
The early prevention and treatment of DR are challenging and are urgent problems to be solved.

Research objectives
Optical coherence tomography angiography (OCTA) was used to evaluate the macular area and demonstrate that it can be used as an early fundus screening method for patients with DM.

Research methods
All selected participants underwent examination for best-corrected visual acuity and intraocular pressure, optometry, slit lamp examination, fundus examination, fundus fluorescein angiography, and OCTA (Heidelberg Engineering, Germany).

Research results
The values of the foveal avascular zone (FAZ), FAZ circularity index, number of branches in the area, and the total of the single branches’ length in the area of the no DR group and the NPDR groups were statistically different from the control group. The said parameters are also statistically different between the two groups.

Research conclusions
OCTA is a new screening tool for patients with DM, and timely monitoring of clinical fundus changes before disease progression might allow for early diagnosis and treatment of DR.

Research perspectives
A novel approach provides novel insights for the diagnosis and treatment of diseases.

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10.1167/iovs.18-24891

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322-332 [PMID: 26419537]:

30382465 DOI: 10.1093/ophth/2019-445


Retrospective Study

Mucin 1 and interleukin-11 protein expression and inflammatory reactions in the intestinal mucosa of necrotizing enterocolitis children after surgery

Hong-Xia Pan, Chang-Song Zhang, Chia-Hui Lin, Min-Min Chen, Xiao-Zhong Zhang, Nong Yu

Abstract

BACKGROUND

Necrotizing enterocolitis (NEC) of the newborn is a frequently occurring clinical disease in infants. The mortality rate of NEC in premature infants is as high as 50%, and the morbidity rate is on the rise. NEC has already caused serious impacts on newborn survival and poses serious threats to both children and families.

AIM

To investigate the expression and significance of mucin 1 (MUC1) and interleukin-11 (IL-11) in the intestinal mucosa of infants with neonatal NEC after surgery.

METHODS

Forty-eight postoperative intestinal mucosal specimens from children with NEC (NEC group) and twenty-two intestinal mucosal specimens from children with...
congenital intestinal atresia (control group) were collected in our hospital. Immunohistochemical staining and Western blot analysis were used to examine the protein expression of MUC-1 and IL-11 in the two groups. The serum levels of tumor necrosis factor-α (TNF-α) and IL-1β in the two groups were measured by enzyme-linked immunosorbent assay, and the relationship between MUC-1 and IL-11 protein expression and serum TNF-α and IL-1β levels was analyzed by the linear correlation method.

RESULTS
The protein expression of MUC-1 and IL-11 in the NEC group was significantly lower than that in the control group, and the difference was statistically significant (P < 0.05). The levels of serum TNF-α and IL-1β in the NEC group were significantly higher than those in the control group (P < 0.05). The protein expression of MUC-1 and IL-11 in the NEC group negatively correlated with serum TNF-α and IL-1β levels (P < 0.05). There was a significant negative correlation between the protein expression of MUC-1 and IL-11 and the levels of serum TNF-α and IL-1β in the NEC group.

CONCLUSION
The protein expression of MUC1 and IL-11 in the intestinal mucosa of children with NEC is significantly downregulated after surgery. This downregulation may be involved in the pathogenesis of this disease and has a certain correlation with inflammatory response factors in children with NEC.

Key Words: Neonatal necrotizing enterocolitis; Mucin 1; Interleukin-11; Inflammation; Intestinal mucosa; Expression

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Core Tip: This study analyzed the expression changes of mucin 1 and interleukin-11 in intestinal mucosa after necrotizing enterocolitis operation in neonatal necrotizing enterocolitis. It may be related to the pathogenesis of the disease, and providing clinical guidance and basis.

DOI: https://dx.doi.org/10.12998/wjcc.v9.i25.7372

INTRODUCTION
In the clinic, neonatal necrotizing enterocolitis (NEC) is a frequently occurring pediatric intestinal inflammatory disease. The mortality of premature infants with NEC is as high as 50%, and the incidence is increasing, which has serious impacts on the quality of life of these children[1,2].

At present, the etiology and specific pathogenesis of neonatal NEC are not completely known. Thus, it is critical to identify reliable and sensitive molecules or genes to reduce the morbidity and mortality of NEC[3]. At present, intestinal mucus is considered an important component of the intestinal mucosal barrier, and mucin is the main macromolecular substance in intestinal mucus, which is critical in ensuring the stability of bacteria and the intestinal mucosal barrier, but there have been few clinical studies on mucin. Interleukin-11 (IL-11) has good mucosal protective effects against intestinal epithelial cell injury due to several factors. Moreover, IL-11 is involved in signal transduction and mediating inflammatory reactions during the pathogenesis of NEC. This study analyzed changes in the expression of mucin 1 (MUC1) and IL-11 in the intestinal mucosa in infants with neonatal NEC after surgery to provide clinical guidance and a basis for treatment.
MATERIALS AND METHODS

Materials
Intestinal mucosal specimens from 48 children with NEC (NEC group) and 22 patients with congenital intestinal atresia (control group) were collected in our hospital from June 2015 to January 2019. The inclusion criteria were as follows: (1) the NEC diagnosis and grading criteria refer to the indexes in Practical Pediatrics by Zhu Futang; (2) the gestational age of the child was 29-36 wk; (3) the child was delivered in our hospital and was 7-35 days old; and (4) the relevant regulations of the Medical Ethics Committee were followed, and informed consent was obtained from the parents of the children. The exclusion criteria were as follows: (1) the presence of intestinal tumors; (2) chromosomal genetic defects; (3) severe infections (septicemia, meningitis), and (4) major diseases associated with other systems.

The gestational age was 29 to 36 wk in the NEC group, with an average of 32.5 ± 1.8 wk, and the group included 25 males and 23 females; the body mass was 2630.4 ± 225.0 g, and the mean age was 17.9 ± 4.2 d, ranging from 7 to 35 d. The gestational age was 29 to 36 wk in the control group, with an average of 33.0 ± 2.0 wk, and the group included 10 males and 12 females; the body mass was 2604.1 ± 203.9 g, and the age was 735 d, with an average of 19.0 ± 6.2 d. There was no significant difference in gestational age, sex, body mass or age between the two groups (P > 0.05).

Immunohistochemical analysis
The diseased intestinal tissue was embedded in paraffin. Continuous sections (4-μm thick) were obtained, routine hematoxylin and eosin staining was performed, and routine dewaxing and hydration treatment was conducted. In addition, the sections were washed twice with phosphate-buffered saline (PBS) for 5 min each. PBS was used to prepare fresh 3% H$_2$O$_2$, and the sections were sealed at room temperature for 5-10 min. Moreover, we heated the 0.01 mol/L sodium citrate buffer solution in a water bath to approximately 95 °C; the human tissue slices were heated for 10-15 min, cooled to room temperature with tap water, and washed for 5 min with PBS. Then, 5% BSA blocking solution was added and incubated for 15 min, and the primary antibody (1:50 dilution) was added dropwise. After an overnight incubation at 4°C, the sections were washed 3 times at room temperature and incubated for 45 min. The secondary antibody was added and incubated for 1 h and washed with 3 times with PBS at room temperature for 2 min each. When the target signal of the DAB chromogenic kit was dark and the background was light, the reaction was terminated with distilled water. Hematoxylin was added and incubated for 20 s, and the sections were washed twice with distilled water for 2 min, dehydrated, and placed into 100% dimethylbenzene for 10 min to create a transparent seal. MUC1-positive cells were yellow, brown, and yellowish brown and were located in the cell membrane.

According to the immunohistochemistry results, MUC1 and IL-11 proteins were stained yellow, brown and yellowish brown and were located in the cell membrane. (1) According to the degree of staining, the samples were assessed as unstained (0 points), light yellow staining (1 point), brown staining (2 points), and brown and black staining (3 points). And (2) The percentages of stained cells were assessed as follows: ≤ 10%: 1 point; 11%-50%: 2 points; 51%-75%: 3 points; and > 75%: 4 points. The product of the staining degree and positive cell score was calculated, and < 3 points was negative, while ≥ 3 points was positive.

Enzyme-linked immunosorbent assay
Fasting venous blood (3 mL) was extracted and centrifuged at 3000 rpm for 5 min. Forty microliters of sample diluent was added to the sample wells of the enzyme-coated plate, and 10 μL of the sample was added. The plate was gently shaken and mixed, sealed, and incubated with 30× concentrated washing solution at 37°C for 30 min. The solution was diluted 30 times with distilled water, the sealing film was removed, the liquid was discarded, and the sample was shaken dry. Each well was filled with washing solution and rested for 30 s. This process was repeated 5 times, and 50 μL of enzyme-labeled reagent was added. After the sealing plate was incubated at 37°C for 30 min, we removed the sealing film, dried the plate, filled each well with washing solution, rested the plate for 30 s, and repeated the process 5 times. Chromogenic agent A (50 μL) was added, and then chromogenic agent B (50 μL) was added. The plate was gently shaken and mixed in the dark at 37°C for 15 min, after which 50 μL of termination solution was added to stop the reaction, and the absorbance (OD value) of each well was measured at a wavelength of 450 nm. The corresponding concentration was determined from the standard curve and was
multiplied by the dilution factor to determine the actual concentration of the sample according to the OD value.

**Statistical analysis**

SPSS 21.0 software was used for statistical analysis. The measurement indexes of age, body mass, gestational age, MUC-1 protein expression and IL-11 protein expression in the two groups are expressed as mean ± SD. In addition, comparisons between the two groups were performed by t-tests, the sex of the two groups was compared by the χ² test, and correlation analysis was performed by Pearson linear correlation analysis.

**RESULTS**

**Comparison of MUC-1 and IL-11 protein levels between the NEC group and the control group**

The protein expression of MUC-1 and IL-11 in the NEC group was significantly lower than that in the control group, and the difference was statistically significant (P < 0.05) (Table 1, Figure 1).

**Immunohistochemical results**

The positive expression rate of MUC-1 in the NEC group (33.33%) was lower than that in the control group (77.27%), and the difference was statistically significant (P > 0.05). (Table 2, Figure 2).

The positive expression rate of IL-11 in the NEC group (27.08%) was lower than that in the control group (81.82%), and the difference was statistically significant (P > 0.05). (Table 3, Figure 3)

**Comparison of serum TNF-α and IL-1β levels between the NEC group and the control group**

The levels of serum tumor necrosis factor-α (TNF-α) and IL-1β in the NEC group were significantly higher than those in the control group (P < 0.05) (Table 4).

**Correlation between the protein expression of MUC-1 and IL-11 and the serum levels of TNF-α and IL-1β in children with NEC**

There was a significant negative correlation between the protein expression of MUC-1 and IL-11 and the serum levels of TNF-α and IL-1β in the NEC group (P < 0.05) (Table 5).

**DISCUSSION**

In the clinic, neonatal NEC is a common clinical disease. The incidence of NEC is increasing, and this disease has recently had serious impacts on the late development and life expectancy of newborns. Factors such as premature delivery, hypoxia, and immune factors impact the intestinal mucosal blood supply and weaken intestinal peristalsis, resulting in the accumulation of food in the intestinal cavity, which affects intestinal function[4,5]. Studies have shown that preterm delivery is an important factor that leads to the occurrence of NEC due to the immature intestinal epithelium, high permeability, underdeveloped immune mechanisms, susceptibility to bacterial translocation, and activated inflammatory cascade reactions, all of which lead to disease. In addition, the development of the intestinal lumen and gastrointestinal peristalsis in premature infants are not perfect, the digestion and hydrolysis of various pathogens and toxins are inadequate, and intestinal peristalsis is slow, which allows food to accumulate in the intestine. This accumulation can lead to gastrointestinal damage, bacterial overgrowth and intestinal flatulence, resulting in the occurrence of NEC[6,7]. On the other hand, studies have shown that hypoxia-ischemia and reperfusion injury to the intestinal wall are also important factors that lead to the occurrence of NEC. To protect the blood vessels of important organs, such as the heart and brain, the gastrointestinal blood supply decreases sharply, and intestinal wall damage is caused by hypoxia. In addition, hypoxia can also cause free radical release and increase local tissue nitric oxide synthesis, leading to organ damage[8,9]. At present, clinical research on the role of cytokines in the pathogenesis of NEC has mainly focused on proinflammatory factors. However, research on protective factors
Table 1 Comparison of mucin 1 protein and interleukin-11 protein between Necrotizing enterocolitis group and control group (mean ± SD, relative expression intensity)

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>MUC-1 protein</th>
<th>IL-11 protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC group</td>
<td>48</td>
<td>0.461 ± 0.108</td>
<td>0.391 ± 0.085</td>
</tr>
<tr>
<td>Control group</td>
<td>22</td>
<td>0.958 ± 0.177</td>
<td>0.920 ± 0.204</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>-14.494</td>
<td>-15.381</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

NEC: Necrotizing enterocolitis; MUC-1: Mucin 1; IL-11: Interleukin-11.

Table 2 Comparison of positive expression rate of mucin 1 protein, n (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MUC-1 protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>NEC group</td>
<td>48</td>
<td>16 (33.33)</td>
</tr>
<tr>
<td>Control group</td>
<td>22</td>
<td>17 (77.27)</td>
</tr>
<tr>
<td>χ²</td>
<td></td>
<td>11.688</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.001</td>
</tr>
</tbody>
</table>

NEC: Necrotizing enterocolitis; MUC-1: Mucin 1.

Table 3 Comparison of positive expression rate of interleukin-11 protein, n (%)

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>IL-11 protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>NEC group</td>
<td>48</td>
<td>13 (27.08)</td>
</tr>
<tr>
<td>Control group</td>
<td>22</td>
<td>18 (81.82)</td>
</tr>
<tr>
<td>χ²</td>
<td></td>
<td>18.317</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.000</td>
</tr>
</tbody>
</table>

NEC: Necrotizing enterocolitis; IL-11: Interleukin-11.

Table 4 Comparison of serum tumor necrosis factor-α and interleukin-1β levels between necrotizing enterocolitis group and control group (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TNF-α (ng/L)</th>
<th>IL-1β (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC group</td>
<td>48</td>
<td>386.6 ± 76.4</td>
<td>18.63 ± 3.02</td>
</tr>
<tr>
<td>Control group</td>
<td>22</td>
<td>260.7 ± 48.8</td>
<td>14.19 ± 2.50</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>7.080</td>
<td>6.010</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

NEC: Necrotizing enterocolitis; TNF-α: Tumor necrosis factor-α; IL-1β: Interleukin-1β.

has been relatively rare[10]. MUC1 and IL-11 in the intestinal mucosa of infants after NEC surgery were analyzed. IL-11 is a platelet-promoting factor produced by bone marrow-derived cells in primates and can participate in a variety of physiological and pathological processes in the human body[11]. Studies have shown that IL-11 can reduce intestinal injury due to various causes. Exogenous IL-11 can promote crypt cell proliferation, reduce
Table 5 Linear correlation results

<table>
<thead>
<tr>
<th>Index</th>
<th>Correlation</th>
<th>TNF-α</th>
<th>IL-1β</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUC-1 protein</td>
<td>r</td>
<td>-0.619</td>
<td>-0.486</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>IL-11 protein</td>
<td>r</td>
<td>-0.577</td>
<td>-0.528</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

MUC-1: Mucin 1; IL-11: Interleukin-11; TNF-α: Tumor necrosis factor-α; IL-1β: Interleukin-1β.

Figure 1 Western-blot results of mucin 1 protein and interleukin-11 protein in necrotizing enterocolitis group and control group. NEC: Necrotizing enterocolitis; MUC-1: Mucin 1; IL-11: Interleukin-11; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase.

Figure 2 Mucin 1 protein immunohistochemical staining. A: The intestinal mucosal tissue of the control group; B: The necrotizing enterocolitis intestinal mucosal tissue. It can be seen that the coloring is deeper in the control group, and the mucin 1 protein expression intensity is stronger, × 200.

As a highly glycosylated transmembrane mucin with a high molecular weight, the structure of MUC1 is highly complex. MUC1 can be expressed in a variety of tissues and organs under normal physiological conditions. MUC1 has a polar distribution and apoptosis, and protect against intestinal injury[12]. The function of human cytokines is to bind to specific receptors on the target cell membrane and transmit signals to the cell to induce signal transduction. The receptor is an important functional protein that mediates the effects of cytokines. IL-11 receptors can form complexes by homologous dimerization and activate intracellular signaling pathways. IL-11 is expressed on the surface of intestinal epithelial cells. The expression of IL-11 on intestinal epithelial cells protects cells and inhibits apoptosis, and enhanced expression of the IL-11 receptor protects cells and inhibits apoptosis, which can delay disease progression[13]. As a consequence, the expression level of IL-11 in NEC-associated intestinal injury is downregulated. This downregulation is not conducive to ligand engagement, can activate the corresponding signaling pathway and plays a protective role in the intestinal tract[14].

As a highly glycosylated transmembrane mucin with a high molecular weight, the structure of MUC1 is highly complex. MUC1 can be expressed in a variety of tissues and organs under normal physiological conditions. MUC1 has a polar distribution and
is not easily recognized by the immune system. MUC1 plays roles in lubrication, protecting cells, maintaining stickiness, identifying cells and maintaining the functional integrity of epithelial cells. In addition, MUC1 can participate in intercellular signal transduction and immune regulation\cite{15,16}. Studies have shown that damage to and repair of the intestinal mucosa can lead to abnormal glycosylation, weaken intestinal mucosal epithelial barrier function, and lead to the release of large amounts of MUC1\cite{17}. Some scholars have pointed out that the MUC1 protein is an important part of maintaining the stability of the intestinal environment and affects cell proliferation, apoptosis and self-phagocytosis through a variety of signaling pathways. The destruction of MUC1 Leads to the formation of an infectious environment, inflammatory diseases or inflammation-related tumors\cite{18}. In addition, MUC1 can regulate the inflammatory response, membrane-bound mucin can regulate inflammation through MUC1, and its extracellular part can bind with bacteria to release its receptor from the cell membrane and activate the nuclear factor kappa B pathway to regulate the inflammatory response. Membrane-bound mucin plays a very important role in regulating the intestinal mucosal barrier, as the last mucin barrier is distributed on the surface of the cell membrane\cite{19,20}.

The results showed that the protein expression of MUC-1 and IL-11 in the NEC group was significantly lower than that in the control group. This result indicated that there was a decrease in the protein expression of MUC-1 and IL-11 in children with NEC. The levels of serum TNF-α and IL-1β in the NEC group were higher than those in the control group. This result indicated that the levels of TNF-α and IL-1β were significantly increased in children with NEC, and the degree of the inflammatory reaction \textit{in vivo} was exacerbated. There was a significant negative correlation between the protein expression of MUC-1 and IL-11 and the levels of serum TNF-α and IL-1β in the NEC group. This study confirmed that there was abnormal protein expression of MUC-1 and IL-11 in children with NEC and that there was a negative correlation with the degree of inflammation. This study provides a new basis for reasonable clinical prediction of the pathogenesis and disease progression in children with NEC. However, the follow-up time in this study was short, and there were few cases in the group. As a consequence, it is necessary to expand the sample size and perform long-term follow-up for in-depth analysis.

CONCLUSION

Overall, the protein expression of MUC1 and IL-11 in the intestinal mucosa of children with NEC was significantly downregulated after surgery. This downregulation may be involved in the occurrence of the disease and has a certain correlation with inflammatory response factors in children with NEC.
ARTICLE HIGHLIGHTS

Research background
In the clinic, neonatal necrotizing enterocolitis (NEC) is a frequently occurring pediatric intestinal inflammatory disease. The mortality of premature infants with NEC is as high as 50%, and the incidence shows an increasing trend, which has serious impacts on the quality of life of children.

Research motivation
This study provides help for the clinical diagnosis and treatment of neonatal NEC.

Research objectives
This study aimed to investigate the expression and significance of mucin 1 (MUC1) and interleukin-11 (IL-11) in the intestinal mucosa of children with neonatal NEC after surgery.

Research methods
Total 48 postoperative intestinal mucosal specimens from children with NEC (NEC group) and 22 intestinal mucosal specimens from congenital intestinal atresia (control group) were collected in our hospital. Immunohistochemical staining and Western-blot technique were used to detect the expression of MUC-1 protein and IL-11 protein in the two groups. The serum levels of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in the two groups were detected by enzyme-linked immunosorbent assay, and the relationship between MUC-1 protein, IL-11 protein and serum TNF-α and IL-1β was analyzed by linear correlation method.

Research results
The protein expression of MUC-1 and IL-11 in the NEC group was significantly lower than that in the control group, and the difference was statistically significant. The levels of serum TNF-α and IL-1β in the NEC group were significantly higher than those in the control group. The protein expression of MUC-1 and IL-11 in the NEC group negatively correlated with serum TNF-α and IL-1β levels. There was a significant negative correlation between the protein expression of MUC-1 and IL-11 and the levels of serum TNF-α and IL-1β in the NEC group.

Research conclusions
The protein expression of MUC1 and IL-11 in the intestinal mucosa of children with NEC is significantly downregulated after surgery. This down regulation may be involved in the pathogenesis of the disease and has a certain correlation with inflammatory response factors in children with NEC.

Research perspectives
MUC1 and IL-11 proteins may be related to the pathogenesis of the disease and have a certain correlation with inflammatory response factors in children with NEC, which has profound clinical significance.

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Pan HX et al. MUC-1 and IL-11 in the intestinal mucosa


Research on the prognosis of different types of microvessels in bladder transitional cell carcinoma

Hai-Bo Wang, Yi Qin, Jin-Yi Yang

BACKGROUND
At present, there is controversy on the role of microvessel density (MVD) in tumors as a prognostic indicator of bladder transitional cell carcinoma (BTCC). However, the MVD in tumors is simply classified based on the expression of several different vascular markers, which has not been related to analytical research on the prognosis of patients with BTCC.

AIM
To explore the classification of blood vessels in tumors and studied the relationship between MVD and the prognosis of patients with BTCC.

METHODS
The tissue mass was detected by tissue microarray and immunohistochemical analysis with monoclonal antibodies against CD31, CD34, CD105, and vascular smooth muscle actin to investigate the MVD in BTCC. The measurement data are expressed as the mean ± SD. The difference between the groups was analyzed by the t-test, the counting data were analyzed by χ² test. The Kaplan-Meier survival curve was estimated by the product-limit method. The log-rank time-series test was employed to compare the tumor-free survival curves.

RESULTS
The MVD was closely related to the pathological grade, invasive depth, and prognosis of BTCC. Significant differences were found between grade I and grade II, grade II and grade III, superficial and invasive type, and the tumor-free survival group and the recurrence or metastasis group (P < 0.01). Multivariate analysis showed that undifferentiated MVD was an independent prognostic factor for patient survival time. An inverse correlation between undifferentiated tumor
MVD and differentiated tumor MVD in BTCC was also shown.

CONCLUSION
The classification of blood vessels in BTCC could act as an important prognostic indicator and may also be of great significance in the treatment of cancer.

Key Words: Bladder transitional cell carcinoma; Microvessel density; Morphological characteristics; Blood vessels; Prognosis

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Core Tip: At present, there is controversy on the role of microvessel density (MVD) in tumors as a prognostic indicator of bladder transitional cell carcinoma. In our experimental study, we investigated the MVD in bladder transitional cell carcinoma through tissue microarray and immunohistochemical analyses. By observing the morphological characteristics of blood vessels and the expression of specific markers, we explored the classification of blood vessels in tumors and studied the relationship between MVD and the prognosis of patients.

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INTRODUCTION
Deriving new blood vessels from existing microvessels is an essential process for tumor growth and hematogenous metastasis[1]. Under normal circumstances, the growth of blood vessels in the human body is in a balanced state due to strict regulation and control, and only under certain conditions, such as wound healing, will the physiological proliferation of blood vessels occur. However, in the tumor-bearing state, angiogenesis will be out of control, showing uncontrollable growth. Once the new blood vessels grow into the tumor and form tumor microcirculation, the tumor will grow exponentially and rapidly, reaching hundreds or even thousands of times its original volume in a short time. The quantification of tumor microvessels can provide an indicator of vascular activity, and microvessel density (MVD) is a frequently used original volume in a short time. The quantification of tumor microvessels can provide an indicator of vascular activity, and microvessel density (MVD) is a frequently used indicator to quantify changing tumor microvessels. Recent reports indicated that an increase in MVD was associated with the poor prognosis of patients with several malignant tumors, including breast cancer, prostate cancer, lung cancer, and nasopharyngeal carcinoma[2-8]. Bladder transitional cell carcinoma (BTCC) is the most common bladder malignant tumor, accounting for about 90% of bladder cell carcinomas, but the underlying metastasis mechanism of BTCC is still unclear.

At present, the value of MVD in predicting the prognosis of BTCC is controversial. Several reports showed that MVD was positively correlated with longer survival time and better prognosis of patients[9-13]. However, at the same time, some researchers reported that MVD was inversely related to the survival rate and prognosis of patients [14-16], whereas others did not find a significant correlation between MVD and the survival rate of patients[17,18]. In the past, vascular markers were generally applied to identify the heterogeneity of blood vessels and reveal different aspects and characteristics of tumor vessels. For example, CD34 is expressed in differentiated endothelial cells, whereas CD31 is expressed in both differentiated and undifferentiated endothelial cells[19]. Recently, it was reported that CD105 was superior to CD34 and CD31 in evaluating tumor angiogenesis since it had a greater affinity for activated endothelial cells[6,20]. In addition, in terms of breast cancer and colorectal cancer showing a lower survival rate of patients, some immunological studies have shown that an increase in MVD determined by CD105 staining was an independent prognostic indicator[21-24].

To date, no studies on vascular differentiation related to the prognosis of cancer, especially the prognosis of BTCC, have been conducted. In this experimental study, we investigated the MVD in BTCC through tissue microarray and immunohistochemical
analyses. By observing the morphological characteristics of blood vessels and the expression of specific markers, we explored the classification of blood vessels in tumors and studied the relationship between MVD and the prognosis of patients.

MATERIALS AND METHODS

Grouping
Sixty-two patients who underwent bladder cancer surgery (no history of chemotherapy, radiotherapy, or immunotherapy before surgery) and were diagnosed with BTCC by pathology, were assigned to the experimental group, including 47 males and 15 females. The age of the patients ranged from 63.2-86.8 years, with an average of 72.5 years. Eighteen patients without bladder disease were assigned to the control group, including 16 cases with benign prostatic hyperplasia and 2 cases with urethral cysts, aged 56.8-78.9 years, with an average age of 71.3 years. Patients with other related diseases were excluded. According to the World Health Organization classification criteria, the experimental group was classified based on tumor pathology. Thirteen cases were classified as highly differentiated (Grade I), 16 cases as moderately differentiated (Grade II), and 33 cases as poorly differentiated (Grade III). In terms of clinical stages, based on the UICC-TNM standard, 26 cases were classified as superficial tumors (Tis-T1) and 36 cases as invasive tumors (T2-T4). During the postoperative follow-up period of 14-38 mo, with an average period of 26.5 mo, 38 cases presented with no tumor recurrence or metastasis (tumor-free survival), while 24 cases showed tumor recurrence and five cases showed tumor metastasis (including two deaths).

Material collection
Three 1-mm tissue blocks were taken from each of the 62 specimens of BTCC and placed into three tissue microarray blocks after combining. The three location blocks of each donor block were randomly sampled from three different parts of the tumor tissue, which avoided necrotic tissue and ensured that they were all tumor cells. The 62 BTCC tissues and the 18 normal bladder tissues without malignant lesions of cases were classified into tissue microarray blocks and routinely sectioned after the tissue microarray blocks were extracted. The specimens in each tissue microarray block were continuously sectioned at a thickness of 4 µm. The remaining BTCC tissue blocks of the 62 cases and the 18 cases of normal bladder tissue without malignant lesions were evaluated by hematoxylin and eosin staining and immunohistochemical analysis.

Immunohistochemical detection
After the specimen was fixed, and the tissue block was cut vertically and transversely, the bladder tumor tissue was fixed externally, embedded in paraffin, and cut into 4 µm- thick slices. The slice was attached to a glass slide treated with APES. The slice was dewaxed with xylene and dehydrated in a graded series of alcohol (from high concentration to low concentration), washed with running water for 10 min, washed with 0.01 mol/L phosphate buffered saline (PBS) for 5 min, and repaired with antigen in microwave oven for 25 min. After natural cooling, it was washed with PBS for 2 × 3 min. H_{2}O_{2} was added to incubate for 10 min at room temperature, followed by washing with PBS for 3 × 3 min. Animal serum sealer was added at room temperature for 20 minutes. Then, the sealer was poured out, and the first antibody working solution prepared in diluent was added and incubated overnight (over 18 h) at 4 °C, followed by washing with PBS for 3 × 3 min. Biotinylated secondary antibody working solution was added and incubated in a wet box at 37 °C for 15 min and then washed with PBS for 3 × 3 min. A streptavidin enzyme label was added and incubated in a wet box at 37 °C for 15 min, followed by washing with PBS for 3 × 3 min, and developed with DAB. The DAB development was controlled under a microscope, and was stopped with water based on deposition levels before being washed with running water for 10 min. The slide was re-dyed with hematoxylin, turned blue with running water, dehydrated to transparency with a series of alcohol concentrations followed by xylene, and sealed with neutral gum. Positive reactions were observed and counted under a microscope. Cells with brownish-yellow granules in the membrane or cytoplasm were considered positive, while those with no brownish yellow granules were considered negative. MVD was counted under × 200 magnification. All brown-stained cells or cell clusters were counted as one MVD value, and the MVD values in five visual fields were recorded. The multi-visual field averaging method was used to repeatedly count multiple points with a computer pathological graphic analyzer, and
the average value was used as the MVD value. The mean value was calculated as the MVD value of one case.

Positive controls were established for each batch of staining (CD31 and CD34 sections of known transitional cell carcinoma of bladder were used as positive controls). MVD counting: MVD was counted under ×200 magnification, and every brown-stained cell or cell cluster was counted as one MVD value. The MVD values in five visual fields were recorded, and the mean value was used as the MVD value of this case.

According to the coloring degree of each high-power visual field and the number of microvessels in the visual field under the optical microscope, the results were judged as follows: When the whole slice was not colored or was pale yellow, it was considered negative, while positive cells were represented by yellow, brown, or tan color. The expression of microvessel number in tumor was detected by the Leica Qwin multimedia pathological image analysis system produced by Leica Company in Germany, and the microvessel value in each visual field was recorded for data analysis.

**Statistical analysis**
The experimental results were analyzed by SPSS 13.0 software, and the Kaplan-Meier survival curve was estimated by the product-limit method. The log-rank time-series test was employed to compare the tumor-free survival curves. The Cox proportional hazards model was used to screen the independent prognostic factors. The measurement data are expressed as the mean ± SD. The difference between the groups was analyzed by the t-test, the counting data were analyzed by χ² test, and P < 0.05 suggested a significant difference.

**RESULTS**

**Two different types of microvessels were observed in BTCC**
In BTCC, most of the blood vessels stained with the CD31 antibody also stained with the CD34 antibody (Figure 1A and B). However, some blood vessels were only stained with the CD31 antibody and not the CD34 antibody (Figure 1B). Peripheral cell coverage of the blood vessel was determined by staining with the smooth muscle actin (SMA) marker of peripheral cells. The results showed that there were peripheral cells around the blood vessels stained by CD34, while no peripheral cells were observed around the CD31+/CD34- microvessels (Figure 1C).

**Comparison between CD31-MVD, CD34-MVD, and CD105-MVD**
In tumor vessels, CD105 was only expressed in CD34-positive vessels. CD34 and CD105 are almost the same markers for tumor microvessels (Figure 2). The mean values of CD34-MVD and CD105-MVD in the 62 cases of BTCC were 139.7 ± 41.8 and 134.9 ± 36.2, respectively, and there was no difference between CD34-MVD and CD105-MVD (P > 0.05).

**The relationship between MVD and clinical indicators**
The MVD value expressed by the microvessel count is shown in the Table 1. MVD was closely related to the pathological grade, invasive depth, and prognosis of BTCC. Significant differences were found between grade I and grade II, grade II and grade III, superficial and invasive type, and the tumor-free survival group and the recurrence or metastasis group (P < 0.01). CD31 and CD34 were weakly expressed in normal bladder tissue. Undifferentiated vessel density was positively correlated with tumor grade and stage.

**Relationship between disease-free survival rate and MVD**
To clearly compare the prognosis of bladder cancer patients with different undifferentiated vessels, we divided all 62 patients into two groups according to the MVD of the undifferentiated vessels in their primary bladder transitional cell tumor tissues. Group A had MVD values lower than the median value and group B had MVD values higher than the median value. The recurrence of the bladder tumor was regarded as the end event, and the Kaplan-Meier tumor-free survival curve of each group was obtained, as shown in Figure 3. After the log-rank time-series test, the difference between the two groups was extremely significant (P = 0.007). The prognosis of the patients with undifferentiated vessels at low MVD values was significantly better than that of the
Table 1 Relationship between microvessel density and the clinicopathological features of bladder transitional cell carcinoma patients

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Case number</th>
<th>MVD-CD31</th>
<th>MVD-CD34</th>
<th>Undifferentiated blood vessel MVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Control group</td>
<td>18</td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Pathological grading</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>13</td>
<td>117 ± 29.3</td>
<td>90 ± 27.5</td>
<td>8</td>
</tr>
<tr>
<td>Grade II</td>
<td>16</td>
<td>150 ± 39.8</td>
<td>120 ± 28.7</td>
<td>6</td>
</tr>
<tr>
<td>Grade III</td>
<td>33</td>
<td>200 ± 43.5</td>
<td>160 ± 29.8</td>
<td>7</td>
</tr>
<tr>
<td>Clinical stages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial type (TIS-T1)</td>
<td>26</td>
<td>120 ± 30.4</td>
<td>100 ± 25.5</td>
<td>20</td>
</tr>
<tr>
<td>Infiltration type (T2-T4)</td>
<td>36</td>
<td>190 ± 37.7</td>
<td>160 ± 32.1</td>
<td>13</td>
</tr>
<tr>
<td>Prognosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No recurrence or metastasis</td>
<td>38</td>
<td>130 ±35.6</td>
<td>110 ± 34.4</td>
<td>26</td>
</tr>
<tr>
<td>Recurrence or metastasis</td>
<td>24</td>
<td>190 ± 45.7</td>
<td>160 ± 41.1</td>
<td>5</td>
</tr>
</tbody>
</table>

MVD: Microvessel density.

patients with undifferentiated vessels at high MVD values.

**DISCUSSION**

Over 90% of malignant urinary tumors are BTCC, which has the biological characteristics of easy invasion and metastasis as well as easy recurrence after surgery\(^3\), and both invasion and metastasis depend upon tumor angiogenesis\(^4\). This was the first report on the correlation between different types of blood vessels in BTCC and prognosis. The determination of MVD involves counting the microvessels in the part of the tumor with the highest density of tumor blood vessels, which helps to understand the degree of active tumor angiogenesis and the relationship between tumor grading and staging. The MVD value is related to the size of the tumor. The MVD in the experimental group was higher than that in the control group, and there was a significant difference between the two groups. At present, the reagents used to identify the microvessels of tumor tissues are mainly markers of vascular endothelial cells, such as the CD31 antibody, CD34 antibody, and VIII factor-related antibodies, or Von Willebrand factors, which are expressed on most endothelial cells and called markers of returning endothelial cells.

The development of solid tumors goes through the stages of pre-angiogenesis and angiogenesis. In the early stage of angiogenesis, the tumor does not secrete or rarely secretes vascular growth factor, and therefore, the tumor does not induce angiogenesis. As a result, the tumor is maintained at a limited volume and metastasis hardly occurs. When the tumor induces host microvascular proliferation, it enters the angiogenic stage, and the tumor cell population increases rapidly with increased tumor volume, showing potential metastasis tendency.

Two different types of microvessels were observed in BTCC. In BTCC, most of the blood vessels stained with the CD31 antibody were also stained with the CD34 antibody, but some blood vessels were stained with the CD31 antibody and not the CD34 antibody. It has been reported that CD34 was only expressed in differentiated endothelial cells, whereas CD31 was expressed in both differentiated and undifferentiated endothelial cells. We also determined the peripheral vascular cell coverage by staining with the SMA marker of peripheral cells. The results showed that there were peripheral cells around the blood vessels stained with anti-CD34, but there were no peripheral cells around the CD31+/CD34- microvessels (Figure 1C). Therefore, there are two types of microvessels in BTCC, CD34+ microvessels and CD31+/CD34- microvessels. Compared to CD34+, CD31+/CD34- blood vessels displayed some morphological characteristics under light microscopy. They showed no lumens or had
Figure 1 Two different types of microvessels were observed in bladder transitional cell carcinoma. A: CD34-stained pictures clearly reveal differentiated blood vessels in bladder transitional cell carcinoma (× 400); B: Other blood vessels are stained with CD31 in the same position. As shown by the arrow position, undifferentiated blood vessels are not stained by the CD34 monoclonal antibody (× 400); C: Smooth muscle actin staining confirms that peripheral cells cover the blood vessels stained by CD34, but no peripheral cells cover the undifferentiated blood vessels in Figure 1B (× 400).

Figure 2 CD34 and CD105 stained pictures. A: CD34 staining clearly revealed differentiated blood vessels in bladder transitional cell carcinoma (× 400); B: CD105 staining in the same position (× 400).

small lumens, with thick walls and small shapes. Based on these observations, we confirmed that the CD34-positive vessels were differentiated vessels, whereas the CD31+/CD34- positive vessels were undifferentiated vessels.

Peripheral cells present with different connections to endothelial cells in human BTCC. In the undifferentiated blood vessels, we did not find peripheral cell coverage, whereas in the differentiated blood vessels, we carefully observed that peripheral cells and CD34+ endothelial cells usually appeared in the peripheral parts of the tumors. Thus, when we used peripheral blood vessel coverage to assess the maturity of the blood vessels, undifferentiated blood vessels were noticeably more immature than the differentiated blood vessels. Although it has been reported that SMA and desmin were
effective markers of tumor peripheral cells in animal models, we found that desmin was not expressed around the tumor in human BTCC.

Stability and repeatability are very important for determining microvessels with different antibodies by immunohistochemistry. For example, the affinity of most CD31 monoclonal antibodies is lower than that of CD34 monoclonal antibodies, which leads to the smaller number of tumor vessels tested[23-25]. Hence, staining with CD31, in this case, will underestimate the MVD[2]. In our study, the quality of the immunohistochemical staining was highly controlled, so a key difference between CD31 and CD34 staining was found in BTCC. We found two different types of blood vessels by directly staining the blood vessels, namely the undifferentiated blood vessels (CD31+/CD34−) and the differentiated blood vessels (CD34+).

Although we assumed that no blood vessels were stained with CD31-CD34+, eight blood vessels whose MVD was slightly higher than that of CD31+ also stained as CD34+. This may be an error in blood vessel staining caused by serial sections. For example, sometimes a single blood vessel may be missed in one section, but it appears as two independent blood vessels in another section.

It was reported that peripheral cell coverage could more accurately reflect whether or not microvessels are mature, although it is not the only index[24]. There are also some other molecular markers, such as SMA, desmin, platelet-derived growth factor receptor-H, and NG2, which can all be used to identify peripheral cells. We compared the expression of immune NG2, desmin, and SMA in peripheral cells of BTCC. Many more peripheral cells were labeled as SMA-positive than peripheral cells labeled desmin-positive or NG2-positive, so desmin and NG2 were not effective markers of peripheral cells. It was observed that in the CD34+ blood vessels, the peripheral cell coverage was also different, which was our conclusion when comparing tumor peripheral cells in animal models[25]. However, the relationship between peripheral cells and vascular endothelial cells remains unclear in the prognosis of patients.

In this study, the MVD of undifferentiated vessels in BTCC was quantified for the first time. The MVD of the undifferentiated vessels was positively correlated with the pathological grade of the patients, and the prognosis of the patients was worse. In addition, it was an independent prognostic factor in multivariate analysis. In contrast, the MVD of the differentiated vessels was negatively correlated with the pathological grade of the patients, and the survival rate of the patients was also longer. In each section, the MVD of the undifferentiated vessels was negatively correlated with that of the differentiated vessels.

When the MVD of the undifferentiated vessels was compared with that of the differentiated vessels, it was found that the prognosis of the patients with fewer undifferentiated vessels, but more differentiated vessels, was better than those with more undifferentiated vessels but fewer differentiated vessels.

Interestingly, when CD31 is considered a broad-spectrum vascular marker for staining all blood vessels, higher MVD indicates lower pathological grade and longer survival of patients. Our results also support that the MVD of the differentiated
vessels was an important factor affecting prognosis in BTCC. The importance of undifferentiated blood vessels is generally ignored in analyzing BTCC. It was reported that the rapid growth of the tumor did not suggest high vascular density and that the MVD of the tumor may not be high. However, sometimes it was lower than that of normal tissues.

Since Kononen and colleague made the first tissue microarray in 1998 [26], tissue microarray has been rapidly popularized worldwide due to its high throughput (large sample capacity), parallel research (uniform test conditions), and high efficiency (greatly reduced test time and reagents). In this experiment, microarray fabrication, slicing, and immunohistochemical staining were completed in only 1 mo. Four markers were detected in 62 samples, and the reagent consumption was much lower compared to the traditional methods. This indicates that tissue microarray technology is an efficient research method, especially suitable for multi-gene research with large sample sizes.

We believe that comparing CD31- and CD34- labeled blood vessels in BTCC by immunohistochemistry cannot show all the circumstances of the tumor vessels, but it can show that a unique CD31+/CD34- blood vessel is closely related to the prognosis of patients. Although undifferentiated blood vessels are considered of great value as the target of targeted therapy, the specific treatment method for this unique type of blood vessel is unclear [27]. Anti-angiogenesis therapy is generally considered to remove the immature or nonfunctional blood vessels to promote the retention of the remaining mature blood vessels [28]. In recent clinical trials, it has been reported in the UK that treatment methods inhibiting tumor cell proliferation and tumor angiogenesis significantly improved the survival rate of patients with urinary system tumors [29, 30]. CD31+CD34- vessels may potentially be the target for further therapies in anti-vascular treatment, which undoubtedly will be a great help for the treatment of malignant bladder tumors.

CONCLUSION

Through this experiment, we quantitatively analyzed two types of MVD in BTCC and compared their relatively different prognostic relationships. The high-density expression of undifferentiated blood vessels can be regarded as an independent prognostic factor for the shorter survival time of patients. In contrast, the high-density expression of differentiated blood vessels can indicate a better prognosis. Our research demonstrates that the vascular structure in BTCC is complex, and in research on angiogenesis regarding this tumor, more detailed studies on vascular classification are needed. Our research is helpful for clinical treatment and undifferentiated blood vessels may be a potential target for vascular treatment. Therefore, in research on anti-angiogenic drugs, drug research targeting undifferentiated blood vessels or differentiated blood vessels or both blood vessels may be a future research direction.

ARTICLE HIGHLIGHTS

Research background

At present, there is controversy on the role of microvessel density (MVD) in tumors as a prognostic indicator of bladder transitional cell carcinoma (BTCC).

Research motivation

The MVD in tumors is simply classified based on the expression of several different vascular markers, which has not been related to analytical research on the prognosis of patients with BTCC.

Research objectives

This study aimed to explore the classification of blood vessels in tumors and studied the relationship between MVD and the prognosis of patients with BTCC.

Research methods

We investigated the MVD in BTCC through tissue microarray and immunohistochemical analyses. By observing the morphological characteristics of blood vessels and the expression of specific markers, we explored the classification of blood vessels in
tumors and studied the relationship between MVD and the prognosis of patients.

**Research results**

Two different types of microvessels in BTCC were identified as undifferentiated (CD31+/CD34+) vessels and differentiated (CD34+) vessels. The MVD of high-grade undifferentiated vessels was positively correlated with a higher tumor grade and shorter survival time of the patients. In contrast, the MVD of high-grade differentiated vessels was positively correlated with lower-grade tumors and longer survival time of the patients. Multivariate analysis showed that undifferentiated MVD was an independent prognostic factor for patient survival time. An inverse correlation between undifferentiated tumor MVD and differentiated tumor MVD in BTCC was also shown.

**Research conclusions**

This was the first report on the correlation between two microvascular types and the prognosis of patients with BTCC. The results showed that the classification of blood vessels in BTCC could act as an important prognostic indicator and may also be of great significance in the treatment of cancer.

**Research perspectives**

Our research is helpful for clinical treatment, and suggests that undifferentiated blood vessels may be a potential target for vascular treatment. Therefore, in research on anti-angiogenic drugs, drug research targeting undifferentiated blood vessels or differentiated vessels may be a future research direction.

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Observational Study

Is burnout a mediating factor between sharps injury and work-related factors or musculoskeletal pain?

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Author contributions: Chen YH and Yeh CJ conceived and designed this manuscript; Jong GP and Yeh CJ analyzed and interpreted the data of this study; Chen YH wrote the original draft; Jong GP and Yeh CJ reviewed and edited the manuscript; Jong GP and Yeh CJ also share equal contribution; all authors were contributed to drafting and/or revising the article; and all authors approved the final version to be published.

Institutional review board statement: Approval of the research protocol: The study protocol was approved by the institutional review board of Chung Shan Medical University Hospital on July 22, 2020 (CSMUH No: CS19150).

Informed consent statement: Written consent was not obtained from the study participants as only de-identified data were obtained, and a waiver of patient consent was provided by the Ethics Committee for this study.

Conflict-of-interest statement: The

Abstract

BACKGROUND
Burnout, musculoskeletal pain, and sharps injuries (SIs) affect medical workers.

AIM
To establish a model between SIs, burnout, and the risk factors to assess the extent to which burnout affects SIs.

METHODS
This questionnaire was used for an observational and cross-sectional study, which was based on members at a hospital affiliated with a medical university in Taichung, Taiwan, in 2020. The valid responses constituted 68.5% (1734 of 2531). The items were drawn from the Nordic Musculoskeletal Questionnaire and Copenhagen burnout inventory and concerned work experience, occupational category, presence of chronic diseases, sleep duration, overtime work, and work schedule. Factor analysis, chi-square test, Fisher exact test, Multiple linear, logistic regression and Sobel test were conducted. The present analyses were performed using SAS Enterprise Guide 6.1 software (SAS Institute Inc., Cary, NC, United States), and significance was set at $P < 0.05$.

RESULTS
Personal and work-related burnout ranks, sex, work experience ranks, occupational groups, drinking in the past month, sleep duration per day, presence of chronic diseases, overtime work ranks, and work schedule were associated with SIs. Frequent upper limb and lower limb pain (pain occurring every day or once a week) determined to be related to SIs. High personal burnout (> Q3) and high work-related burnout (> Q3) mediated the relationship between SIs and frequent lower limb pain. Similarly, frequent lower limb pain mediated the relationship of SIs with high personal and high work-related burnout. High personal and high work-related burnout mediated the relationships of SIs with overtime work and irregular shift work. The mediating model provides strong evidence of an association between mental health and SIs.

CONCLUSION
Burnout was determined to contribute to SIs occurrence; specifically, it mediated the relationships of SIs with frequent musculoskeletal pain, overtime work, and irregular shift work.

Key Words: Personal burnout; Work-related burnout; Sharps injuries; Musculoskeletal pain; Mediating factor; Overtime work

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Core Tip: Burnout affects approximately half of all nurses, physicians, and other clinicians. Sharps injuries, which frequently occur among health care workers, constitute a critical problem. Our study found burnout was determined to contribute to sharps injuries occurrence; specifically, it mediated the relationships of sharps injuries with frequent musculoskeletal pain, overtime work, and irregular shift work. Results from the present study suggest that if the problem of burnout is ignored, training or safe operation may not be sufficient to effectively prevent work-related injuries. To the best of our knowledge, this finding has never been reported.

Citation: Chen YH, Tsai CF, Yeh CJ, Jong GP. Is burnout a mediating factor between sharps injury and work-related factors or musculoskeletal pain? World J Clin Cases 2021; 9(25): 7391-7404
DOI: https://dx.doi.org/10.12998/wjcc.v9.i25.7391

INTRODUCTION
In May 2018, burnout was recognized as an “occupational phenomenon” in the International Classification of Diseases, 11th Revision (ICD-11) of the World Health Organization. Burnout is a state of physical, emotional, and mental exhaustion that results from long-term involvement in work situations that are emotionally demanding[1]. The specific definition of burnout in the ICD-11 is “a syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed.”

Burnout is responsible for high physician turnover and reduced clinical hours, which cause total losses of approximately 4.6 billion dollars in the United States each year[2]. Moreover, burnout affects approximately half of all nurses, physicians, and other clinicians[3]. Studies on resident physicians and nurses have indicated that most cases of burnout are personal or work-related. Studies have noted that work-related burnout (WB) and personal burnout (PB) occur in 30% and 50% of individuals with burnout, respectively[4]. Notably, burnout also affects the patient-related quality of care[5]. The numerous reasons for the development of burnout include basic demographic characteristics such as sex[4,6] and age[7]; occupational factors such as work experience (WE)[8], overtime (OT) work[9], and shift work[10]; lifestyle habits such as sleep duration (SLD)[10,11] and exercise[11]; and health status (e.g., the presence of chronic diseases)[12].
In the United States, 13% of the workforce experience losses in productivity stemming from a painful physical condition, amounting to an estimated US$61.2 billion in pain-related lost productive time each year\[^{13}\]. Musculoskeletal (MS) pain due to traumatic/micro traumatic events (often secondary to occupational postures/attitudes/activities)\[^{15}\].

The United States Centers for Disease Control and Prevention defines sharp injuries (SI) as an exposure event (blood/body fluid exposure) that occurs when a needle or other sharp object penetrates the skin. SI frequently occurs among health care workers and constitutes a critical infective problem upon contamination of the sharp object. As one study noted, 0.42 hepatitis B infections, 0.05 to 1.30 hepatitis C infections, and 0.04 to 0.32 human immunodeficiency virus (HIV) infections develop per 100 cases of SI per year. The literature review conducted in that study revealed that SIs led to mean costs of €1966 if the source patient was HIV positive and had coinfections of hepatitis B and hepatitis C\[^{16}\]. SI occurrence has been reported to be associated with occupational factors such as WE\[^{17}\], work hours\[^{18}\], and shift work schedules\[^{19}\] as well as demographic characteristics such as sex\[^{20}\] and age\[^{21}\]. Moreover, one article asserted that the experience of SIs was related to the mental health of health care workers\[^{22}\].

Therefore, the relationship between burnout level (as measured using a routine questionnaire) and SI deserves scholarly attention with regard to the prevention of work-related injuries among medical personnel. In the present study, a model of causal relationships between SI, burnout, and work-related risk factors was established to assess the extent to which burnout affects SI. This investigation serves as a basis on which the impact of mental health on occupational injuries can be further explored in the future. Specifically, the present study examined the relationship between mental health and occupational injuries, with burnout and SI as agent variables.

**MATERIALS AND METHODS**

This questionnaire was used for an observational and cross-sectional study, which was based on members at a hospital affiliated with a medical university in Taichung, Taiwan, in 2020. Of the 2531 individuals to whom the questionnaire was sent, 1838 (72.6%) completed the questionnaire. After exclusion for missing data, 1734 questionnaires (68.5%) were determined to be valid.

The participants’ WE (years) and occupational category were provided by the occupational safety department of the hospital. On the questionnaire, the participants were asked whether they had a listed chronic disease (CD), with the selection of one or more diseases classified as a “yes” response. The participants were also asked whether they had experienced a SI in the past year. In response to the question on smoking in the past month, “never” or “have quit smoking” were classified as “no.” As for drinking in the preceding month, answers of “seldom” or “every day” were classified as “yes,” whereas “never” was classified as “no.” SLD was classified as < 5, 5–6, 6–7, 7–8, or > 8 h. The participants were asked whether they exercised at least once a day, at least once a week, at least once a month, less than once a month, or never. Possible responses to the question on OT work were the following: seldom, fewer than 45 h per month, 45–80 h per month, and more than 80 h per month. The responses were classified as seldom, < 45 h per month, and > 45 h per month accordingly. As for work schedule, the options given were day shift work, night shift work, irregular shift work, and regular shift work.

This study adopted the Nordic MS Questionnaire (NMQ) modified and translated by the Taiwan Institute of Occupational Safety and Health\[^{23}\]. The NMQ, which is used in the investigation of the site and frequency of MS pain, was developed in a project funded by the Nordic Council of Ministers. The NMQ has acceptable reliability\[^{23}\] and has been applied in a wide range of occupational groups, including nurses\[^{24}\]. Items on the NMQ include questions on the presence of pain attributable to work-related factors in the preceding year and on the pain sites, the options for which were the neck (N1), left shoulder (N2), right shoulder (N3), upper back (N4), waist or lower back (N5), left elbow (N6), right elbow (N7), left wrist (N8), right wrist (N9), left hip/thigh/buttock (N10), right hip/thigh/buttock (N11), left knee (N12), right knee (N13), left ankle (N14), and right ankle (N15). If a participant answered “yes” to the question on the experience of work-related pain over the past year, they were instructed to indicate its frequency: every day, once a week, once a month, or once
every half year. Pain occurring every day or once a week was defined as frequent MS (FMS) pain and was scored as 1. Pain occurring once a month or once every half year was scored as 0.

In the present study, factor analysis was conducted on the NMQ results to determine the underlying variables that explained most of the questionnaire. According to the principle proposed by Hair et al.[25], factors that should be retained have feature vector values exceeding 1. Through varimax rotation, the standardized scoring coefficients constituted new factor loadings and were defined as new factors according to the corresponding significance of the factor loadings.

The Copenhagen burnout inventory (CBI), which comprises three scales assessing PB, WB, and client-related burnout, has extremely high internal reliability and low nonresponse rate.[26]. The present study used the Chinese version of CBI, which has proven to be a reliable and valid tool for assessment of burnout problems.[27]; thus, it was used to evaluate burnout in the present study, with a focus on PB and WB. The first six items, which concern PB, are as follows: C1: “How often do you feel tired?” C2: “How often are you physically exhausted?” C3: “How often are you emotionally exhausted?” C4: “How often do you think ‘I can’t take it anymore’?” C5: “How often do you feel worn out?” C6: “How often do you feel weak and susceptible to illness?”

Items 7–13, which concern WB, are as follows: C7: “Is your work emotionally exhausting?” C8: “Do you feel burnt out because of your work?” C9: “Does your work frustrate you?” C10: “Do you feel worn out at the end of the working day?” C11: “Are you exhausted in the morning at the thought of another day at work?” C12: “Do you feel that every working hour is tiring for you?” C13: “Do you have enough energy for family and friends during leisure time?”

The response options—“always”, “often”, “sometimes”, “seldom”, and “never/almost never”—are scored as 100, 75, 50, 25, and 0 points, respectively, except for item C13, which is inverse scored (i.e., the responses are scored as 0, 25, 50, 75, and 100 points, respectively). Levels of PB and WB are represented by the mean of the total PB and WB scores (the sum of scores on items C1–C6 and items C7–C13), respectively.

The categorical variables were subjected to the chi-square test or Fisher exact test. Significance in the differences among the means of continuous variables was determined using the t test or one-way ANOVA. Multiple linear or logistic regression was conducted to control the interference of potential risk factors in the association between the independent variables (IVs) and the dependent variable (DV)—specifically, to determine whether adjustments to variables significantly affected IV–DV associations. Mediation effects were analyzed on the basis of the strategy proposed by Baron and Kenny[28] in which: (1) The IV significantly affects the mediator (first-stage effect); (2) The IV significantly affects the DV in the absence of the mediator; (3) The mediator has a significant unique effect on the DV (second-stage effect); and (4) The effect of the IV on the DV weakens upon addition of the mediator to the model. A method for mediation suitable for a combination of categorical and continuous variables, developed by Iacobucci[29], was used; the (formula 1) are as follows.

\[
\bar{Y} = b_{01} + cX \\
\bar{R} = b_{02} + aX \\
\bar{Y} = b_{03} + c'X + bm \\
Z_a = \bar{a}/s_a \\
Z_b = \bar{b}/s_b
\]

Where \(X\) is an IV; \(Y\) is a DV; \(M\) is the adjusted variable (i.e., the mediating factor) in a simple mediation model; \(a\) is a logistic/Linear regression coefficient of \(X\) against \(M\) when \(M\) and \(X\) are a DV and IV, respectively; \(b\) is the logistic/Linear regression coefficient of \(M\) against \(Y\) in a simple mediation model; \(c\) is the logistic/Linear regression coefficient of \(X\) against \(Y\); and \(c'\) is the logistic/Linear regression coefficient of \(X\) against \(Y\) with \(M\) as the adjusting variable. The standard errors of \(a\) and \(b\) are represented by \(s_a\) and \(s_b\), respectively.

The original formula of the Sobel test was rederived into formula 2.

\[
Z_{\text{mediation}}(Z_M) = \frac{\frac{a \times b}{s_a \times s_b}}{\sqrt{\frac{Z_a^2 + Z_b^2}{s_a^2 + s_b^2} + 1}}
\]

Results exceeding |1.96| and |2.57| (for a two-tailed test) are significant at \(\alpha = 0.05\) and \(\alpha = 0.01\), respectively. The present analyses were performed using SAS Enterprise Guide 6.1 software (SAS Institute Inc., Cary, NC, United States), and significance was set at \(P < 0.05\).
RESULTS

As shown in Table 1, the mean PB and WB scores were 36.69 ± 17.59 and 34.19 ± 16.29, respectively. SI incidence was 8.42%. Q1, Q2, and Q3 represented the lower quartile, median, and upper quartile, respectively. The highest proportions of SIs (12.55% and 12.42%) corresponded to PB and WB (rank > Q3 for both), respectively. Differences in SI occurrence were significant among the PB or WB ranks. Women reported higher PB and WB than men (37.39 vs 33.64 and 34.89 vs 31.13, respectively; \( P < 0.01 \) for both), but SIs were more common in men (13.85% vs 7.17%; \( P < 0.01 \)). Regarding WE, ranks > Q2 and ≤ Q3 corresponded to the highest PB level (mean = 38.94 ± 17.60), whereas a rank > Q3 corresponded to the lowest WB level (mean = 31.36 ± 15.46). Moreover, ranks > Q1 and ≤ Q2 with regard to WE corresponded to the highest proportion of SI occurrence (12.21%). Significant differences in the proportion of SI occurrence and in the levels of PB and WB were noted among occupational groups, with nurses experiencing the highest PB and WB (41.22 and 39.33). Notably, SIs occurred most commonly among physicians (15.86%). Levels of PB (mean = 39.51) and WB (mean = 36.17) were significantly higher in participants who reported drinking during the preceding month, as was SI occurrence (11.41%). SLD was significantly associated with PB level, WB level, and SI occurrence. The highest PB and WB (mean scores = 48.52 and 41.82, respectively) were observed in the participants who reported sleeping ≤ 5 h per night, as was the highest SI occurrence (14.52%). The participants who exercised daily reported significantly lower PB and WB (mean scores = 31.27 and 28.94, respectively) than those who exercised less frequently, but no significant difference in SI occurrence was noted. Compared with those without such conditions, the participants with CD had significantly higher levels of PB and WB (mean scores = 38.69 and 35.43, respectively) and were more likely to have sustained an SI (10.53%). Burnout levels and SI occurrence differed significantly according to the monthly number of OT hours. Specifically, the participants who worked > 45 h per month had the highest PB and WB (mean scores = 48.51 and 43.73, respectively). These individuals were also the most likely to have sustained an SI (16.98%). Burnout levels and SI occurrence also differed significantly with work schedule. Specifically, the participants who worked irregular shifts reported the highest PB and WB (mean scores = 43.54 and 40.90, respectively) as well as the highest SI occurrence (13.45%).

Table 2 presents information on the sites and occurrence of MS pain experienced over the 12 mo as well as the sites and proportion of MS pain that occurred at least once a week (i.e., FMS pain). Because the eigenvalues of factors 1 and 2 exceeded 1, these factors were retained. Although the eigenvalue of factor 3 was lower than 1, it was retained for the maximum explaining questionnaire. The factor loadings were converted into standardized scoring coefficients through varimax rotation. The relatively large factor loading values in bold for factors 1, 2, and 3 correspond to pain in the upper trunk, lower limbs, and upper limbs, respectively. Frequent upper torso pain (FUTP) occurred in the neck, both shoulders, and upper back, and its standardized coefficient was defined as FUTP. For frequent lower limb pain (FLLP), sites included both hip/thigh/buttocks, both knees, and both ankles, and its standardized coefficient was defined as FLLP. Frequent upper limb pain (FULP) occurred in both elbows and both wrists, and its standardized coefficient was defined as FULP. The explained variation in FUTP, FLLP, and FULP was 73.86%, 23.11%, and 8.67%, respectively. This indicated that the participants experienced upper trunk pain most frequently, followed by lower limb and upper limb pain. Although FULP had the smallest explained variation of the three, it was retained because the present study was focused on the relationship between SI and upper limb pain.

Table 3 shows that the participants who had experienced an SI in the preceding year had significantly higher FLLP and FULP scores than those who had not, but no significant differences were noted for the FUTP score. In short, FLLP and FULP were identified as risk factors for SIs.

Because of the extremely high proportion of SIs corresponding to PB or WB ranks > Q3 (Table 1), PB rank was reclassified as PB > Q3 and PB ≤ Q3, and WB rank was reclassified as WB > Q3 and WB ≤ Q3. PB > Q3 and WB > Q3 corresponded to high PB level (HPBL) and high WB level (HWBL), respectively. Similarly, the participants who worked irregular shifts had significantly higher PB and WB scores; therefore, the work schedule was reclassified as irregular work shifts (IRWS) and other work schedules. Moreover, because SIs were only reported by nine participants who worked > 45 h of OT per month, OT work was reclassified as an experience of OT (EOT) work and seldom worked OT.
### Table 1 Descriptive statistics concerning the results of the Copenhagen burn inventory and occurrence of sharps injuries (n = 1734)

<table>
<thead>
<tr>
<th>Characters</th>
<th>n</th>
<th>PB score mean ± SD</th>
<th>WB score mean ± SD</th>
<th>SI Subject (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SI in past one year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; Q3</td>
<td>542</td>
<td>56.93 ± 12.20</td>
<td>-</td>
<td>68 (12.55)</td>
</tr>
<tr>
<td>&gt; Q2 and ≤ Q3</td>
<td>482</td>
<td>37.22 ± 3.31</td>
<td>-</td>
<td>30 (6.22)</td>
</tr>
<tr>
<td>&gt; Q1 and ≤ Q2</td>
<td>394</td>
<td>27.08 ± 2.09</td>
<td>-</td>
<td>29 (7.36)</td>
</tr>
<tr>
<td>≤ Q1</td>
<td>316</td>
<td>13.12 ± 6.79</td>
<td>-</td>
<td>19 (6.01)</td>
</tr>
<tr>
<td><strong>PB ranks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>325</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1409</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WE ranks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Q1</td>
<td>375</td>
<td>36.23 ± 17.73</td>
<td>34.72 ± 17.37</td>
<td>34 (9.07)</td>
</tr>
<tr>
<td>&gt; Q1 and ≤ Q2</td>
<td>434</td>
<td>37.29 ± 17.98</td>
<td>35.12 ± 16.10</td>
<td>53 (12.21)</td>
</tr>
<tr>
<td>&gt; Q2 and ≤ Q3</td>
<td>487</td>
<td>38.94 ± 17.60</td>
<td>35.48 ± 16.06</td>
<td>38 (7.80)</td>
</tr>
<tr>
<td>&gt; Q3</td>
<td>438</td>
<td>34.07 ± 16.73c</td>
<td>31.36 ± 15.46c</td>
<td>21 (4.79)</td>
</tr>
<tr>
<td><strong>Occupation groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors</td>
<td>145</td>
<td>37.10 ± 17.37</td>
<td>34.11 ± 16.78</td>
<td>23 (15.86)</td>
</tr>
<tr>
<td>Nurses</td>
<td>627</td>
<td>41.22 ± 17.27</td>
<td>39.33 ± 15.55</td>
<td>55 (8.77)</td>
</tr>
<tr>
<td>Others</td>
<td>962</td>
<td>33.67 ± 17.20c</td>
<td>30.84 ± 15.82c</td>
<td>68 (7.07)</td>
</tr>
<tr>
<td><strong>Right-handed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1663</td>
<td>36.89 ± 17.64c</td>
<td>34.31 ± 16.31c</td>
<td>142 (8.54)</td>
</tr>
<tr>
<td>No</td>
<td>71</td>
<td>31.87 ± 15.62c</td>
<td>31.34 ± 15.48c</td>
<td>4 (5.63)</td>
</tr>
<tr>
<td><strong>Drinking in past month</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>561</td>
<td>39.51 ± 17.05c</td>
<td>36.17 ± 16.03c</td>
<td>64 (11.41)</td>
</tr>
<tr>
<td>No</td>
<td>1173</td>
<td>35.34 ± 17.69c</td>
<td>33.24 ± 16.33c</td>
<td>82 (6.99)</td>
</tr>
<tr>
<td><strong>Smoking in past month</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
<td>31.60 ± 16.80c</td>
<td>25.89 ± 17.04c</td>
<td>2 (16.67)</td>
</tr>
<tr>
<td>No</td>
<td>1722</td>
<td>36.72 ± 17.60c</td>
<td>34.24 ± 16.27c</td>
<td>144 (8.36)</td>
</tr>
<tr>
<td><strong>SLD (per day) ranks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 5 h</td>
<td>62</td>
<td>48.52 ± 20.62c</td>
<td>41.82 ± 17.57c</td>
<td>9 (14.52)</td>
</tr>
<tr>
<td>&gt; 5 and ≤ 6 h</td>
<td>566</td>
<td>41.04 ± 17.91c</td>
<td>38.26 ± 16.47c</td>
<td>54 (9.54)</td>
</tr>
<tr>
<td>&gt; 6 and ≤ 7 h</td>
<td>771</td>
<td>34.91 ± 16.38c</td>
<td>32.35 ± 15.40c</td>
<td>66 (8.56)</td>
</tr>
<tr>
<td>&gt; 7 h</td>
<td>335</td>
<td>31.23 ± 16.47c</td>
<td>29.89 ± 15.80c</td>
<td>17 (5.07)</td>
</tr>
<tr>
<td><strong>Exercise per day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>133</td>
<td>31.27 ± 18.88c</td>
<td>28.84 ± 17.87c</td>
<td>11 (8.27)</td>
</tr>
<tr>
<td>No</td>
<td>1601</td>
<td>37.14 ± 17.41c</td>
<td>34.63 ± 16.08c</td>
<td>135 (8.43)</td>
</tr>
</tbody>
</table>
Table 2 Sites of musculoskeletal pain and factor analysis of the Nordic musculoskeletal questionnaire, n (%)  

<table>
<thead>
<tr>
<th>Pain site</th>
<th>Pain past 12 months</th>
<th>FMS pain</th>
<th>Factor loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects</td>
<td>Subjects</td>
<td>Factor 1: Upper torso</td>
</tr>
<tr>
<td>Neck</td>
<td>636 (36.68)</td>
<td>405 (23.36)</td>
<td>0.29</td>
</tr>
<tr>
<td>Left shoulder</td>
<td>370 (21.34)</td>
<td>234 (13.49)</td>
<td>0.27</td>
</tr>
<tr>
<td>Right shoulder</td>
<td>444 (25.61)</td>
<td>283 (16.32)</td>
<td>0.29</td>
</tr>
<tr>
<td>Upper back</td>
<td>327 (18.86)</td>
<td>210 (12.11)</td>
<td>0.19</td>
</tr>
<tr>
<td>Waist or lower back</td>
<td>529 (35.01)</td>
<td>300 (17.30)</td>
<td>0.12</td>
</tr>
<tr>
<td>Left elbow</td>
<td>65 (3.75)</td>
<td>35 (2.02)</td>
<td>-0.03</td>
</tr>
<tr>
<td>Right elbow</td>
<td>126 (7.27)</td>
<td>81 (4.67)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Left wrist</td>
<td>103 (5.94)</td>
<td>67 (3.86)</td>
<td>-0.03</td>
</tr>
<tr>
<td>Right wrist</td>
<td>205 (11.82)</td>
<td>110 (6.34)</td>
<td>-0.02</td>
</tr>
<tr>
<td>Left hip/thigh/buttock</td>
<td>70 (4.04)</td>
<td>48 (2.77)</td>
<td>-0.04</td>
</tr>
<tr>
<td>Right hip/thigh/buttock</td>
<td>70 (4.04)</td>
<td>45 (2.60)</td>
<td>-0.04</td>
</tr>
<tr>
<td>Left knee</td>
<td>95 (5.48)</td>
<td>51 (2.94)</td>
<td>0.04</td>
</tr>
<tr>
<td>Right knee</td>
<td>88 (5.08)</td>
<td>51 (2.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>Left ankle</td>
<td>42 (2.42)</td>
<td>31 (1.79)</td>
<td>-0.06</td>
</tr>
<tr>
<td>Right ankle</td>
<td>51 (2.94)</td>
<td>39 (2.25)</td>
<td>-0.05</td>
</tr>
<tr>
<td>Eigenvalues</td>
<td>4.02</td>
<td>1.26</td>
<td>0.47</td>
</tr>
<tr>
<td>Explained variation (%)</td>
<td>73.86</td>
<td>23.11</td>
<td>8.67</td>
</tr>
</tbody>
</table>

The relatively large factor loading values were marked in bold for corresponding to musculoskeletal pain sites.

**Figure 1** shows the mediation effect of burnout in the association between SIs and the risk factors. The value of $c$ must be statistically significant and greater than that of $c'$. Moreover, the values of $a$ and $b$ must be statistically significant. In addition, $a \times b$ and $c-c'$ must differ significantly and be able to be tested by calculating the $Z_{medication}$ value ($Z_m$). HPBL partially mediated the relationships of SI with FLLP ($Z_m = 2.84$),
Table 3 Differences in frequent musculoskeletal pain scores between participants who had and had not experienced an sharps injury in the preceding year

<table>
<thead>
<tr>
<th>FMS pain score</th>
<th>With SIs in past year</th>
<th>Without SIs in past year</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td></td>
</tr>
<tr>
<td>FUTP</td>
<td>0.11 ± 0.97</td>
<td>-0.01 ± 0.86</td>
<td></td>
</tr>
<tr>
<td>FLLP</td>
<td>0.24 ± 1.17</td>
<td>-0.02 ± 0.78</td>
<td></td>
</tr>
<tr>
<td>FULP</td>
<td>0.16 ± 0.96</td>
<td>-0.02 ± 0.70</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05.

bP < 0.01. FMS: Frequent musculoskeletal; FUTP: Frequent upper torso pain; Sis: Sharps injuries.

Figure 1 Mediation effects of high personal burnout level/high work-related burnout level in the association between sharps injuries and X.

aP < 0.05, bP < 0.01, cP < 0.001. 1: Frequent lower limb pain; 2: Frequent upper limb pain; 3: Experience of overtime vs seldom worked overtime; 4: Doctors vs Nurses and others; 5: Irregular work shifts vs other work schedules; a: The logistic regression coefficient of risk factors for the association between sharps injury (SI) and risk factors; s_aj: The standard error of a_j. b: The logistic regression coefficient of burnout as an adjusted variable with regard to the association between SI and X_j. s_bj: The standard error of b_j. SI: Sharps injuries; HPBL: High personal burnout level; HWBL: High work-related burnout level.

FULP (Z_m = 2.70), EOT work (Z_m = 3.03), and IRWS (Z_m = 2.84). HWBL partially mediated the relationships of SI with FLLP (Z_m = 2.54), FULP (Z_m = 2.56), EOT work (Z_m = 2.65), and IRWS (Z_m = 2.70). A strong relationship between FMS pain and burnout was observed, but whether FMS pain also mediated the relationship between SI and burnout remains to be determined. Figure 2 shows FLLP significantly mediated the relationships of SI with HPBL (Z_m = 2.44) and HWBL (Z_m = 2.40). By contrast, the mediating effect of FULP was not significant. Neither FLLP nor FULP mediated the relationships of SI with EOT work, being a physician, and IRWS.

From the analytical results (Table 1–3, Figure 1 and 2), the following inferences can be made: an increase in the frequency of limb pain was closely correlated with an increase in SI incidence, and an increase in burnout level caused by an increase in the frequency of limb pain increased SI occurrence. The participants with HPBL accounted for a higher proportion of the SIs that occurred, and the increase in FLLP caused by HPBL also raised the proportion of SI occurrence. The participants with EOT work were more likely to sustain an SI, as were the participants experiencing serious burnout caused by OT work, which would increase the rate of SI occurrence. Similarly,
Chen YH et al. Burnout is a mediating factor

Figure 2 Mediation effects of frequent lower limb pain/frequent upper limb pain in the association between sharps injuries and X. a\textsubscript{i}P < 0.05, b\textsubscript{i}P < 0.01, c\textsubscript{i}P < 0.0001. : High personal burnout level; : High work-related burnout level; : Experience of overtime vs seldom worked overtime; : Doctors vs Nurses and others; : Irregular work shifts vs other work schedules; a: The logistic regression coefficient of risk factors for the association between sharps injuries (SI) and risk factors; s\textsubscript{ai}: The standard error of a\textsubscript{i}; b: The logistic regression coefficient of burnout as an adjusted variable with regard to the association between SI and X; s\textsubscript{bi}: The standard error of b\textsubscript{i}. SI: Sharps injurie; FLLP: Frequent lower limb pain; FULP: Frequent upper limb pain.

The participants with IRWS were also more likely to sustain an SI, as were the participants experiencing serious burnout caused by IRWS, which would increase the rate of SI occurrence.

Constructed on the basis of the results presented in Figure 1 and 2 is a simple mediation model that indicates the existence of direct or mediating relationships between SI and FLLP, HPBL/HWBL, and EOT work or IRWS. HPBL and HWBL mediated the SI–FLLP relationship. Similarly, FLLP was a mediating factor in the relationships of SI with HPBL and HWBL. Furthermore, HPBL and HWBL mediated the relationships of SI with EOT work and IRWS.

DISCUSSION

In line with reports that both PB and WB levels are significantly higher among female resident physicians[4] and that male nurses experience burnout syndrome less commonly than female nurses[6], the women in the present sample reported significantly higher PB and WB than the men (Table 1). Regarding SIs, a study indicated that male health workers were 10 times more likely to sustain an SI than were female health workers[30]. The men in the present study were more likely to sustain SIs than the women (13.85% vs 7.17%).

Studies have reported that nurses and clinicians working OT are more likely to experience burnout[9]. In one study, an increase in weekly work hours increased the occurrence of SIs among nurses[31]. As shown in Table 1, a dose–response relationship between SI and OT work (> 45, < 45 h, or seldom) was observed. Similar results were noted for relationships of PB and WB with OT. Specifically, more OT work hours increased SI occurrence and the mean levels of PB and WB, and PB and WB was positively associated with SIs. These results suggest that OT work was related to PB and WB level as well as to SI occurrence. PB and WB may contribute critically to the relationship between SI and OT work; this possibility warrants further investigation. As shown in Figure 1, PB and WB partially mediated the relationship between SI and
EOT work; the effects were significant. These results suggest that EOT work affected SI directly or indirectly (through an unknown path). Studies have noted that increased OT was significantly associated with impairments in attention, executive function[32], and stress response[33]. Whether OT work affects SI incidence through these factors remains to be determined.

One study noted that burnout syndrome was more common among nurses working irregular shifts than among those working regular shifts[6]. In the same vein, studies have observed that working regular shifts exerted protective effects against SIs[19,21]. Consistent with results from other studies, in the present study, the highest mean PB and WB was reported by participants working irregular shifts (Table 1). As shown in Figure 1, PB and WB also partially mediated the relationship between SI and irregular shifts, indicating that irregular shifts may have affected SI through burnout in some participants; in others, irregular shifts may have exerted direct effects on SI through other routes.

A large study conducted in the Netherlands on MS pain occurring over 12 mo reported that lower back pain occurred the most frequently (43.9%), followed by shoulder pain (30.3%) and neck pain (31.4%)[14]. In line with these results, the corresponding occurrence of low back pain, shoulder pain, and neck pain in the present study was 35.01%, 46.95%, and 36.68%, respectively (Table 2). A study on seven occupational groups in Norway reported a significant association between burnout and MS pain[34]. In the present study, the frequency of limb pain (lower or upper) was positively associated with HPBL and HWBL (a = 0.28, P < 0.0001; a = 0.28, P < 0.0001; Figure 1). A cross-sectional study on burnout and occupational accidents in which the Maslach Burnout Inventory (MBI) questionnaire was administered to employees in the occupational medicine department of a hospital reported that each one-unit increase in the burnout score corresponded to a 9% increase in the risk of injury[35]. In a study on Chinese nurses in which the MBI questionnaire was again used, emotional exhaustion was positively associated with SI occurrence[36]. Regarding the present results obtained from the CBI, SI occurrence differed significantly in PB (P < 0.01) and WB ranks (P < 0.01) (Table 1). As shown in Figure 2, HPBL (c = 0.72, P < 0.001) and HWBL (c = 0.63, P < 0.01) were positively associated with SI occurrence. The present results are consistent with those from other studies that used the MBI. However, in an extension of the literature, we further explored the causal relationships between SI, work-related risk factors, and burnout through the analysis of mediating effects. As shown in Figure 2, FLLP also mediated the relationships of SI with HPBL and HWBL, indicating that FLLP and HPBL or HWBL form a vicious circle with SI (Figure 3). These findings serve as a valuable reference for SI prevention. To test for significance, we used the Zm formula developed by Iacobucci[29], which can effectively test for mediating effects in samples exceeding 300 when X, Y, and M are categorical variables. The present sample size of 1734 more than meets this requirement. Therefore, the Zm formula was suitable.

WE, drinking in the preceding year, SLD, exercise, and CD, variables adjusted in the model, were identified as risk factors for SI and burnout. The significant association of these variables with SI and burnout is supported by results from other studies. For example, studies have indicated that individuals with less WE are at a higher risk of sustaining SIs[17], and the report of burnout was significantly positively associated with higher alcohol consumption[37]. Moreover, PB has been demonstrated to be significantly associated with impaired sleep quality[11], and reductions in SLD increase the risk of occupational injury[38]. University students or nurses who engage in physical activity or exercise have been noted to report significantly lower levels of PB and fatigue[11], and individuals with burnout appear to be more susceptible to physical illness than those without burnout[39]. Therefore, the adjustment of these variables was both necessary and appropriate for reducing the impacts of possible confounders on the SI model.

The burnout mediation model regarding SI and occupational risk factors (e.g., OT work, irregular shift, and MS pain) provides strong evidence of an association between mental health and SIs. The literature mostly examines the relationship between SI and the work process or the use of protective equipment; deeper psychological factors are seldom explored. The relationship between SIs and work-related injuries not induced by burnout warrants further investigation. A study on 112 workers in metal melting industries reported no significant association between occupational burnout and unsafe actions[40]. Despite the small sample size in that study, results from both that study and the present study suggest that if the problem of burnout is ignored, training or safe operation may not be sufficient to effectively prevent work-related injuries. Therefore, to mitigate the problem of work-related injuries, institutions should take effective countermeasures to alleviate burnout among medical personnel.
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Figure 3 Simple mediation model for burnout and frequent lower limb pain. X and Y are the independent and dependent variables, respectively, whereas M is the mediating factor of sharps injuries (Y) and X. FLLP: Frequent lower limb pain; HPBL: High personal burnout level; HWBL: High work-related burnout level; EOT: The experience of overtime (work); IRWS: Irregular work shifts.

This study was performed in the context of the coronavirus disease 2019 pandemic, which may have been more demanding on medical personnel than the non-pandemic period. Therefore, a similar study that assesses the regular work conditions and exposure of health care workers during the non-pandemic period should be replicated and compared with the result of the pandemic period.

CONCLUSION

Burnout was determined to contribute to SI occurrence; specifically, it mediated the relationships of SI with FUTP, FLLP, EOT, and IRWS. FLLP also mediated the relationship between SI and burnout, forming a vicious circle of burnout and FLLP that further increased the frequency of SIs. To the best of our knowledge, this finding has never been reported. The present findings serve as a reference for the management of mental health and the prevention of SIs among medical personnel worldwide.

ARTICLE HIGHLIGHTS

Research background
Burnout affects approximately half of all nurses, physicians, and other clinicians. Sharps injuries, which frequently occur among health care workers, constitute a critical problem in the hospital.

Research motivation
Studies conducted in many countries revealed the relationship between burnout level (as measured using a routine questionnaire) and sharps injury deserves scholarly attention with regard to the prevention of work-related injuries among medical personnel. However, studies assessing the extent to which burnout affects sharps injuries are scarce.

Research objectives
To be established a model between sharps injuries, burnout, and the risk factors to assess the extent to which burnout affects sharps injuries.

Research methods
A questionnaire was used for an observational and cross-sectional study, which was based on members at a hospital affiliated with a medical university in Taichung, Taiwan, in 2020. The valid responses constituted 68.5% (1734 of 2531). The items were drawn from the Nordic Musculoskeletal Questionnaire and Copenhagen burnout inventory and concerning work experience, occupational category, presence of chronic diseases, sleep duration, overtime work, and work schedule. Factor analysis, chi-
square test, Fisher exact test, multiple linear, logistic regression, and Sobel test were conducted.

Research results
Our study found burnout was determined to contribute to sharps injuries occurrence; specifically, it mediated the relationships of sharps injuries with frequent musculoskeletal pain, overtime work, and irregular shift work.

Research conclusions
Burnout was determined to contribute to SIs occurrence; specifically, it mediated the relationships of sharps injuries with frequent musculoskeletal pain, overtime work, and irregular shift work.

Research perspectives
A similar study that assesses the regular work conditions and exposure of health care workers during the non-pandemic period should be replicated and compared with the result of the pandemic period.

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9. Stimpfel AW, Sloane DM, Aiken LH. The longer the shifts for hospital nurses, the higher the levels of burnout and patient dissatisfaction. Health Aff (Millwood) 2012; 31: 2501-2509 [PMID: 23129681].


Role of international normalized ratio in nonpulmonary sepsis screening: An observational study

Jing Zhang, Hui-Min Du, Ming-Xiang Cheng, Fa-Ming He, Bai-Lin Niu

Abstract

BACKGROUND
Currently, there is a lack of sepsis screening tools that can be widely used worldwide. Pulmonary sepsis can be of sufficient concern to physicians due to their noticeable symptoms, which usually rely less on screening tools.

AIM
To investigate the efficiency of the international normalized ratio (INR) for the early rapid recognition of adult nonpulmonary infectious sepsis.

METHODS
This is a prospective observational study. A total of 108 sepsis patients and 106 nonsepsis patients were enrolled according to relevant inclusion and exclusion criteria. Commonly used clinical indicators, such as white blood cell, neutrophil count, lymphocyte count, neutrophil-lymphocyte count ratio (NLCR), platelets (PLT), prothrombin time, INR, activated partial thromboplastin time, and quick Sequential “Sepsis-related” Organ Failure Assessment (qSOFA) scores were recorded within 24 h after admission. The diagnostic performances of these clinical indicators were analyzed and compared through multivariate logistic regression analysis, Spearman correlation, and receiver operating characteristic curve analysis.
RESULTS

The INR value of the sepsis group was significantly higher than that of the nonsepsis group. INR has superior diagnostic efficacy for sepsis, with an area under the curve value of 0.918, when those preexisting diseases which significantly affect coagulation function were excluded. The diagnostic efficacy of the INR was more significant than that of NLCR, PLT, and qSOFA (P < 0.05). Moreover, INR levels of 1.17, 1.20, and 1.22 could be used to categorize the relative risk of nonpulmonary infections sepsis into three categories: low, medium and high risk, respectively.

CONCLUSION

The INR is a promising and easily available biomarker for diagnosis, and it can be used as one of the indicators for early screening of adult nonpulmonary infectious sepsis. When its value is higher than the optimal cutoff value (1.22), high vigilance is required for adult nonpulmonary infectious sepsis.

Key Words: Sepsis; Coagulopathy; International normalized ratio; Screening tool; Quick Sequential “Sepsis-related” Organ Failure Assessment

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Core Tip: The international normalized ratio (INR) has high specificity and sensitivity in the early identification of adult nonpulmonary source of sepsis. Sepsis is highly suspected when the INR value exceeds 1.22 in patients with non-pulmonary infection, especially for those patients without preexisting underlying disease or medication history that affects coagulation function. Due to its low cost, fast detection and easy interpretation, INR is suitable for the primary screening of sepsis for emergency patients, outpatient patients, particularly in low and middle-income countries.

INTRODUCTION

The incidence of sepsis has been increasing year by year, and it has become one of the leading causes of death in intensive care unit (ICU) patients[1]. Studies have confirmed that sepsis results in a "bimodal" distribution of death times, which are early death within a few days and late death within a few weeks or months[2,3]. Early death is mainly caused by an aggressive inflammatory response, while persistent immunosuppression leads to late death. Owing to the mechanism of late immunosuppression not being clear, immunomodulatory treatment is not yet very effective, and more than 40 large clinical studies of early anti-inflammatory therapy have also failed; early recognition might be an important way to improve the treatment of sepsis in the short term[4]. At present, Sepsis-3 is newly defined as sequential impairment of organ function due to suspected infection along with the Sequential “Sepsis-related” Organ Failure Assessment (SOFA) score increased 2 points or more[5], which emphasizes organ dysfunction caused by infection. Although Sepsis-3 increased the specificity of in-hospital diagnosis[6], it was not widely used in clinical practice because of its multiple complex indicators; it is difficult to carry out rapidly and widely in low and middle-income areas, especially in emergency and outpatient departments, and in nonintensive care units. The quick SOFA (qSOFA) score, as a fast, simple, and noninvasive screening tool, is widely used in clinical practice. However, Askim et al[7] found that the qSOFA score had a low sensitivity to screen sepsis, and Williams et al[8] found that the sensitivity was only 29.7% when the qSOFA score was ≥ 2 points for screening sepsis. Thus, the qSOFA score as a rapid screening tool for sepsis remains controversial.
In clinical practice, the clinical symptoms of patients with pulmonary infections are often conspicuous, which are likely to arouse the vigilance and attention of clinicians. Therefore, for outpatients with pulmonary infection, sepsis screening tools usually are less necessary. However, patients with nonpulmonary infections, such as abdominal and urinary tract infections, are more likely to deteriorate into sepsis or septic shock, with the incidence of both as high as 50%9. Therefore, these patients are more likely to need tools for rapid sepsis screening. Usually, a good screening tool should not only have sufficient sensitivity and specificity, but also be able to reflect the physiological characteristics of the disease.

Sepsis is a severe systemic inflammatory response that manifests with widespread inflammation, as well as endothelial and coagulation dysfunction[10]. A mass of studies has shown that sepsis patients are associated with different degrees of coagulopathy, which exists over the whole process in sepsis[11]. Stimulated by inflammatory factors, coagulopathy appears from the early pro-coagulant state of sub-clinical symptoms to the disseminated intravascular coagulation (DIC) at the terminal stage [12]. The platelet count, an indicator of coagulopathy status, also appear in the diagnostic criteria of Sepsis-3[13]. Thus, further exploration of the indicators of coagulation function status is expected to develop new screening tools for sepsis. Currently, there are many tools for coagulation function tests, such as conventional coagulation examinations [including parameters: Prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), etc.], thromboelastography (TEG)[12], rotational thromboelastometry (ROTEM)[14], etc. However, TEG and ROTEM are more commonly used in cardiovascular surgery to evaluate platelet function, coagulation and fibrinolytic systems, and blood transfusion in the early resuscitation stage of trauma patients[15,16]. In addition, TEG and ROTEM cannot be routinely performed in medical institutions at all levels. In contrast, the conventional coagulation examinations can be used as screening tools for the early and rapid identification of sepsis. In particular, the development of Point-of-Care INR Test further shorten its detection time[17]. Currently, blood cell analysis, as a routine test, has been widely performed in clinical practice. Thus, the purpose of this study was to explore the efficiency of routine indicators of blood cells and coagulation function in the early rapid recognition of adult nonpulmonary infectious sepsis.

MATERIALS AND METHODS

Study population
This was a prospective observational study with a small sample size conducted in the Department of the Emergency and Intensive Care Unit of The First Affiliated Hospital of Chongqing Medical University, which is a 3200-bed tertiary care teaching hospital with an annual load of approximately 154000 patients. Patients with suspected infection were enrolled in this study from August 2019 to July 2020. The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University in compliance with the Declaration of Helsinki.

According to the Sepsis-3 criteria, the study subjects were divided into nonsepsis and sepsis groups. There were not consecutive patients enrolled. The inclusion criteria were the following: Age > 18-years-old and not limited by sex; and patients with confirmed nonpulmonary infections. The exclusion criteria were the following: Age < 18-years-old; patients with some preexisting diseases that may have notably affected their coagulation function, such as chronic liver diseases, hematologic system diseases, or patients who had previously undergone long-term treatment with immunosuppressants or anticoagulants; and those patients with incomplete data. The sex, age, and other basic data of all of the included patients were recorded. Acute Physiology and Chronic Health Evaluation II (APACHE II), SOFA and qSOFA scores were assessed on the day of admission within 24 h. These indicators, as well as white blood cell (WBC), neutrophil count (N#), lymphocyte count (L#), neutrophil-lymphocyte count ratio (NLCR), platelets (PLT), PT, INR and APTT, were recorded. Patients were assigned to the sepsis group when their SOFA score increased by 2 or more points, that is, when they met the diagnostic criteria for Sepsis-3.

Defining suspected infection and low-medium-high risk of sepsis
The first suspected infections were defined as a combination of antibiotics (either orally or intravenously) and body fluid cultures (pleural effusion, blood, abdominal effusion, urine, etc.). We need make sure that the combination of culture and antibiotics occurred within a specific time frame. If antibiotics were given first, culture
samples need be obtained within 24 h. If culture samples were performed firstly, antibiotics must be given within 24 h. The time at which either of the above two events occurred was defined as the "onset" of infection. The sites of infection in deep tissue were determined by CT scan, while superficial lesions could be identified by physical examination. In order to obtain the predictive efficacy of different INR values on the low, medium and high risk of sepsis, we defined the positive predictive rate below 10%, around 50%, and above 85% as low, medium and high risk of sepsis, respectively.

**Relevant biomarkers and determination**

Peripheral venous blood samples were collected immediately after admission. Peripheral blood cell (including WBC, L#, N#, NL, PLT) were analyzed by the Sysmex XN-9000 (Kobe, Japan) through flow cytometry, and coagulation tests (including INR, PT, APTT) were measured with the Sysmex CS-5100 (Shanghai, China). All the tests were carried out in the Medical Laboratory of our hospital according to the standard procedures, the quality of which have been certified by the American Society of Pathologists.

**Statistical analysis**

The SPSS software, version 24.0 (IBM Corp. Armonk, NY, United States) and MedCalc software, version 19.0 (MedCalc Software, Belgium) were used for statistical analysis. All of the measured data in this study were subject to normal distributions, which were analyzed by the Kolmogorov-Smirnov test. Data were expressed as mean ± SD. For comparisons of two independent group of samples, Student’s t-test was employed. The chi-square test was used to compare the composition ratio between the two groups. Logistic regression analysis was performed to analyze the significance of INR in the early identifying of sepsis, through the univariate and multivariate analysis (forward, LR). The receiver operating characteristic (ROC) curves were plotted by the software. INR, PT, PLT, WBC, NLCR and qSOFA were compared for their efficacy in the early identification of sepsis, according to the area under their ROC curves (AUC). The cut-off points, sensitivities, specificities, positive predictive values, and negative predictive values of these indicators were, respectively, calculated to evaluate their diagnostic efficiency. Relationship of INR value with SOFA score and APACHE II score were analyzed through Spearman’s rank correlation.

**RESULTS**

**Patient enrollment and comparison of baseline characteristics**

301 patients were initially enrolled in this study, of whom 201 met all the inclusion criteria and were identified as study subjects (Figure 1). The baseline characteristics of the patients are shown in Table 1. There were no differences between the nonsepsis and sepsis groups in sex, age, or infection site (all $P > 0.05$), indicating that the baseline data were comparable.

The comparison of WBC, NLCR, INR, PLT, PT, APTT and other indices and levels between the sepsis and nonsepsis groups is shown in Table 2, and it was found that all of them were significantly higher in the sepsis group than in the nonsepsis group ($P < 0.05$).

**Analysis of factors influencing the identification of sepsis**

Univariate and multivariate analyses for the diagnosis of sepsis showed that WBC, NLCR, the INR, PLT, PT, APTT, and qSOFA were of significance in the diagnosis of sepsis ($P < 0.05$) (Table 3). Logistic regression multivariate analysis was performed on WBC, NLCR, the INR, PLT, PT, APTT, and qSOFA, among which WBC, NLCR, the INR, PLT, and PT were statistically significant ($OR = 0.875, 95\%CI: 0.772-0.992, P = 0.037; OR = 1.145, 95\%CI: 1.069-1.226, P < 0.001; OR = 27.106, 95\%CI: 5.038-145.825, P < 0.001; OR=0.981, 95\%CI: 0.97-0.991, P < 0.001; OR = 1.475, 95\%CI: 1.032-2.106, P = 0.033$, respectively); Thus, WBC, NLCR, the INR, PLT, and PT were associated with the diagnosis of sepsis, while APTT and qSOFA were not.

**Comparative analysis of ROC curves**

ROC curve analysis displayed that the INR had the largest AUC value for the diagnosis of sepsis: 0.918 (95\%CI: 0.857-0.959) (Figure 2 and Table 4). The AUC values for other biomarkers were, respectively, as follows: PT 0.868 (95\%CI: 0.796-0.921); PLT 0.841 (95\%CI: 0.766-0.9); NLCR 0.83 (95\%CI: 0.754-0.891); qSOFA 0.638 (95\%CI: 0.548-
Table 1 Population and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sepsis</th>
<th>Nonseps</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52 (48.1)</td>
<td>59 (55.7)</td>
<td>0.083</td>
</tr>
<tr>
<td>Female</td>
<td>56 (51.9)</td>
<td>47 (44.3)</td>
<td></td>
</tr>
<tr>
<td>Age, yr (mean ± SD)</td>
<td>55 ± 9</td>
<td>52 ± 15</td>
<td>0.12</td>
</tr>
<tr>
<td>Body mass index (mean ± SD)</td>
<td>24.1 ± 2.2</td>
<td>23.8 ± 2.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Site of infection, n (%)</td>
<td></td>
<td></td>
<td>0.832</td>
</tr>
<tr>
<td>Abdominal</td>
<td>50 (46.3)</td>
<td>47 (44.3)</td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>36 (33.3)</td>
<td>35 (33.0)</td>
<td></td>
</tr>
<tr>
<td>Skin and others</td>
<td>14 (13.0)</td>
<td>18 (17.0)</td>
<td></td>
</tr>
<tr>
<td>Multiple sites</td>
<td>8 (7.4)</td>
<td>6 (5.7)</td>
<td></td>
</tr>
</tbody>
</table>

SD: Standard deviation.

Table 2 Comparison of the international normalized ratio, white blood cell, neutrophil-lymphocyte count ratio, platelet, prothrombin time, activated partial thromboplastin time, Sequential “Sepsis-related” Organ Failure Assessment scores, quick Sequential “Sepsis-related” Organ Failure Assessment scores and Acute Physiology and Chronic Health Evaluation II scores between the sepsis and nonsepsis groups

<table>
<thead>
<tr>
<th></th>
<th>Sepsis</th>
<th>Nonseps</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (× 10^9/L)</td>
<td>12.90 ± 8.76</td>
<td>9.88 ± 5.09</td>
<td>0.022</td>
</tr>
<tr>
<td>NLCR</td>
<td>28.45 ± 21.05</td>
<td>10.44 ± 11.87</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>INR</td>
<td>1.49 ± 0.47</td>
<td>1.11 ± 0.15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PLT (× 10^9/L)</td>
<td>135.09 ± 92.35</td>
<td>229.5 ± 72.83</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PT (s)</td>
<td>17.42 ± 4.76</td>
<td>13.86 ± 1.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>46.06 ± 10.30</td>
<td>36.88 ± 12.11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SOFA</td>
<td>6.93 ± 2.69</td>
<td>0.72 ± 0.45</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>qSOFA</td>
<td>1.17 ± 0.66</td>
<td>0.79 ± 0.75</td>
<td>0.003</td>
</tr>
<tr>
<td>APACHE II</td>
<td>18.81 ± 6.90</td>
<td>9.29 ± 4.14</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. APACHE II: Acute Physiological and Chronic Health Score II; APTT: Activated partial thromboplastin time; INR: International normalized ratio; NLCR: Neutrophil-lymphocyte count ratio; PLT: Platelet; PT: Prothrombin time; qSOFA: Quick Sequential “Sepsis-related” Organ Failure Assessment; SD: Standard deviation; SOFA: Sequential “Sepsis-related” Organ Failure Assessment; WBC: White blood cell.

0.721); and WBC 0.599 (95%CI: 0.508-0.684). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for WBC, NLCR, the INR, PT, PLT, and qSOFA are depicted in Table 4. The sensitivity and specificity were 90.0% (95%CI: 0.805-0.959) and 84.48% (95%CI: 0.726-0.927), and the PPV and NPV were 87.5% (95%CI: 0.793-0.928) and 87.5% (95%CI: 0.775-0.934), respectively, when the INR cutoff value was 1.22.

The correlation of INR with SOFA and APACHE II score, and low-medium-high risk of sepsis according to INR

Since SOFA score and APACHE II score are not Gaussian distribution, Spearman’s rank correlation method was used. It can be found that there is a strong correlation between INR value and SOFA score (r = 0.660, 95%CI: 0.574-0.731, P < 0.001), while there is a weak correlation between INR value and Apache II score (r = 0.457, 95%CI: 0.341-0.560, P < 0.001). When INR value was less than or equal to 1.17, 1.20 and greater than or equal to 1.22, respectively, with PPV of 8.24%, 55.6% and 87.5%, there were low, medium, and high risk of sepsis (Figure 3).
### Table 3: Analysis of influencing factors for the diagnosis of sepsis

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>WBC (× 10^9/L)</td>
<td>1.066 (1.007-1.128)</td>
<td>0.029</td>
</tr>
<tr>
<td>NLCR</td>
<td>1.092 (1.051-1.135)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>INR</td>
<td>35.214 (12.887-96.223)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PLT (× 10^9/L)</td>
<td>0.985 (0.980-0.991)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PT (s)</td>
<td>1.686 (1.458-2.903)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>1.091 (1.045-1.139)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>qSOFA</td>
<td>2.122 (1.265-3.559)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

APTT: Activated partial thromboplastin time; CI: Confidence intervals; INR: International normalized ratio; NLCR: Neutrophil-lymphocyte count ratio; OR: Odds ratio; PLT: Platelet; PT: Prothrombin time; qSOFA: Quick Sequential “Sepsis-related” Organ Failure Assessment; WBC: White blood cell.

### Table 4: Performance characteristics of the single biomarker for diagnosing sepsis

<table>
<thead>
<tr>
<th></th>
<th>AUC (95% CI)</th>
<th>Cut-off value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (× 10^9/L)</td>
<td>0.599 (0.508-0.684)</td>
<td>11.29</td>
<td>48.57</td>
<td>72.41</td>
<td>68</td>
<td>53.8</td>
</tr>
<tr>
<td>NLCR</td>
<td>0.83 (0.754-0.891)</td>
<td>11.86</td>
<td>81.43</td>
<td>77.59</td>
<td>81.4</td>
<td>77.6</td>
</tr>
<tr>
<td>INR (× 10^9/L)</td>
<td>0.918 (0.857-0.959)</td>
<td>1.22</td>
<td>90</td>
<td>84.48</td>
<td>87.5</td>
<td>87.5</td>
</tr>
<tr>
<td>PLT</td>
<td>0.841 (0.766-0.9)</td>
<td>180</td>
<td>80</td>
<td>82.76</td>
<td>84.8</td>
<td>77.4</td>
</tr>
<tr>
<td>PT (s)</td>
<td>0.868 (0.796-0.921)</td>
<td>15.3</td>
<td>80</td>
<td>87.93</td>
<td>88.9</td>
<td>78.5</td>
</tr>
<tr>
<td>qSOFA ≥ 2</td>
<td>0.638 (0.548-0.721)</td>
<td>28.57</td>
<td>79.31</td>
<td>62.5</td>
<td>47.9</td>
<td></td>
</tr>
</tbody>
</table>

AUC: Area under curves; INR: International normalized ratio; NLCR: Neutrophil-lymphocyte count ratio; NPV: Negative predictive value; PLT: Platelet; PT: Prothrombin time; PPV: Predictive positive value; qSOFA: Quick Sequential “Sepsis-related” Organ Failure Assessment; WBC: White blood cell; 95% CI: 95% confidence intervals.

### DISCUSSION

Early diagnosis and timely treatment of sepsis can improve the prognosis and reduce the mortality of sepsis. Although Sepsis-3 revealed organ dysfunction caused by infection, it is difficult to diagnose early for patients who have severe infections not reaching significant organ failure[13]. In clinical practice, blood culture is still used to diagnose sepsis. Due to culture time, it will take a longer time and has a less positive rate, it usually leads to delayed and missed diagnoses of sepsis. Exploring new and effective markers for the screening of sepsis is necessary. Zboromyrska et al[18] studied multiplex real-time polymerase chain reaction, the Magicplex™ Sepsis test, the specificity of which was up to 95%, while the sensitivity was only 29%. Dong et al[19] found that members of the miR-148 family (miR-148A/B and miR-152) were candidate biomarkers for sepsis by studying the Gene Expression Omnibus dataset GSE12624, but further study is required to evaluate the diagnostic performance. Guo et al[20] found that the AUC value of miR-495 in the diagnosis of sepsis was 0.915 when the cutoff value was 0.655, the sensitivity was 89.5%, and the specificity was 83.0%. Although all these new markers have their own advantages, the disadvantage is that their detection takes a long time, costs a lot, and has limited efficiency, which is difficult to carry out in economically underdeveloped areas. As we learn more about the pathophysiology of sepsis, we may be able to go back and develop new screening indicators for tests routinely performed in the laboratory.

Coagulopathy is one of the characteristic pathophysiological changes of sepsis, which exists across the whole process in sepsis and is a critical factor for the occurrence, development, and prognosis of sepsis[21]. With the persistence of infection or sepsis, the consumption of coagulation factors and decrease of platelets will occur, as well as the bleeding and dysfunction of the skin, mucous membranes and other...
Figure 1  Study population.

Figure 2  Receiver operating characteristic curve of white blood cell, neutrophil-lymphocyte count ratio, platelet, prothrombin time, international normalized ratio and quick Sequential “Sepsis-related” Organ Failure Assessment score within 24 h after admission between sepsis and nonsepsis. The results showed that the area under the curve of international normalized ratio (INR), prothrombin time (PT), neutrophil-lymphocyte count ratio (NLCR), platelet (PLT), quick Sequential “Sepsis-related” Organ Failure Assessment (qSOFA), and white blood cell count (WBC) in the diagnosis of sepsis were 0.918, 0.868, 0.83, 0.841, 0.638 and 0.599, respectively, and they were statistically significant ($P < 0.05$). The study indicates that the INR could be a helpful diagnostic biomarker in sepsis.

The results showed that the area under the curve of international normalized ratio (INR), prothrombin time (PT), neutrophil-lymphocyte count ratio (NLCR), platelet (PLT), quick Sequential “Sepsis-related” Organ Failure Assessment (qSOFA), and white blood cell count (WBC) in the diagnosis of sepsis were 0.918, 0.868, 0.83, 0.841, 0.638 and 0.599, respectively, and they were statistically significant ($P < 0.05$). The study indicates that the INR could be a helpful diagnostic biomarker in sepsis.
Lyons et al.[30] found that coagulopathy was closely related to the severity and mortality of sepsis, and with the extension of the INR, the more severe that the sepsis was, the higher that the mortality was. Recent studies of coronavirus disease 2019 patients with secondary bacterial infection have also reported that prolonged INR time is a monitoring indicator in severe patients, and the longer the INR time is, the worse the prognosis of patients[31-33]. This study also found that there was a strong correlation between INR value and SOFA score ($r = 0.660$). The SOFA score was correlated with the prognosis of sepsis, which also suggested that INR had a good predictive value of nonpulmonary infectious sepsis from another perspective. In particular, when INR was less than or equal to 1.17, between 1.17 and 1.20, or greater than or equal to 1.22, the high positive predictor rates of sepsis could be broken into low, medium and high levels. All the above related studies have indicated that INR could be used as one of the early screening indicators for sepsis; however, there are many underlying diseases that can affect INR. Although relevant conclusions in this study were drawn under corresponding exclusion criteria, it is true that in clinical practice, there are still a small number of potentially infected patients with those underlying diseases that cannot be detected at initial presentation. For this condition, when their INR reach the high-risk value of sepsis, e.g., more than 1.22, sepsis should be highly suspected because they are at higher risk of adverse outcomes when they are missed.

Many studies have found qSOFA to be of low sensitivity as a sepsis screening tool [7]. Our study also confirmed that the sensitivity of qSOFA was only 28.57%, the specificity was 79.31%, and the AUC was 0.638 (95% CI: 0.548-0.721). However, because qSOFA is a non-invasive and fast screening method, setting it as a preliminary screening is still feasible. Because infection and stress can cause neutropenia and lymphopenia, neutrophil lymphocyte count ratio (NLCR) has attracted more and more attention of clinical researchers[34]. Fuss et al.[35] found that the NLCR level of sepsis
Zhang J et al. INR in nonpulmonary sepsis screening

Platelets play an important role in sepsis because they are at the intersection of the immune system, coagulation cascade, and endothelial cells[37,38]. Patients who had sustained thrombocytopenia or a drop in PLT of > 30% during their ICU stay had higher mortality[39]. Therefore, thrombocytopenia was considered to be an independent risk factor for death in patients with sepsis or septic shock[40]. However, as one of the diagnostic criteria for Sepsis-3, Sepas et al[41] found, when the platelet count was less than 229 × 10^9/L, the sensitivity and specificity of the diagnosis of acute appendicitis were only 24% and 75%, respectively. Similarly, our study also showed that when the platelet count was less than 180 × 10^9/L, the sensitivity and specificity of the diagnosis of sepsis were 80.0% and 82.76%, respectively, which were still lower than those of the INR. Furthermore, the base range of platelets was larger, and the sensitivity was lower, which could easily lead to delayed diagnosis of sepsis with delayed treatment and increased mortality of sepsis patients. Therefore, whether INR could replace platelet count as one of the indicators of SOFA score in sepsis criteria in the future still needs further studies with large sample size and multiple centers.

CONCLUSION

The INR has high specificity and sensitivity in the early identification of adult nonpulmonary infectious sepsis. When the INR value exceeds 1.22 in patients with nonpulmonary infection, sepsis should be highly suspected, especially for those patients without preexisting underlying disease or medication history that affects coagulation function. Due to its low cost, rapid detection and easy interpretation of the results, it is particularly suitable for the preliminary screening of sepsis in emergency patients, outpatient patients and patients in economically backward areas.

ARTICLE HIGHLIGHTS

Research background
Currently, there is a lack of sepsis screening tools that can be widely used worldwide. Pulmonary sepsis can be of sufficient concern to physicians due to their noticeable symptoms, which usually rely less on screening tools.

Research motivation
To investigate the efficiency of the international normalized ratio (INR) for the early rapid recognition of adult nonpulmonary infectious sepsis.

Research objectives
A total of 108 sepsis patients and 106 nonsepsis patients were enrolled according to relevant inclusion and exclusion criteria.

Research methods
Commonly used clinical indicators, such as white blood cell, neutrophil count, lymphocyte count, neutrophil-lymphocyte count ratio (NLCR), platelets (PLT), prothrombin time, INR, activated partial thromboplastin time and quick Sequential “Sepsis-related” Organ Failure Assessment (qSOFA) scores, were recorded within 24 h after admission. The diagnostic performances of them were analyzed and compared through multivariate logistic regression analysis, Spearman correlation, and receiver operating characteristic curve analysis.

Research results
The level of the INR was significantly prolonged in the sepsis group. The INR had high diagnostic performance for sepsis, with an area under the curve value of 0.918 (95%CI: 0.857-0.959), when the preexisting diseases that significantly affect coagulation function were excluded. The diagnostic efficacy of the INR was more significant than that of NLCR, PLT and qSOFA (P < 0.05). Moreover, INR levels of 1.17, 1.20, and 1.22 in burn patients was significantly higher than in common burn patients. Relevant studies have also found that NLCR could be a simple and feasible indicator for the prediction of sepsis after percutaneous nephrolithotomy[36]. Our study showed that the diagnostic value of NLCR in diagnosing adult nonpulmonary infectious sepsis was lower than that of the INR.
could be used to delineate patients as low, medium or high risk for nonpulmonary infectious sepsis, respectively.

**Research conclusions**

The INR is a promising and easily available biomarker for diagnosis, and it can be used as one of the indicators for early screening of adult nonpulmonary infectious sepsis. When its value is higher than the optimal cutoff (1.22) value, high vigilance is required for adult nonpulmonary infectious sepsis.

**Research perspectives**

Due to its low cost, fast detection and easy interpretation, INR is suitable for the primary screening of sepsis for emergency patients and outpatients, particularly in low and middle-income countries. Sepsis is highly suspected when the INR value exceeds 1.22 in patients with non-pulmonary infection, especially for those patients without preexisting underlying disease or medication history that affects coagulation function.

**ACKNOWLEDGEMENTS**

We would like to thank Prof. Peng B, Department of Statistics, Chongqing Medical University, for his advice on the statistics in this study.

**REFERENCES**


requiring invasive mechanical ventilation (COVID-19 HD): a structured summary of a study protocol. 


Randomized Controlled Trial

Clinical effectiveness of adding probiotics to a low FODMAP diet: Randomized double-blind placebo-controlled study

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Author contributions: Turan B, Soytürk M and Bengi G contributed equally to this work, designed the research and drafted the manuscript; Soytürk M and Akpınar H provided administrative and technical support; Cehreli R participated in the regulation, follow-up and evaluation of the diets of patients.

Institutional review board statement: The study was reviewed and approved by the Institutional Ethics committee of Dokuz Eylül University Izmir.

Clinical trial registration statement: This study was conducted with the approval of the Clinical Research Ethics Committee of Dokuz Eylul University (approval No. 2017/01-02) and the Medicines and Medical Devices Agency of the Ministry of Health of Turkey (approval No. 67116).

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

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Abstract

BACKGROUND
There are various studies showing the relationship between irritable bowel syndrome (IBS) and diet, and some dietary adjustments are recommended to reduce symptoms. In recent years, there is a growing number of studies that show a 4-8 wk low fermentable oligo, di- and mono-saccharides and polyols (FODMAP) diet has a 50%-80% significant effect on symptoms in IBS patients. There is strong evidence suggesting that changes in fecal microbiota have an impact on IBS pathogenesis. Based on this argument, probiotics have been used in IBS treatment for a long time. As is seen, the FODMAP diet and probiotics are used separately in IBS treatment.

AIM
To evaluate the effectiveness of adding probiotics to a low FODMAP diet to control the symptoms in patients with IBS.

METHODS
The patients who were admitted to the Gastroenterology Clinic of Dokuz Eylül University Hospital and diagnosed with IBS according to Rome IV criteria were enrolled into the study. They were randomized into 2 groups each of which consisted of 50 patients. All patients were referred to a dietitian to receive dietary recommendations for the low FODMAP diet with a daily intake of 9 g. The patients were asked to keep a diary of foods and beverages they consumed. The patients in Group 1 were given supplementary food containing probiotics (2 g) once a day in addition to their low FODMAP diet, while the patients in Group 2 were given a placebo once a day in addition to their low FODMAP diet. Visual
INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional disorder characterized by symptoms of chronic abdominal pain, changes in bowel habits and defecation[1]. Although its prevalence varies by country, about one in five people around the world is affected by this disease. IBS is more common among women and people under the age of 50. The course of this disorder is chronic, episodic or relapsing[2]. The pathogenesis of IBS is complex and multifactorial. Visceral hypersensitivity, psychosocial factors, changes in the gut-brain axis and gastrointestinal motility, immune dysregulation and dysbiosis are considered to be the most critical factors that affect etiopathogenesis[3]. IBS causes recurring admission to clinics, redundant medical examinations and unnecessary procedures. Thus, it not only deteriorates the quality of life of patients, but it also increases healthcare costs significantly and causes workforce loss[4].
In addition to medical treatment, the doctor-patient relationship and diet and lifestyle changes play an essential role in the treatment of IBS[5]. Treatment may include various diets, antispasmodics, loperamide, antidepressants, psychological treatments (psychotherapy, hypnosis, etc.), laxatives, biofeedback, probiotics or prebiotics. Although these treatment(s) relieve the symptoms in some patients, some patients do not get better sufficiently, hence requiring other treatment options.

There are various studies showing the relationship between IBS and diet, and some dietary adjustments are recommended to reduce symptoms. One of them is the elimination diet, which is widely used in IBS treatment. In recent years, there is a growing number of studies that show a 4-8 wk low fermentable oligo, di- and monosaccharides and polyols (FODMAP) diet has a 50%-80% significant effect on symptoms in IBS patients[3,6,7]. The term FODMAP refers to all short-chain carbohydrates. These substances are not appropriately absorbed and rapidly fermented by intestinal bacteria. Thus, it is thought that intraluminal fluid content and an increase in colonic hydrogen production increase the symptoms[8]. Excessive consumption of these carbohydrate derivatives (fructose, fructooligosaccharides, sorbitol) may trigger IBS symptoms due to their direct or indirect effects on microbiota, intestinal barrier, immune response and visceral sensitivity[9-11]. Patient’s demographic characteristics, microbiota composition and metabolism as well as IBS subtype and patient’s adherence to diet in particular may affect the effectiveness of a low FODMAP diet[12]. Evidence suggests that microbiota plays a vital role in the pathophysiology of IBS[13]. The studies show that Lactobacillus and Bifidobacterium decrease while proinflammatory bacterial species, Enterobacteriaeae in particular, increase relatively in IBS[12]. It is thought that low FODMAP diet’s reducing colonic motility may harm bacterial flora. Hence, according to a study on the fecal microbiota comparing the patients on a low FODMAP diet and those on a regular diet, it was found that Bifidobacteria spp. rate and concentration decrease in those who followed a low FODMAP diet[14]. Another study showed that the rate of fecal bacteria in those who follow a low FODMAP diet is 47% less than those who follow an Australian-type diet, and there is an increase in the number of harmful bacteria with a decrease in beneficial bacteria[15].

However, there are also some studies showing that although a low FODMAP diet decreases the number of bacteria, it does not affect their diversity[16]. The low FODMAP diet positively affects IBS symptoms, but it may have adverse effects on colon health. The components of the FODMAP diet act as a substrate for bacteria[17]. Butyrate, a short-chain fatty acid formed as a result of bacterial fermentation, is not only an energy source for colon epithelium but also an important regulator and immunomodulator for colonocyte proliferation and apoptosis[18,19]. Recent studies have reported that a low FODMAP diet reduces proinflammatory cytokines such as interleukin 6 and interleukin 8. It also changes the content of fecal bacteria and decreases the amount of fecal butyric acid[12]. Furthermore, there is doubt regarding the long-term sustainability of this diet, its long-term effects on symptoms and possible nutritional deficiencies[3].

Probiotics balance intestinal flora by limiting the colonization of pathogenic bacteria [15]. As mentioned above, there is strong evidence suggesting that changes in fecal microbiota have an impact on IBS pathogenesis. Based on this argument, probiotics have been used in IBS treatment for a long time[20].

As is seen, the FODMAP diet and probiotics are used separately in IBS treatment. These are preferred treatments today thanks to their relatively high efficiency and low side effects. Combining both may enhance symptom control in patients. However, the negative impact of a low FODMAP diet on intestinal flora and its long-term side effects are still ambiguous. Furthermore, although the rate of adherence to diet is high, there is also a group of patients who cannot tolerate it. We added probiotics to the low FODMAP diet in our study considering that it may affect symptom control in IBS and that it has a potential to prevent possible harmful effects of the low FODMAP diet on the intestinal flora. This randomized double-blind prospective controlled study aimed to find out how probiotic supplementation to a low FODMAP diet affected symptoms in all subtypes of IBS.

**MATERIALS AND METHODS**

**Patients and study design**

This randomized double-blind prospective study included 100 patients between the ages of 18 and 65 years, who were admitted to the Gastroenterology Clinic of Faculty
of Medicine of Dokuz Eylul University between December 1, 2017 and December 24, 2018, who were newly and/or previously diagnosed with IBS according to Rome IV criteria and whose IBS treatment were not modified in the last 4 wk. For both treatment groups, the mean effect size was determined as 0.5 for the comparison of IBS symptom severity scale (IBS-SSS) and Visual Analog Scale (VAS) scores, taking 50 patients for each group at 80% power and 95% confidence interval. Based on their IBS subtypes, the patients were classified as IBS-D (diarrhea dominant type), IBS-C (constipation dominant type) and IBS-mixed type. This prospective study was designed in compliance with the ethical rules set forth by the Helsinki Declaration, and we took the consent of all patients by asking them to fill in informed consent forms before the study. Patients were randomly assigned to two groups as follows: 21 d low FODMAP diet + probiotic (Group 1) and 21 d low FODMAP diet + placebo (Group 2). We tossed a coin to randomly categorize the patients into two groups, and neither the patient nor the researcher was informed about the treatment administered to the patient. When we ran out of the product in the probiotic or placebo group, the patient was given the product used in the other group.

Patients with inflammatory bowel disease, celiac disease, history of bowel operation and diabetes mellitus who were currently using food supplements such as probiotics were excluded from the study. In addition, patients with alarm symptoms such as fever, anemia and weight loss, those who had a family history of colon cancer, patients whose body mass index was 18 and below and pregnant women were excluded from the study. Based on the above-mentioned exclusion criteria, 12 patients were excluded from the study (Figure 1).

The demographic data (age, gender, occupation) of all patients were recorded, and they were asked in detail about their history of chronic diseases (hypertension, cerebrovascular disease, hypothyroidism, coronary artery disease, osteoporosis, asthma, depression, urinary incontinence, neuromuscular disorders, severe osteoarthritis), drugs they use, operations they had (thyroidectomy, tonsillectomy, appendectomy, etc.), dominant symptoms and treatments they received.

This study was conducted with the approval of the Clinical Research Ethics Committee of Dokuz Eylul University (approval no. 2017/01-02) and the Medicines and Medical Devices Agency of the Ministry of Health of Turkey (approval No. 67116).

**Dietary advice and probiotic/placebo**

An expert dietitian had a face-to-face conversation for at least 45 min with each patient to explain the diet to be followed throughout the study. Furthermore, patients were given the low FODMAP diet therapy (Table 1) and informed about the foods they must avoid (Supplementary material) to ensure that they consume sufficient amounts of calcium and fiber.

Nobel Ilac San. ve Tic. A.S. Istanbul, Turkey® provided probiotic and placebo drugs. As a probiotic, supplementary food containing probiotics (2 g) once a day was prescribed to patients. This product contained *Streptococcus thermophilus* (5.4x10^8 cfu), *Bifidobacterium lactis* (5.4 x 10^8 cfu), *Lactobacillus acidophilus* (4.5 x 10^8 cfu), *Lactobacillus plantarum* (4 x 10^8 cfu) and *Bifidobacterium breve* (4 x 10^8 cfu). Placebo products were identical capsules without any probiotics. The active and placebo products were similar in appearance, taste and smell and bottled in identically.

All patients were asked to keep a diary of the foods and beverages they consumed. Furthermore, they were called by phone every week to follow up with their adherence to diet in terms of probiotic/placebo compliance. We used the diaries of the patients to evaluate their adherence to the given diet. The percentage of cheatings within a diet during the day was calculated separately, and the daily dietary compliance was averaged. Patients who adhered to their diet for 17 d (> 80%) of the 21 d diet were considered to have adhered to their diet. The symptoms of patients were evaluated with the below-mentioned scale and scoring systems before and after 21 d of a low FODMAP diet + placebo or a low FODMAP diet + probiotic and the resulting data were analyzed. During the study, the patients were not allowed to use drugs that could affect their symptoms (laxatives, antidiarrheal drugs, etc.).

**Evaluation of symptoms by questionnaires**

For patients diagnosed with IBS according to Rome IV criteria, we used the following scales for evaluation: VAS to evaluate pain before and after 21 d of a low FODMAP diet + probiotic/placebo, Bristol Stool Scale to evaluate IBS type and any changes in stool and IBS-SSS to evaluate the severity of IBS symptoms.

The following results were accepted as clinical improvement after the evaluation of 21 d treatment: a decrease of at least 50 points in the IBS-SSS score, a decrease of more than 10 mm in pain severity according to VAS and change in stool characterization to...
Table 1 Content of low fermentable oligo, di- and monosaccharides and polyols diet recommended for patients

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommended Intake (g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>1600-2000 kcal/d</td>
</tr>
<tr>
<td>Protein</td>
<td>75-90 g/d</td>
</tr>
<tr>
<td>Fat</td>
<td>75-85 g/d</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>186-240 g/d</td>
</tr>
<tr>
<td>Starch</td>
<td>120-25 g/d</td>
</tr>
<tr>
<td>Sugars</td>
<td>50-75 g/d</td>
</tr>
<tr>
<td>Non-starch polysaccharide</td>
<td>13-16 g/d</td>
</tr>
<tr>
<td>Total FODMAPs¹</td>
<td>9.0-9.6 g/d</td>
</tr>
<tr>
<td>Fructans</td>
<td>2.5-3.5 g/d</td>
</tr>
<tr>
<td>GOS</td>
<td>0.8-1.4 g/d</td>
</tr>
<tr>
<td>Lactose</td>
<td>4.3-4.5 g/d</td>
</tr>
<tr>
<td>Total fructose</td>
<td>12.7-5.9 g/d</td>
</tr>
<tr>
<td>Excess fructose</td>
<td>1.9-2.0 g/d</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>0.3-0.5 g/d</td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.1-0.2 g/d</td>
</tr>
</tbody>
</table>

¹Total fermentable oligo, di- and monosaccharides and polyols (FODMAPs) are calculated as the sum of individual carbohydrates including excess fructose (not total fructose). Data are mean total and individual FODMAPs (g/d), energy (kcal/d) and nutrient intake (g/d). FODMAPs: Fermentable oligo, di- and monosaccharides and polyols; GOS: Galacto-oligosaccharides.

Figure 1 Study flow diagram. IBS: Irritable bowel syndrome; FODMAP: Fermentable oligo, di- and monosaccharides and polyols; IBD: Irritable bowel disease.

Type 3 and Type 4 according to Bristol Stool Chart.

Statistical analysis

The SPSS 22.0 version (SPSS Inc, Chicago, IL, United States) package program was
used to perform all statistical analyses. Demographic data, symptoms and IBS subtypes were analyzed descriptively. The Shapiro-Wilk Test was used to test the compatibility of the numerical variables to normal distribution. Numerical variables were described with mean and standard deviation while categorical variables were described with frequency and percentage values. The Mann-Whitney U Test was used to compare differences between two independent means. The relationship between two independent categorical variables was measured using the \( \chi^2 \) Test. The Wilcoxon Signed-rank Test was used to compare the relationship between two dependent means. The conformity between two dependent categorical variables was evaluated using the Kappa Test. The Mann-Whitney U Test was used to determine the difference between two independent medians. The relationship between two independent numerical variables was analyzed using Spearman’s Correlation. The confidence level of the study was 95%, and the \( P \) value below 0.05 was considered to be significant.

**RESULTS**

**Subjects**

Fifteen patients (15%; 7 from Group 1, 8 from Group 2) out of 100 patients, who were included in the study, left the study during the follow-up period. The patients left the study due to the following reasons: workload, being unreachable by phone, increased bloating, family problems and difficulty in following the diet (Figure 1).

A total of 85 patients completed the study, 43 patients from Group 1 and 42 patients from Group 2. A total of 62 of them (72.9%) were female while 23 of them (27.1%) were male, and the mean age of the patients was 43.6 ± 13.0. Breakdown by gender shows that 33 patients (76.7%) in Group 1 and 29 patients (69.0%) in Group 2 were female. The mean age was 43.6 ± 12.2 in Group 1 and 43.6 ± 14.0 in Group 2, i.e. they were similar.

Some patients had comorbid diseases such as Hashimoto’s thyroiditis, hypertension and allergic asthma. In this study, 69.4% of the patients had a comorbid disease, while 30.6% did not have any comorbidities. A total of 35 (41.2%) patients underwent an abdominal operation, 19 (44.2%) of whom were in the probiotic group, while 16 (38.1%) of them were in the placebo group. The patients in both groups had similar demographic characteristics. Table 2 summarizes demographic data, comorbidities, history of treatments and drug use of all patients.

The breakdown of IBS subtypes shows that the most common group is IBS-C, followed by IBS-D. The least common type is mixed IBS (Table 3).

**Gastrointestinal symptoms response**

The VAS score, IBS-SSS total score and IBS-SSS sub-parameters measured before treatment were similar in both groups (Table 4).

The average VAS score of the patients in Group 1 before treatment was 4.6 ± 2.7 with an average IBS-SSS score of 310.0 ± 78.4. The mean VAS score decreased to 2.0 ± 1.9, and the mean IBS-SSS score decreased to 172.0 ± 93.0. The VAS score, IBS-SSS total score and IBS-SSS sub-parameter scores of Group 1 significantly reduced after treatment (\( P < 0.001 \)). In Group 1, the IBS-SSS score of 37 (86.04%) patients decreased by more than 50 points (Table 4).

The average VAS score of the patients in Group 2 before treatment was 4.7 ± 2.7 with an average IBS-SSS score of 317.0 ± 87.5. The mean VAS score decreased to 1.8 ± 2.0, and the mean IBS-SSS score decreased to 175.0 ± 97.7. The VAS score, IBS-SSS total score and IBS-SSS sub-parameter scores of Group 2 significantly reduced after treatment (\( P < 0.001 \)). In Group 2, the IBS-SSS score of 36 (85.71%) patients decreased by more than 50 points (Table 4). In conclusion, abdominal pain and symptoms in the scope of IBS-SSS in both groups decreased significantly after treatment. Furthermore, no side effects were observed in any of the patients that were included in this study.

The results showed that the scores of 38 (79.2%) out of 48 patients who had severe IBS before treatment improved after treatment. In Group 1 and Group 2, the IBS-SSS scores of 20 (80.0%) and 18 (78.3%) patients out of 25 and 23 patients, respectively, with severe IBS decreased after treatment. When we evaluated the changes in the VAS and IBS-SSS scores of the patients before and after the treatment, we observed that the scores decreased significantly in both groups, and the scores decreased similarly in Group 1 and Group 2 (Tables 5 and 6).

When changes in stool shape were analyzed with Kappa according to the Bristol Stool Scale after treatment, it was found that there were significant changes in both groups. When the results of all patients were analyzed, stool type after treatment was
### Table 2 Patients' demographic characteristics, comorbidities and treatments they received

<table>
<thead>
<tr>
<th></th>
<th>Total, n = 85</th>
<th>Group 1, n = 43</th>
<th>Group 2, n = 42</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>43.6 ± 13.0</td>
<td>43.6 ± 12.2</td>
<td>43.6 ± 14.0</td>
<td>0.888</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>62 (72.9)</td>
<td>33 (76.7)</td>
<td>29 (69.0)</td>
<td>0.425</td>
</tr>
<tr>
<td>Male</td>
<td>23 (27.1)</td>
<td>10 (23.3)</td>
<td>13 (31.0)</td>
<td></td>
</tr>
<tr>
<td>Employment status, n (%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>49 (57.6)</td>
<td>25 (58.1)</td>
<td>24 (57.1)</td>
<td>0.926</td>
</tr>
<tr>
<td>Yes</td>
<td>36 (42.4)</td>
<td>18 (41.9)</td>
<td>18 (42.9)</td>
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</tr>
<tr>
<td>Comorbid diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>67 (78.8)</td>
<td>36 (83.7)</td>
<td>31 (73.8)</td>
<td>0.263</td>
</tr>
<tr>
<td>Yes</td>
<td>18 (21.2)</td>
<td>7 (16.3)</td>
<td>11 (26.2)</td>
<td></td>
</tr>
<tr>
<td>Allergic asthma, n (%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>77 (90.6)</td>
<td>36 (83.7)</td>
<td>41 (97.6)</td>
<td>0.058</td>
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<td>8 (9.4)</td>
<td>7 (16.3)</td>
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<td>Hypertension, n (%)</td>
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<td></td>
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<tr>
<td>No</td>
<td>72 (84.7)</td>
<td>38 (88.4)</td>
<td>34 (81.0)</td>
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<td>Yes</td>
<td>13 (15.3)</td>
<td>5 (11.6)</td>
<td>8 (19.0)</td>
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<td>Gastritis, n (%)</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>77 (90.6)</td>
<td>37 (86.0)</td>
<td>40 (95.2)</td>
<td>0.265</td>
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<tr>
<td>Yes</td>
<td>8 (9.4)</td>
<td>6 (14.0)</td>
<td>2 (4.8)</td>
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</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td></td>
<td></td>
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<td></td>
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<td>78 (91.8)</td>
<td>40 (93.0)</td>
<td>38 (90.5)</td>
<td>0.713</td>
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<td>Yes</td>
<td>7 (8.2)</td>
<td>3 (7.0)</td>
<td>4 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>80 (94.1)</td>
<td>41 (95.3)</td>
<td>39 (92.9)</td>
<td>0.676</td>
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<td>Yes</td>
<td>5 (5.9)</td>
<td>2 (4.7)</td>
<td>3 (7.1)</td>
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<tr>
<td>Comorbidity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>26 (30.6)</td>
<td>12 (27.9)</td>
<td>14 (33.3)</td>
<td>0.587</td>
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<td>Yes</td>
<td>59 (69.4)</td>
<td>31 (72.1)</td>
<td>28 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Abdominal surgery, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>50 (58.8)</td>
<td>24 (55.8)</td>
<td>26 (61.9)</td>
<td>0.568</td>
</tr>
<tr>
<td>Yes</td>
<td>35 (41.2)</td>
<td>19 (44.2)</td>
<td>16 (38.1)</td>
<td></td>
</tr>
<tr>
<td>Drug use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systematic drug use, n (%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28 (32.9)</td>
<td>14 (32.6)</td>
<td>14 (33.3)</td>
<td>0.939</td>
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<tr>
<td>Yes</td>
<td>57 (67.1)</td>
<td>29 (67.4)</td>
<td>28 (66.7)</td>
<td></td>
</tr>
<tr>
<td>PPI use, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>67 (78.8)</td>
<td>32 (74.4)</td>
<td>35 (83.3)</td>
<td>0.315</td>
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<td>Yes</td>
<td>18 (21.2)</td>
<td>11 (25.6)</td>
<td>7 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric drug use, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>71 (83.5)</td>
<td>34 (79.1)</td>
<td>37 (88.1)</td>
<td>0.262</td>
</tr>
</tbody>
</table>
Turan B et al. Clinical effectiveness of probiotics and low FODMAP diet

<table>
<thead>
<tr>
<th></th>
<th>Group 1, n = 43</th>
<th>Group 2, n = 42</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCB use, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (16.5)</td>
<td>9 (20.9)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>No</td>
<td>69 (81.2)</td>
<td>36 (83.7)</td>
<td>33 (78.6)</td>
</tr>
<tr>
<td>Beta-blocker use, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (18.8)</td>
<td>7 (16.3)</td>
<td>9 (21.4)</td>
</tr>
<tr>
<td>No</td>
<td>75 (88.2)</td>
<td>38 (88.4)</td>
<td>37 (88.1)</td>
</tr>
</tbody>
</table>

Group 1: Low fermentable oligo, di- and monosaccharides and polyol diet + probiotic; Group 2: Low fermentable oligo, di- and monosaccharides and polyol diet + placebo. PPI: Proton pump inhibitor; CCB: Calcium canal blocker; SD: Standard deviation.

### Table 3 Irritable bowel syndrome sub-type breakdown by groups

<table>
<thead>
<tr>
<th>IBS subtype, n (%)</th>
<th>Total, n = 85</th>
<th>Group 1, n = 43</th>
<th>Group 2, n = 42</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>43 (50.6)</td>
<td>23 (53.5)</td>
<td>20 (47.6)</td>
<td>0.415</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (27.1)</td>
<td>9 (20.9)</td>
<td>14 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>19 (22.4)</td>
<td>11 (25.6)</td>
<td>8 (19.0)</td>
<td></td>
</tr>
</tbody>
</table>

Group 1: Low fermentable oligo, di- and monosaccharides and polyol diet + probiotic; Group 2: Low fermentable oligo, di- and monosaccharides and polyol diet + placebo. IBS: Irritable bowel syndrome.

### Table 4 Comparison of visual analogue scale and irritable bowel syndrome symptom severity scale scores before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td></td>
</tr>
<tr>
<td>VAS</td>
<td>4.6 ± 2.7</td>
<td>2.0 ± 1.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IBS-SSS</td>
<td>310.0 ± 78.4</td>
<td>172.0 ± 93.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pain severity</td>
<td>49.4 ± 24.1</td>
<td>24.4 ± 20.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Abdominal pain severity</td>
<td>52.9 ± 23.9</td>
<td>26.7 ± 21.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Abdominal distention severity</td>
<td>65.1 ± 25.1</td>
<td>34.3 ± 25.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Satisfaction with intestinal habits</td>
<td>70.9 ± 24.9</td>
<td>41.6 ± 33.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IBS quality of life</td>
<td>74.8 ± 22.1</td>
<td>44.6 ± 26.1</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

P': Comparison between both groups before treatment. Group 1: Low fermentable oligo, di- and monosaccharides and polyols (FODMAP) diet + probiotic, Group 2: low fermentable oligo, di- and monosaccharides and polyols diet + placebo. VAS: Visual analogue scale; IBS-SSS: Irritable bowel syndrome symptom severity scale; IBS: Irritable bowel syndrome; SD: Standard deviation.

evaluated as normal (type 3-4) in 19 out of 29 patients (65.5%) with stool type 5-6-7 (diarrhea predominant) and in 18 out of 34 patients (52.9%) with stool type 1-2 (constipation predominant). In Group 1, the stool type was evaluated as normal (type 3-4) after treatment in 9 (75.0%) out of 12 patients who had stool type 5-6-7 (IBS-D) and in 12 (70.6%) out of 17 patients who had stool type 1-2 (IBS-C). In Group 2, the stool type was evaluated as normal (type 3-4) after treatment in 10 (58.8%) out of 17 patients who had stool type 5-6-7 (IBS-D) and in 6 (35.3%) out of 17 patients who had stool type 1-2 (IBS-C) (Table 7). All patients were evaluated, and no severe side effects were observed except for increased bloating in 4 patients.
Table 5 Comparison of the change in visual analogue scale and irritable bowel syndrome symptom severity scale scores in both groups before and after treatment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Total, n = 85</th>
<th>Group 1, n = 43</th>
<th>Group 2, n = 42</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS [Median (min-max)]</td>
<td>-50.0 [-100.0-40.0]</td>
<td>-50.0 [-100.0-0.0]</td>
<td>-58.3 [-100.0-40.0]</td>
<td>0.778</td>
</tr>
<tr>
<td>IBS-SSS [Median (min-max)]</td>
<td>-47.3 [-100.0-30.0]</td>
<td>-43.5 [-93.0-0.0]</td>
<td>-50.0 [-100.0-30.0]</td>
<td>0.871</td>
</tr>
<tr>
<td>Pain severity</td>
<td>-50.0 [-100.0-50.0]</td>
<td>-50.0 [-100.0-0.0]</td>
<td>-50.0 [-100.0-50.0]</td>
<td>0.799</td>
</tr>
<tr>
<td>Abdominal pain severity</td>
<td>-50.0 [-100.0-50.0]</td>
<td>-50.0 [-100.0-0.0]</td>
<td>-50.0 [-100.0-50.0]</td>
<td>0.857</td>
</tr>
<tr>
<td>Abdominal distention severity</td>
<td>-50.0 [-100.0-0.0]</td>
<td>-50.0 [-100.0-0.0]</td>
<td>-50.0 [-100.0-0.0]</td>
<td>0.561</td>
</tr>
<tr>
<td>Satisfaction with intestinal habits</td>
<td>-50.0 [-100.0-203.0]</td>
<td>-50.0 [-100.0-100.0]</td>
<td>-50.0 [-100.0-203.0]</td>
<td>0.953</td>
</tr>
<tr>
<td>IBS quality of life</td>
<td>-50.0 [-100.0-51.5]</td>
<td>-50.0 [-100.0-0.0]</td>
<td>-50.0 [-100.0-51.5]</td>
<td>0.960</td>
</tr>
</tbody>
</table>

Group 1: Low fermentable oligo, di- and monosaccharides and polyols (FODMAP) diet + probiotic, Group 2: low fermentable oligo, di- and monosaccharides and polyols diet + placebo. VAS: Visual analogue scale; IBS-SSS: Irritable bowel syndrome symptom severity scale; IBS: Irritable bowel syndrome.

Table 6 Irritable bowel syndrome symptom severity scale scores before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Before treatment, n (%)</th>
<th>Kappa</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>All patients</td>
<td>Asymptomatic</td>
<td>3 (50.0)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>3 (50.0)</td>
<td>22 (71.0)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0 (0)</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0 (0)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Group 1</td>
<td>Asymptomatic</td>
<td>2 (66.7)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1 (33.3)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0 (0)</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Group 2</td>
<td>Asymptomatic</td>
<td>1 (33.3)</td>
<td>1 (6.2)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>2 (66.7)</td>
<td>11 (68.8)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>0 (0)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0 (0)</td>
<td>1 (6.2)</td>
</tr>
</tbody>
</table>

Group 1: Low fermentable oligo, di- and monosaccharides and polyols (FODMAP) diet + probiotic, Group 2: low fermentable oligo, di- and monosaccharides and polyols diet + placebo.

The rate of adherence of 85 patients, who completed the study, to the FODMAP restricted diet was 92%, being 90% in Group 1 and 94% in Group 2. There was no significant difference between these two groups (P = 0.066). All patients in the study completely adhered to their probiotic and placebo doses. Although there was no statistically significant relationship between the change in scores with increased adherence to the diet in Group 1, the enhanced dietary adherence in Group 2 was found to decrease the VAS scores, IBS-SSS total score, satisfaction with bowel habits and IBS quality of life sub-score significantly (Table 8).

**DISCUSSION**

IBS is a chronic disease that reduces quality of life, and the desired results are still not achievable with the current treatment options. Therefore, there is an ongoing search for effective and long-term treatments. There are many studies showing that both a low FODMAP diet and probiotics alone have a positive effect on IBS symptoms[21-
Table 7 Comparison of stool changes in groups before and after treatment according to the Bristol stool scale

<table>
<thead>
<tr>
<th>After treatment</th>
<th>Before treatment</th>
<th>Type 1, 2</th>
<th>Type 3, 4</th>
<th>Type 5-7</th>
<th>Kappa</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Type 1, 2</td>
<td>12 (35.3)</td>
<td>2 (9.1)</td>
<td>2 (6.9)</td>
<td>0.175</td>
<td>0.006</td>
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<tr>
<td></td>
<td>Type 3, 4</td>
<td>18 (52.9)</td>
<td>16 (72.7)</td>
<td>19 (65.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 5-7</td>
<td>4 (11.8)</td>
<td>4 (18.2)</td>
<td>8 (27.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>Type 1, 2</td>
<td>4 (23.5)</td>
<td>2 (14.3)</td>
<td>1 (8.3)</td>
<td>0.061</td>
<td>0.448</td>
</tr>
<tr>
<td></td>
<td>Type 3, 4</td>
<td>12 (70.6)</td>
<td>10 (71.4)</td>
<td>9 (75.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 5-7</td>
<td>1 (5.9)</td>
<td>2 (14.3)</td>
<td>2 (16.7)</td>
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<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>Type 1, 2</td>
<td>8 (47.1)</td>
<td>0 (0)</td>
<td>1 (5.9)</td>
<td>0.26</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Type 3, 4</td>
<td>6 (35.3)</td>
<td>6 (79.0)</td>
<td>10 (58.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 5-7</td>
<td>3 (17.6)</td>
<td>2 (25.0)</td>
<td>6 (35.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Group 1: Low fermentable oligo, di- and monosaccharides and polyols (FODMAP) diet + probiotic, Group 2: low fermentable oligo, di- and monosaccharides and polyols diet + placebo.

Table 8 The relationship between adherence to diet and changes in visual analogue scale and irritable bowel syndrome symptom severity scale scores

<table>
<thead>
<tr>
<th>Scores</th>
<th>Group 1; adherence to diet</th>
<th>Group 2; adherence to diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P value</td>
</tr>
<tr>
<td>VAS</td>
<td>0.226</td>
<td>0.145</td>
</tr>
<tr>
<td>IBS-SSS</td>
<td>0.226</td>
<td>0.144</td>
</tr>
<tr>
<td>Pain severity</td>
<td>0.233</td>
<td>0.133</td>
</tr>
<tr>
<td>Abdominal pain severity</td>
<td>0.298</td>
<td>0.052</td>
</tr>
<tr>
<td>Abdominal distention severity</td>
<td>0.001</td>
<td>0.995</td>
</tr>
<tr>
<td>Satisfaction with intestinal habits</td>
<td>0.092</td>
<td>0.557</td>
</tr>
<tr>
<td>IBS quality of life</td>
<td>0.264</td>
<td>0.088</td>
</tr>
</tbody>
</table>

Group 1: Low fermentable oligo, di- and monosaccharides and polyols (FODMAP) diet + probiotic, Group 2: Low fermentable oligo, di- and monosaccharides and polyols diet + placebo. The discrepancy between the initial and final values of the evaluated scores (visual analogue scale, irritable bowel syndrome, etc.) was proportioned to the initial value to create a new variable called "percentage change from baseline" ((last value - initial value)/initial value). The correlation of this variable with dietary compliance in two different groups was investigated. The relationship between the improvement in other scores (numerical) and the diet compliance score (numerical) was investigated. The “r” values we received provide us with knowledge about the relationship’s course and power. VAS: Visual analogue scale; IBS-SSS: Irritable bowel syndrome symptom severity; IBS: Irritable bowel syndrome.

However, there is a group of patients who cannot adhere to a low FODMAP diet and are therefore not treated successfully. There is also some evidence showing that a low FODMAP diet may have adverse effects on microbiota, and long-term use of this diet may have unintended consequences[26,27]. Adding probiotics to a low FODMAP diet may increase treatment success and have a positive effect on the unintended consequences on microbiota due to this dietary approach. From this point of view, this randomized double-blind prospective controlled study aimed to find out whether adding probiotics to a low FODMAP diet contributes to the success of treatment of all subtypes of IBS.

Visceral hypersensitivity due to luminal distension is an important cause of IBS-related gastrointestinal symptoms. A low FODMAP diet has a positive effect on such symptoms by decreasing fluid content in the intestinal lumen and hence gas production. Many clinical studies showed that a low FODMAP diet significantly relieved symptoms in approximately 50% to 80% of IBS patients[28-30].
Böhn et al[31] from Sweden included 75 patients diagnosed with IBS according to Rome III criteria in their multicenter, double-blind parallel-group study. They included 38 patients on a 4-wk-long FODMAP restricted diet, while 37 patients in the other group were asked to adhere to a different diet that is frequently recommended to patients with IBS. The severity of symptoms was evaluated by using IBS-SSS. The study concluded that there was a decrease in IBS symptoms in both groups (P < 0.0001 in both groups) with similar decrease rates (P = 0.62). In that study, the IBS-SSS score of 19 patients (50%) who followed a low FODMAP diet decreased by 50 points or more compared to their scores before the study. In our study, we also saw that the IBS-SSS score decreased more than 50 points compared to the baseline in 37 (86.04%) patients in Group 1 and in 36 (85.71%) patients in Group 2. In another randomized controlled trial study by Harvie et al[32], a total of 23 patients in the interventional group were asked to follow a low FODMAP diet (10.0 ± 7.9 g/d), while 27 patients in the control group were given a regular diet. It was found that there was a significant difference between changes in FODMAP content and relief of symptoms. Furthermore, a low FODMAP diet was proved to have a positive effect on patient quality of life. In our study, the patients were given 9 g of FODMAP on average per day, and the severity of symptoms decreased significantly. We did not use IBS Quality of Life in our study; still, significant improvement was achieved with a low FODMAP diet in both groups in the parameter that shows the quality of life parameter, which is a subgroup of the IBS-SSS scores (P < 0.01 in both groups).

If symptoms cannot be relieved with a diet, first of all, the patient’s adherence to diet must be examined. Adherence to a low FODMAP diet was reported to be 76% and 80% in two different studies that administered a diet for 3 wk and 6 wk, respectively[7, 24]. According to the study of Shepherd et al[3], the adherence to a low FODMAP diet in the long term (14 mo) was reported to be 77%. In our study, we used a 3 wk long diet, adherence to which was 90% in Group 1 and 94% in Group 2. The fact that there was no difference between two groups with regards to adherence to diet shows that adding probiotics to a low FODMAP diet is not of additional benefit to patients’ adherence to the diet. These high adherence rates may be the result of the success of the diet in symptom control as well as the fact that the patients were adequately informed about their diet by an expert dietician. A dietician and a doctor also closely monitored them during the study. In their study investigating the efficiency of and adherence to a long-term low FODMAP diet in IBS patients, Weynants et al[33] stated that patients who visited a dietician multiple times could choose the right nutritional products easily, and their adherence to the diet was higher.

Dietary approaches for IBS generally aim to diversify patient’s nutritional intake as much as possible while controlling the symptoms at a maximum level with fewer restrictions[34]. While treating IBS, it is recommended to apply a low FODMAP diet in three stages. According to this recommendation, FODMAP is restricted in the initial stage, then FODMAP is reintroduced in the second stage, and the treatment is tailored to the needs of the patient in the last stage. The type of FODMAP containing food that triggers the symptoms and the amount of FODMAP in a diet may vary from person to person. Consequently, in the studies investigating the efficiency of a low FODMAP diet in the initial appointment in IBS, the amounts of FODMAP in diet are variable. Böhn et al[31] significantly controlled the symptoms with an average of 3.8 g of FODMAP per day, while Staudacher et al[28] achieved significant symptom control with a daily intake of 17.7 g of FODMAP. In our study, symptoms were relieved, and quality of life was enhanced in more than 85% of our patients with a daily average of 9 g of FODMAP. Over time, the FODMAP amount in diet can be modified and tailored to the needs of individual patients based on their symptom response and tolerance.

A FODMAP restricted diet may worsen constipation as it has low fiber content, and it decreases the amount of water in the small intestine[30]. However, the studies in which a low FODMAP diet was used reported symptom response in all subgroups of IBS including IBS-C[31,32,35]. In our study, out of all IBS cases, 53.5% of the patients in Group 1 and 47.6% in Group 2 were constipation predominant type, and symptom response was significant in both groups. Furthermore, both groups had a similar response rate. This finding supports the argument that a low FODMAP diet can be applied in all subtypes of IBS[6,7,31]. In the group of patients who took probiotics and had both IBS-D and IBS-C, the appearance of stool turned to be highly normal, although not statistically significant (kappa= 0.061, P = 0.448).

It is not clear how significant the changes are in microbiota after a low FODMAP diet. Our knowledge is restricted to the results of the short-term studies in which a low FODMAP diet was applied, and there is limited data on their long-term consequences. A 4 wk study on how a low FODMAP diet causes changes in microbiota and on the effects of probiotics showed that the proportion of total bacteria (Bifidobacterium
species in particular) in the gastrointestinal lumen decreased[28]. This blind study included 104 patients, who were diagnosed with IBS according to Rome III criteria, and they were randomly categorized into four groups of sham diet, a low FODMAP diet, placebo and multistrain probiotic formulation. The amount of Bifidobacterium species in stool samples was significantly lower in patients who followed a low FODMAP diet (8.8 rRNA genes/g) when compared to the patients on sham diet (9.2 rRNA genes/g) (P = 0.008). The amount found in the probiotic group (9.1 rRNA genes/g) was significantly higher than the placebo group (8.8 rRNA genes/g) (P = 0.019), and it was seen that a low FODMAP diet did not affect microbiota diversity in fecal samples. In this study, symptom response rates were higher in the low FODMAP diet group and the sham diet group (57% and 38%, respectively, P = 0.051) according to the intention-to-treat analysis. The total mean IBS-SSS score was significantly lower in the low FODMAP diet group (173 ± 95) compared to the sham diet group (224 ± 89) (P = 0.001). At the same time, there was no difference between the probiotic group (207 ± 98) and the placebo group (192 ± 93), (P = 0.721).

We also found that a low FODMAP diet ensured significant improvement in IBS symptoms in all patients; however, adding probiotics to the diet did not have an additional effect on symptom response. VAS scores before treatment were 4.6 ± 2.7 and 4.7 ± 2.7 for Group 1 and Group 2, respectively, and these scores decreased to 2.0 ± 1.9 and 1.8 ± 2.0 after treatment (P < 0.001 and P < 0.001). Before treatment, the IBS-SSS scores were 310.0 ± 78.4 and 317.0 ± 87.5 for Group 1 and Group 2, respectively, which decreased to 172.0 ± 93.0 and 175.0 ± 97.7 after treatment (P < 0.001 and < 0.001). As is seen, symptoms were relieved significantly in both groups.

The multistrain probiotic preparation that was used in the study of Staudacher et al[28] contained Streptococcus thermophilus DSM 24731, Bifidobacterium breve DSM 24742, Bifidobacterium longum DSM 24736, Bifidobacterium infantis DSM 24737, Lactobacillus acidophilus DSM 24735, Lactobacillus plantarum DSM 24730, Lactobacillus paracasei DSM 24733 and Lactobacillus delbrueckii subsp. bulgaricus DSM 24734, while the probiotic preparation we used in our study contained Streptococcus thermophilus (5.4 × 10⁸ cfu), Bifidobacterium lactis (5.4 × 10⁶ cfu), Lactobacillus acidophilus (4.5 × 10⁶ cfu), Lactobacillus plantarum (4 × 10⁶ cfu) and Bifidobacterium breve (4 × 10⁶ cfu). It was found that the multistrain probiotics used in both studies did not provide an additional positive effect on the symptoms. Staudacher et al[28] did not include IBS-C patients in their study. In our study, around half of the patients in both the probiotics and placebo groups had IBS-C. To the best of our knowledge, no study has been conducted on the effects of adding probiotics to a low FODMAP diet.

In their randomized unblinded controlled study, Pedersen et al[36] compared the efficiency of treatment with a 6 wk low FODMAP diet and Lactobacillus rhamnosus (LGG) in 123 patients with IBS. The study showed that the IBS-SSS score significantly decreased in all three groups (P < 0.001 for low FODMAP, P < 0.01 for LGG and P = 0.03 for the control group) after 6 wk of treatment. The scores decreased more in both low FODMAP and LGG groups compared to the control group. Considering the subtypes of IBS in this study, IBS-SSS score was significantly reduced with a low FODMAP diet and LGG in both IBS-D and IBS-mixed type groups (133 ± 122 vs 68 ± 107, 133 ± 122 vs 34 ± 95 respectively, P < 0.01), while there was no significant decrease in patients with IBS-C. In this study, the difference between results can be explained by the use of LGG and by the fact that the majority of the patients in this study were female patients with IBS-D.

Our study is a randomized controlled study that included all IBS subtypes and examined the effects of probiotic supplementation to a low FODMAP diet on IBS symptoms. Our study’s limitation is that we did not analyze stool microbiota before and after treatment of the patient group that received probiotics or placebo in addition to the FODMAP restricted diet.

CONCLUSION

In conclusion, a low FODMAP diet significantly relieved IBS symptoms in all IBS subtypes in the initial phase; however, adding probiotics to the diet did not make an additional contribution to symptom relief. Further longer term research using different probiotics is needed to examine the efficiency of probiotic supplementation to a low FODMAP diet in IBS.
ARTICLE HIGHLIGHTS

Research background
Irritable bowel syndrome (IBS) has a complicated pathogenesis involving many factors. IBS patients apply to clinics again and again and undergo numerous examinations and procedures that may not be necessary at all. Among the tools for treating IBS, various diets, antispasmodics, loperamide, antidepressants, psychological therapies (psychotherapy, hypnosis, etc.), laxatives, biofeedback, prebiotics or probiotics can be used. Even though some or all of these treatments relieve the symptoms in some patients, some of the patients do not recover sufficiently and may need other treatment alternatives. Because the presence of a relationship between IBS and diet has been shown by various studies, some diet modifications are recommended to reduce symptoms. The elimination diet is a widely used treatment of IBS. Recently, a gradually increasing number of studies have shown a 50%-80% significant effect of a 4-8 wk low fermentable oligo, di- and mono-saccharides and polyols (FODMAP) diet on the symptoms of IBS patients. The efficacy of a low FODMAP diet may depend on factors such as the demographic characteristics, microbiota composition and metabolism besides the IBS subtype and particularly dietary adherence of the patients. There is evidence to suggest the vital role of microbiota in pathophysiology of IBS. The balance of the intestinal flora is corrected by probiotics by way of limiting the pathogenic bacteria colonization. Reasoning on this argument, probiotics have been used in treatment of IBS for a long time.

Research motivation
A low FODMAP diet and probiotics are used individually in IBS treatment. Today, they are preferable treatments due to their relatively high efficacy and few side effects. Combination of these two may improve symptom control in patients. However, the negative effects of a low FODMAP diet on intestinal flora and its long-term adverse effects are still inconclusive. Also, even though the dietary adherence rate is high, a group of patients still cannot tolerate it. Having the potential of preventing possible harmful effects of low FODMAP diet on the intestinal flora, adding probiotics into it may affect control of IBS symptoms.

Research objectives
This randomized double-blind prospective controlled study aimed to find out how probiotic supplementation to a low FODMAP diet affects symptoms in all subtypes of IBS.

Research methods
This double-blind randomized prospective study included 100 patients aged 18-65 newly and/or previously diagnosed with IBS as per the Rome IV criteria whose IBS treatment was not changed during the last 4 wk. According to their IBS subtypes, the patients were divided into subgroups categorized as IBS-diarrhea dominant type, IBS-constipation dominant type and IBS-mixed type. Patients were randomly assigned to two groups: 21 d low FODMAP diet + probiotic (Group 1) and 21 d low FODMAP diet + placebo (Group 2). A coin was tossed to categorize the patients into two groups randomly and neither the patient nor the researcher knew about the treatment administered to the patient. Each patient had a face-to-face explanatory conversation lasting at least 45 min with an expert dietitian about the diet to be followed throughout the trial. The provider of the probiotic and placebo drugs was Nobel Ilac San. ve Tic. A.S. Istanbul, Turkey®. Supplementary food containing probiotics (2 g) was prescribed to patients once a day as a probiotic. This product contained Streptococcus thermophilus (5.4 × 10^8 cfu), Bifidobacterium lactis (5.4 × 10^8 cfu), Lactobacillus acidophilus (4.5 × 10^8 cfu), Lactobacillus plantarum (4 × 10^8 cfu) and Bifidobacterium breve (4 × 10^8 cfu). Placebos were identical-looking capsules without any probiotics. All the participants were asked to record all the foods and beverages they consumed in a diary. Moreover, by weekly phone calls their dietary adherence in terms of probiotic/placebo compliance was monitored. Before and after applying a 21 d low FODMAP diet + placebo or a low FODMAP diet + probiotic, the symptoms of the patients were evaluated with the reference scale and scoring systems, and the results obtained were analyzed. We used the following scales to evaluate the patients: visual analogue scale (VAS) to evaluate pain before and after a 21 d low FODMAP diet + probiotic/placebo, Bristol Stool Scale to identify IBS type and any changes observed in stool and IBS-Symptom Severity Scale (IBS-SSS) to evaluate the severity of IBS symptoms. In the evaluation made after 21 d treatment, the following outcomes were acknowledged as clinical improvement: a
decrease of at least 50 points in the IBS-SSS score, a decrease of more than 10 mm in pain severity according to VAS and change in stool characterization to Type 3 and Type 4 according to the Bristol Stool Chart.

Research results
A total of 85 patients, 43 from Group 1 and 42 from Group 2, completed the study to the end. IBS subtype breakdown showed that the most common subgroup was the constipation-predominant IBS, which was followed by diarrhea-predominant IBS. In both groups, the VAS score, IBS-SSS total score and IBS-SSS sub-parameters measured before treatment were similar. There was a significant decrease in the VAS score, IBS-SSS total score and IBS-SSS sub-parameter scores of Groups 1 and 2 after treatment ($P < 0.001$). The IBS-SSS score of 37 (86.04%) patients in Group 1 and 36 (85.71%) patients in Group 2 decreased by more than 50 points. In conclusion, in both groups abdominal pain and symptoms within the scope of IBS-SSS decreased significantly after treatment. Moreover, no side effects were observed in any of the patients that were included in this study. Treatment outcomes showed that the scores of 38 (79.2%) out of 48 patients who had severe IBS improved after treatment. Significant changes in stool shape were found in both groups when they were analyzed with Kappa index according to the Bristol Stool Scale after treatment. The average adherence rate of the 85 patients who completed the study to the FODMAP restricted diet was 92%, being 90% in Group 1 and 94% in Group 2. There was no significant difference between these two groups ($P = 0.066$).

Research conclusions
According to our findings, a low FODMAP diet significantly relieved IBS symptoms in all IBS subtypes at the initial phase; however, adding probiotics to the diet made no additional contributions to symptom relief.

Research perspectives
The limitation of our study was that we did not analyze stool microbiota of the patient group that received probiotics or placebo in addition to the FODMAP restricted diet before and after treatment. Further and longer term research using different probiotics is needed to assess the efficacy of probiotic supplementation to a low FODMAP diet in IBS.

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Our dietitian Ferya Bertan met with patients face-to-face during the study and organized the diet treatment. Unfortunately, we are so sorry she passed away in a traffic accident after the study completion. We dedicate this work to her. We also thank Professor Pembe Keskinolgu and Tolga Cevizci for their assistance with statistical analysis.

REFERENCES
Clinical effectiveness of probiotics and low FODMAP diet


Association between COVID-19 and anxiety during social isolation: A systematic review

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Abstract

BACKGROUND

The uncertainties about coronavirus disease 2019 (COVID-19), the change in routine, lifestyles and the reduction of physical contact can cause stress, anxiety, emotional overload, poor sleep and even physical health complications.

AIM

To evaluate the scientific publications available on the relationship between COVID-19 and anxiety experienced in the general population, during the period of social isolation, adopted by governmental organizations and public health policymakers as a measure to contain the spread of cases.

METHODS

A literature search was performed systematically exploring the PubMed and Medline databases using the following terms classified as MeSH descriptors: (“anxiety” AND “pandemic” AND “COVID-19”). For the search, in the Biblioteca Virtual em Saúde – BVS, Science.gov, Web of Science and National Library plat-
forms, the following keywords were used: ("anxiety" AND "coronavirus" AND "social isolation"). Thirty-seven peer-reviewed articles were found. PRISMA and the Downs & Black checklist were used for qualitative evaluation.

RESULTS
After applying the inclusion criteria, seven (n = 7) original scientific articles were selected. The collated evidence demonstrated increased levels of symptoms of anxiety and depression during the period of social isolation. The population between 21 to 40 years was most affected. The risk of severe depression was twice as high at the epicenter of the pandemic. Sleep quality was significantly impaired. Questions about politics, religion, and consumption of products from China were found to generate fear and anticipate probable changes in the pattern of post-pandemic consumption. Social isolation exacerbated feelings of extreme hopelessness, sadness, loneliness and suicidal ideation.

CONCLUSION
We conclude that there is a potential relationship between social isolation during the COVID-19 pandemic and symptoms of anxiety. It is important to note that the direct and indirect costs of not identifying the detrimental effects of this phenomenon and neglecting strategies for intervention could lead to a significant psychological burden on society in several aspects after social isolation.

Core Tip: There is a potential relationship between social isolation during the coronavirus disease 2019 pandemic and symptoms of anxiety. The population between the age of 21 to 40 years is notably most affected. The risk of severe depression is noted to be twice as high at the epicenter of the pandemic. Sleep quality was significantly impaired. It is important to note that the direct and indirect costs of not identifying the detrimental effects of this phenomenon and neglecting strategies for intervention could lead to a significant psychological burden on society in several aspects after social isolation.

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INTRODUCTION
In December 2019 a group of patients was hospitalized due to viral pneumonia caused by a microbial agent, hitherto unidentified. The patients were epidemiologically linked to the Huanan seafood market in Wuhan, Hubei Province, China. Shortly afterward, a new coronavirus that infects humans, which probably originates from bats, was identified as the etiologic agent that caused the hospitalizations. Until then, among the various types of coronavirus, majority caused only mild clinical symptoms, except for severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus. However, the new typing identified in Wuhan also proved to be dangerous[1,2].

The spread of the coronavirus was a decisive contributor to unleashing an unprecedented worldwide public health crisis. Transmission of this virus occurs through droplets and aerosols that disperse through the air when someone contagious sneezes, coughs, or speaks[3]. Another form of transmission can also occur through contact and fomites on which the virus can lodge for hours, or days[4,5].
In this context, coronavirus disease 2019 (COVID-19) manifests clinically from mild to severe and varies substantially according to the age and sexual characteristics of the patients. One of the most frequent manifestations in mild and moderate cases is predominantly olfactory dysfunction. Severe cases present with a higher risk for older men with comorbid underlying hypertension, cardiovascular, malignant and chronic renal diseases with signs of dyspnea and nausea[6,7].

The uncertainties about COVID-19, the change in routine, lifestyles and the reduction of physical contact can cause stress, anxiety, emotional overload, poor sleep and even physical health complications. A report released by the Centers for Disease Control and Prevention released a report in August 2020 highlighting the considerable rise in adverse mental health conditions. The most affected groups identified were younger adults, ethnic minority groups, essential workers, and adult caregivers. The coronavirus pandemic brought panic and fear in various aspects of individual lives. Therefore, in addition to the need for attention to the physical and biological aspects related to this disease, it is relevant to carry out an analysis of the aspects related to the mental and emotional health of people who are following the guidelines of global health authorities, to maintain social isolation as a strategy to reduce contagion by the coronavirus[5].

In case of exposure to frightening situations, a cascade of events involving hormones and neurotransmitters such as serotonin, dopamine, norepinephrine is activated in humans, which prepare the individual to react, which represents positive anxiety, which helps to maintain the species in nature[8,9]. With extended periods of social isolation, vulnerable groups of people start to manifest, the signs of pathological anxiety, which in addition to activating the state of constant alertness, enhances the feeling of fear and despair to cope with unexpected circumstances and future uncertainties. This condition presents itself as generalized discomfort in homeostasis, as it alters cardiorespiratory systems (tachycardia, shortness of breath), digestion bringing changes in appetite and usually accompanied by sleep disorders[10].

This constellation of disorders associated with the limbic system, the brain unit specialized in dealing with emotions when it comes to anxiety is still little explored in situations such as the COVID-19 pandemic. Sensations of fear, pathological anxiety generated by the process of social isolation, quarantine and restrictions adopted by most health authorities in nations affected by the coronavirus are important at the same time they have an impact on the economy, fall in income generation and rising unemployment[8,10].

This systematic review aimed to evaluate the scientific publications available on the relationship between COVID-19 and the anxiety experienced by individuals in the general population, during the period of social isolation.

**MATERIALS AND METHODS**

**Study design**

It is a qualitative systematic review to identify original articles about the relationship between COVID-19 and the anxiety experienced by the general population over the age of 18 years, in the period of social isolation.

**Search method to identify studies**

The search and selection of studies were carried out in the Pubmed and Medline databases using the following terms classified as keywords of the MeSH: (“anxiety” AND “pandemic” AND “COVID-19”). For the search, in the Biblioteca Virtual em Saúde - BVS, Science.gov, Web of Science and National Library platforms, the following keywords were used: (“anxiety” AND “coronavirus” AND “social isolation”). The keywords were combined using the boolean operator AND, with a reference period established for the bibliographic survey from 2019 to 2020, and data extraction were from March 1 to April 30, 2020. An active search was also carried out on the references of the selected articles.

**Determination of eligibility**

**Inclusion criteria**: The following items were observed: Original research articles that discussed the association of “anxiety”, “social isolation”, “coronavirus”, detected in the title and/or abstract structure; studies carried out with the general population over the age of 18 years, and manuscripts must be published in English.
Exclusion criteria were: Studies that did not present a degree for the measurement (scales) of anxiety symptoms related to COVID-19 were excluded. Besides that, articles structured in the modalities: systematic review; narrative review; speeches; editorials; conference abstracts were excluded. Duplicate articles, reviews performed exclusively with gray literature, studies on COVID-19 and anxiety with specific groups of the population at greatest risk, such as health professionals, adolescents, children, pregnant women, and people with comorbidities (diabetes, systemic arterial hypertension, oncological disease, mental disorder, neurological or renal pathology) were also excluded.

Study selection
Initially, the titles and abstracts of the articles found in the search were manually reviewed, to identify the studies that met the eligibility criteria. Then the full texts were evaluated including reference lists to identify other relevant articles. Both procedures were performed by two independent reviewers, with blinding. Subsequently, the divergences were compared and actions were taken to adjust them in a consensual way.

Data extraction
After the application of the descriptors, combined with each other, in an integrated search in the fields, information about data of interest was extracted in predefined forms, with the inclusion of fields for the annotation of health outcome variables, data sources of outcomes, year of publication of studies, the period of occurrence of the assessed outcomes, locations investigated and origin. From the data of each study were selected: author/date, objective, method, result, and conclusion.

The PRISMA tool (Preferred Reporting Items for Systematic Reviews and Meta-analyses) was used as a guide in the selection of review articles[11,12].

Quality assessment
The scientific articles examined in this systematic review study were evaluated concerning the methodological adequacy used in the sample selection, collection, and data analysis from the scores of the quality assessment instrument Checklist Downs & Black, adjusted for observational studies, with a scale ranging from 0 to 15 points[13].

Following items were examined in each study: Definition of objectives and outcome measures; definition of inclusion and exclusion criteria, as well as the period and place of the study; sampling procedures (population, attrition, bias, standard deviation, confidence interval); description of methods for measuring outcomes; and adequate statistical analysis (calculation of power and control of confounding factors).

Statistical analysis
The main results of the selected studies were grouped into thematic categories and discussed based on a narrative synthesis. To define the thematic categories, the content analysis technique was adopted, the tool used to assess the quality of the studies was the condensation matrix of meanings, which helped in the systematization of the items assessed as to the components of methodological quality. The extracted data were based on the results evaluated in each cross-sectional study.

RESULTS

Selection of studies
Of the total of 37 articles that were found in the databases the breakdown was as follows: (n = 2) case reports; (n = 1) lecture; (n = 2) editorials; (n = 15) review articles; and (n = 12) original articles.

The evaluation performed by pairs of reviewers during the initial screening strategy removed (n = 20) articles that did not meet the selection criteria. Manuscripts were also removed in the modalities of literature reviews, editorials, and case reports (n = 10), resulting in (n = 7) studies submitted to full reading and analysis (Figure 1). There was 100% interobserver agreement.

Study characteristics
The origin of the studies evaluated in this review is highlighted in four countries: The United State of American, China, Iran, and Turkey.
When evaluating the objectives of the studies described in this systematic review, all declared that they sought to fill the gaps in the literature with regards to mental health in the case of the COVID-19 epidemic, in the general population. These studies also attempt to address the lack of application tools to measure the impact of social isolation for those who suffer with disorders like anxiety, stress, and depression.

Regarding methods, all studies used a cross-sectional design, using psychometric scales\[^{14}\] applied via the internet from social networks, self-reported already tested for anxiety in other studies, such as the Beck Anxiety Inventory (BAI), used in two of the studies examined in this sample\[^{15-19}\].

**Instruments used**

The most common scales used were: Personal Social Capital Scale\[^{16}\], Likert Scale, Self-Rating Anxiety Scale (SAS) and Stanford Acute Stress Reaction Scale\[^{20}\]; The Pittsburgh Sleep Quality Index questionnaire\[^{17,20}\]; Self Reporting Questionnaire\[^{17}\]; The Depression Anxiety Stress Scales (DASS)\[^{19}\]; BAI; and Beck Depression Inventory-II\[^{18}\]. In addition to these, the Alcohol Use Disorders Identification Test\[^{18}\]; The Warwick Edin Scale\[^{18}\]; Work and Social Adjustment Scale\[^{16}\]; Coronavirus-related anxiety assessment scale - Coronavirus Anxiety Scale (CAS), made specifically for the measurement of anxiety signs related to COVID-19\[^{16}\]. The Self-Assessment Anxiety Scale (SAS) was also used; Self-Assessment Depression Scale\[^{15}\]; Hospital Anxiety and Depression Scale; and Health and Anxiety Inventory\[^{14,20}\]; and DASS\[^{19}\].

**Variation in sample size and variables studied**

The studies used the scales in populations with varied sample numbers, the smallest with 170 respondents and the largest with 10754. In all the studies, more than one scale was used, in addition to the fields for declaring the respondents’ demographic data. An instrument of process technological innovation was identified, from the creation of CAS as the first published psychometric scale, related to COVID-19, validated in a large sample\[^{16}\].

The main sociodemographic variables most used were sex, age, education, place of residence, history of smoking, previous history of mental disorder, cohabitation with people over 60 years old. The number of household members; use of health services...
and; comorbidities of chronic disease were the other commonly studied variables.

The relative variables collected on the psychometric scales, applied via the internet from social networks, measured the symptoms of self-reported anxiety, compatible with important symptoms such as fear, stress, and generalized anxiety disorder (GAD).

**Main findings with statistical significance**

When the results of the studies were evaluated, the scales measured symptoms of self-reported anxiety, compatible with important symptoms of panic attacks and GAD, such as dizziness, nausea, and abdominal discomfort[21,22].

Findings with statistical significance signaled the following risk factors that lead to increased likelihood to develop anxiety symptoms, such as place of residence in an urban area, subjects with a history of emotional instability or previous mental disorders, constant exposure to news, (or other media outlets that focused on deaths), morbidities of chronic illness, death of relatives or close friends due to COVID-19. There was evidence that the levels of anxiety and depression were detected on a larger scale during the isolation period[14,20].

A study demonstrated significant evidence that young people aged 21 to 40 were in a more vulnerable position in terms of mental health conditions and alcohol use (6 times higher risk for men)[19]. The risk of severe depression was twice as high in Hubei when compared to the population of other provinces in China (the epicenter of the pandemic)[17].

In most studies, quality of sleep was mentioned as a very impaired element and when associated with the profession, the effect was most pronounced for the personnel involved in the healthcare and business sectors. Issues related to international politics, religion, consumption of products from China, were also mentioned as the object of much fear and a probable change in the consumption pattern for the future. Extreme hopelessness and suicidal ideation were also reported in the worst moments of loneliness experienced during social isolation[8,9,17].

There was a linear correlation for severity in anxiety symptoms related to exposure to news about the coronavirus. News of the death of a relative or close person also contributed to exacerbating the symptoms. Overburdened hospitals and the fear of the collapse of the health care system were also cited as being of great relevance for increasing levels of anxiety in the confined population[21].

A narrative summary of these studies is presented in Table 1. The peculiarities of the content of each original study are highlighted. All studies also stated that there was no conflict of interest.

**DISCUSSION**

This systematic review identified from the studies selected in the sample the presence of a significant correlation between COVID-19 and anxiety in the period of social isolation. The most significant findings confirmed: the predominancy of anxiety generated during the period of social isolation in the younger age group (20-40 years), the important role of the internet in the pandemic, and government action on strategic measures for mental health was insufficient.

**The anxiety generated during the period of social isolation**

The results from this systematic review corroborate the findings of identifying the risk factors for the development of anxiety and depression as a result of social isolation related to COVID-19 in various dimensions (gender, age, lifestyle, economy, place of residence, psychological, cognitive, behavioral and emotional aspects). It was observed that women of younger age, single, widows, divorced, who live alone, slept little and felt loneliness, were associated with a higher risk of problems in the components of anxiety and/or depression[14,23]. There was a perception that loneliness has different effects between genders, when compared, lonely women are more prone to developing anxiety whereas men were noted to be more prone to depression[24].

The physical distancing or social isolation, although protect against the spread of the disease resulted in loneliness especially for vulnerable groups, generating anxiety and distress, which are the most common mental health complaints. Other adverse outcomes include psychiatric suffering, rise in suicidal ideation, and higher concerns among women about the impact of the pandemic[25,26].
Table 1 Brief description of the articles selected in the literature review on associations between coronavirus disease 2019 and anxiety during the period of social isolation (n = 7)

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Location, year</th>
<th>Sample</th>
<th>Objective</th>
<th>Psychosometric Scales</th>
<th>Statistical analysis</th>
<th>Key results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayrak Özdin and Özdin</td>
<td>Turkey, 2020</td>
<td>343</td>
<td>To assess levels of depression, health anxiety in Turkish society during the COVID-19 pandemic and examine the factors that affect them.</td>
<td>Hospital Anxiety and Depression Scale; Health and Anxiety Inventor.</td>
<td>Logistic regression and multiple linear regression.</td>
<td>Risk factors for depression and anxiety, living in urban areas. Risk factor for depression, female, residing in urban areas and previous psychiatric illness.</td>
<td>The groups most affected psychologically by the pandemic are women, individuals with previous and current psychiatric illnesses, who living in urban areas, and those with a comorbid chronic disease</td>
</tr>
<tr>
<td>Lei et al [15], 2020</td>
<td>China, 2020</td>
<td>1,593</td>
<td>To evaluate and compare the prevalence and associated factors of anxiety and depression among the public affected and unaffected by quarantine during the COVID-19 outbreak.</td>
<td>SAS; Self-assessment depression scale.</td>
<td>χ² test and U Mann-Whitney test, and ANOVA.</td>
<td>The most affected group, prone to have poor health and worrying about getting infected.</td>
<td>The prevalence of anxiety and depression in the affected group is higher than the unaffected group, during the COVID-19 outbreak, with factors associated with serious material damage and low self-perceived health status</td>
</tr>
<tr>
<td>Lee [16], 2020</td>
<td>United States, 2020</td>
<td>775</td>
<td>To develop and evaluate the properties of a mental health screening scale that health professionals and researchers can readily use to identify likely cases of dysfunctional anxiety associated with coronavirus.</td>
<td>Work and Social Adjustment Scale, adapted; CAS.</td>
<td>It was used to examine the construct validity and diagnostic viability of the coronavirus anxiety symptoms using a series of correlations and receiver operating characteristic analyses.</td>
<td>The anxiety measured by CAS regarding Coronavirus was strong and positively correlated with functional incapacity, confrontation with alcohol or drugs, negative religious confrontation, extreme hopelessness, and passive suicidal ideation.</td>
<td>The results support the use of the CAS scale as an accurate diagnostic tool for mental health screening with strong classification characteristics, efficient and valid for research and clinical practice, and the first created to assess anxiety directly related to COVID-19</td>
</tr>
<tr>
<td>Yuan et al [17], 2020</td>
<td>China, 2020</td>
<td>939</td>
<td>To compare the emotional state, somatic responses, quality of sleep and behavior of people in Hubei province with non- endemic provinces in China for two weeks in February 2020.</td>
<td>Stress Response Questionnaires; PSQI.</td>
<td>χ² tests and ANOVA.</td>
<td>Sleep disorders have increased significantly in people aged 18 to 24. COVID-19 anxiety was positively correlated with all somatic symptom signatures and the full scale score. The subscales of somatic symptoms were all highly and positively correlated, and the correlations with GAD were higher than for the COVID-19 anxiety score.</td>
<td>There are levels of anxiety that affect quality of life during epidemics, including periods of population quarantine or self-isolation</td>
</tr>
<tr>
<td>Ahmed et al [18], 2020</td>
<td>China, 2020</td>
<td>1.074</td>
<td>To approach in literature Gap in psychological morbidity induced by the current COVID-19 epidemic also systematically reviews the prevalence of Political problems due to the prolonged confinement of itizens.</td>
<td>Beck's Anxiety Inventory; Beck Depression Inventory II; Alcohol Use Disorders Identification Test; Warwick Edin-Scale</td>
<td>Descriptive statistics and t² test.</td>
<td>There were significant differences in depression and alcohol abuse among respondents from different localities. Young people aged 21-40 are more vulnerable in terms of mental health and alcohol use, with the risk being six times higher among men.</td>
<td>It has been exposed that simple infection does not cause psychological problems, but a social behaviour due to infection/illness. The prevalence of anxiety, depression and alcohol use due to isolation and widespread economic damage has made many people psychologically problematic</td>
</tr>
<tr>
<td>Moghanibashi-Mansourieh</td>
<td>Iran, 2020</td>
<td>10.754</td>
<td>To assess the level of anxiety of the general Iranian</td>
<td>Depression Anxiety Stress Scales</td>
<td>They were analyzed by descriptive.</td>
<td>The level and severity of anxiety symptoms were significantly higher.</td>
<td>The more people followed the news about the coronavirus,</td>
</tr>
</tbody>
</table>
The prevalence of mental disorders during periods of the epidemic, especially anxiety, reduces individuals’ resilience against virus infection and can cause irreparable economic, social, cultural, and psychological problems for people in the future (immune system under shock)[22]. The COVID-19 pandemic has a significant influence on mental health. In this perspective, close monitoring of the vulnerable group and early recognition and treatment is a priority according to a study that analyzed psychological health during this global pandemic crisis[25-27]. Another study supports the findings of our review, we show that female gender, higher education, and younger age are associated with a higher risk of experiencing anxiety (P < 0.05). Women, young people, with low physical activity, and singles were associated with higher depression levels (P < 0.05)[24].

The two faces of the internet in the COVID-19 pandemic

The results showed that the people who closely follow the news on the COVID-19 experienced greater symptoms of anxiety. Although necessary to keep the general public updated with the progress of the pandemic, it is also of prime importance to provide outlets for moral support and emotional wellbeing for the general public. This is markedly unexplored at the moment and provides a good point of a potential intervention[19,25,27]. Another study reports that less frequent check-in on current affairs was associated with 19% lower risk of worsening the symptoms of anxiety[24]. The experience of isolated and quarantined people is stressful and makes face-to-face and other communication impossible. The wide range of information about the COVID-19 epidemic through digital media, often with false content, was associated with increased concern and anxiety for people in social isolation[28].

The role of governments in strategic measures for mental health

From the point of view of public health administrators and policymakers, it is necessary to concentrate efforts to plan and execute interventions on the negative effects of social isolation, particularly anxiety, sadness, loneliness, as well as symptoms of post-traumatic stress, which can effectively meet the needs of individuals[26,29-31].

Strengths and limitations

Most of the studies at the time of inception of this idea before data collection were narrative reviews, editorial with opinions, case reports, which reveal a low and medium quality of studies due to little methodological rigor and high risk of bias. In this systematic review, all the studies included were of the cross-sectional type, which

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sample Size</th>
<th>Year</th>
<th>Design</th>
<th>Methods</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Xiao et al[20], 2020 | China, 2020 | 170 | To Investigate the effects of social capital on sleep quality and the mechanisms involved in people who were isolated at home for 14 days in January 2020 during the COVID-19 epidemic in central China | Anxiety Scale Self-Rating Questionnaire; SASR; PSQI; Likert Scale | Path analysis, or multiple regression analysis; using Pearson correlation analysis (r) and structural equation modeling with a bootstrap number set as 500 to test | The results showed that the people who closely follow the news on the COVID-19 experience greater symptoms of anxiety. |}

revealed the first attempts of original works. Some of the studies still had some methodological problems, such as the sample selection (questionnaires available to the population over 18 years old, with access to popular social media in respective countries of origin). The responses were self-reported, so this is considered a limitation [14-20].

All studies were cross-sectional and sought to adapt the method to an atypical pandemic situation, in which personal contact was not possible. Among the strengths of the methodology of the studies, the large number of individuals surveyed in most of the studies stands out, some of them with national representativeness. The novelty of creating a scale to measure the specific anxiety symptoms for COVID-19 in some of the studies should be highlighted.

Sample selection revealed an important risk of bias in the studies. In the study carried out in China more than 50% of the participants were from Wuhan, the epicenter of COVID-19[18].

Internet is a great source of health information and has the potential to influence its users. On the other hand, with the evolving literature, we have witnessed that the information found on the internet may not have the desired scientific rigor and many published scientific articles have been retracted due to fundamental scientific flaws. This implies great concern for scientific societies, governments, and users.

Our systematic review identifies certain areas where a strategic approach can make a difference in the psychological health of people at risk. There is an opportunity to develop and implement a gender-sensitive psychosocial protocol to reduce anxiety. In the times of pandemics, special support is needed to help people with mental disorders and prevent the deterioration of symptoms[27].

CONCLUSION

By identifying the populations and their sociodemographic variables (gender, housing, marital status, education) and comorbidities at greater risk for mental health in this pandemic (previous psychiatric illnesses), we found that it is necessary to recognize the repercussion degree and magnitude of this pandemic in people's lives, which significantly alters the psychodynamics of each one and social interactions.

The total lack of scientific knowledge about the behavior of COVID-19 in its preventive, epidemiological, clinical, and therapeutic aspects has generated fear in people regarding health care, being aggravated by the necessary social isolation, a positive measure to reduce contagion, but not for the mental health of the most vulnerable groups. Added to this, the economic uncertainty aroused a feeling of powerlessness to reverse the situation, further aggravating the levels of anxiety.

The psychological routine care services do not absorb the demand generated by a pandemic, requiring an investment by the state, and educational and research institutions, in actions that have the potential to act beneficially on the adverse effects, including late effects, of social isolation in people's lives, such as psychological support that strengthens self-confidence and trust in disease control measures (preventive, therapeutic, educational, and recreational). Besides, promote solidarity and economic support networks, for the less favored social classes, to minimize the effects of the pandemic on the economic health of the population.

We conclude that there is a potential relationship between social isolation during the COVID-19 pandemic and symptoms of anxiety. It is important to note that the direct and indirect costs of not identifying the detrimental effects of this phenomenon and neglecting strategies for intervention could lead to a significant psychological burden on society in several aspects after social isolation. This study represents a first approximation on this important theme, which needs to be revisited from future studies, considering longer reference periods.

ARTICLE HIGHLIGHTS

Research background

The uncertainties about coronavirus disease 2019 (COVID-19), the change in routine, lifestyles and the reduction of physical contact can cause stress, anxiety, emotional overload, poor sleep and even physical health complications.
Research motivation
We are more than 1 year into the pandemic and more and more literature is evolving around the psychosocial effects of social isolation during this period. We were motivated to do a deep literature review of the scientific literature available and provide pragmatic insight to the problem.

Research objectives
Our objective was to evaluate the scientific publications available on the relationship between COVID-19 and anxiety experienced in the general population, during the period of social isolation, adopted by governmental organizations and public health policymakers as a measure to contain the spread of cases.

Research methods
A literature search was performed systematically exploring the Pubmed and Medline databases using the following terms classified as MeSH descriptors: (“anxiety” AND “pandemic” AND “COVID-19”). For the search, in the Biblioteca Virtual em Saúde – BVS, Science.gov, Web of Science and National Library platforms, the following keywords were used: (“anxiety” AND ”coronavirus” AND ”social isolation”). Thirty-seven peer-reviewed articles were found. PRISMA and the Downs & Black checklist were used for qualitative evaluation.

Research results
The collated evidence demonstrated increased levels of symptoms of anxiety and depression during the period of social isolation. The population between the ages of 21 to 40 years was most affected. The risk of severe depression was twice as high at the epicenter of the pandemic. Sleep quality was significantly impaired. Questions about politics, religion, and consumption of products from China were found to generate fear and anticipate probable changes in the pattern of post-pandemic consumption. Social isolation exacerbated feelings of extreme hopelessness, sadness, loneliness and suicidal ideation.

Research conclusions
We conclude that there is a potential relationship between social isolation during the COVID-19 pandemic and symptoms of anxiety. It is important to note that the direct and indirect costs of not identifying the detrimental effects of this phenomenon and neglecting strategies for intervention could lead to a significant psychological burden on society in several aspects after social isolation. This study represents a first approximation on this important theme, which needs to be revisited from future studies, considering longer reference periods.

Research perspectives
Direction of the future research: We aim to maintain this as a live systematic review and provide timely updates on the evolving literature concerning to this very relevant issue.

ACKNOWLEDGEMENTS
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Avascular necrosis of the first metatarsal head in a young female adult: A case report and review of literature

Ronald Wing Hei Siu, Jeremy Ho Pak Liu, Gene Chi Wai Man, Michael Tim Yun Ong, Patrick Shu Hang Yung

CASE REPORT

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Abstract

BACKGROUND

This case study describes an atypical presentation of avascular necrosis (AVN) of the first metatarsal head, which is largely unfounded in the literature.

CASE SUMMARY

A healthy 24-year-old female initially presented with pain at the first metatarsophalangeal joint (MTPJ) and was diagnosed with AVN by physical examination and magnetic resonance imaging. The patient demonstrated atypically poor progress in recovery, despite being in otherwise good health and being of young age, with no history of corticosteroid or alcohol use. The patient also did not have any history or clinical features of autoimmune disease or vasculitis, such as systemic lupus erythematosus. The patient was managed with conservative treatment for 18 mo, which allowed for gradual return of full range of motion of the first MTPJ and subsiding pain, permitting the patient to return to high-intensity sports training and full weight-bearing. Throughout her recovery, many differential diagnoses were ruled out through specific investigations leading to further reinforcement of the diagnosis of AVN of the 1st metatarsal head.

CONCLUSION

Atypical AVN may occur with no predisposing risk factors. Treatment is mainly conservative, with unclear guidelines in literature on management.

Key Words: Avascular necrosis; Osteonecrosis; Metatarsal head; Atypical; Avascular necrosis; Young; Female; Foot and ankle; Sports medicine; Case report
INTRODUCTION

The present case of avascular necrosis (AVN) of the first metatarsal (MTT) head occurred in a young, healthy female adult with pain of the first metatarsophalangeal joint. Initially, conservative treatment with analgesics did not show much improvement in relieving pain. However, after continuous treatment for 2 mo, the swelling subsided with reduced pain. After 4 mo of follow-up monitoring, improved range of motion of the first metatarsophalangeal joint was observed, but the pain had disappeared. No other complications developed during 18-mo of follow-up monitoring. The purpose of this case report is to indicate that an efficient and precise diagnosis of the patient’s case is important as it significantly changes the prognosis and management for such a condition.

AVN, also known as osteonecrosis, is a pathologic process involving the compromise of bone vasculature leading to the death of bone and marrow cells[1]. It is not a rare diagnosis and can involve several locations in the skeletal system[2]. The process is most often progressive, resulting in joint destruction within a few months to two years in the majority of patients[3]. In the United States alone, approximately 20000-30000 new cases are reported annually[4]. However, the exact cause of AVN remains to be elucidated. Although the most common sites of AVN in the foot are the second MTT head (Freiberg disease), calcaneus (Sever disease) and talus (Dias disease), it is not exceptional to occur at the first MTT head[5]. In adults, the most common cause of AVN of the first MTT head secondarily arose from iatrogenic insult to vascularity by a distal first MTT osteotomy (Mitchell osteotomy) for correction of hallux valgus deformity[6]. There are two current literature reports on bilateral first MTT head idiopathic AVN in adolescents[7,8]. As there is currently no literature reports on unilateral idiopathic first MTT head AVN in adult patients, the present study aims to describe a new case of unilateral idiopathic AVN of the first MTT head in an adult patient.

CASE PRESENTATION

Chief complaints

A 24-year-old woman, a recreational rugby player, attended our outpatient clinic on May 2017, complaining of right big toe pain.

History of present illness

Patient denied of any history of trauma. Patient was not suffering from a fever, nor had any history of alcohol or any other substance abuse, and no history of corticosteroid use.
History of past illness
Patient experienced good past health. She did not have any history of trauma to the right foot, nor have any history of vasculitis, Caisson Disease or alcoholism. She did not take any medication (including corticosteroids) and had no known allergies.

Personal and family history
No significant personal or family history was noted.

Physical examination
On physical examination, mild swelling of the first metatarsophalangeal joint (MTPJ) was revealed, with failed active interphalangeal joint flexion to 0 degrees. Passive range of motion was full. Tendons of Flexor Hallucis Longus were intact. Clinical appearance of the feet, sensation and local perfusion of the toes were normal. No significant impairment to activities of daily living were noted. Weight-bearing was affected by pain.

Laboratory examinations
No laboratory testing was conducted.

Imaging examinations
X-ray films of the foot did not show any obvious fractures or bony defects; therefore a magnetic resonance imaging (MRI) was performed.

MRI of the right big toe showed an abnormal linear signal within the marrow cavity of the first MTT head, along with a suspected serpiginous line with bony oedema present at the dorsal aspect of both the distal phalangeal base and proximal phalangeal head (Figure 1).

Supplementary computed tomography (CT) scan showed no fracture line, however, did show diffuse sclerosis at the MTT head. Cartilage was grossly intact. The impression was early AVN of the first MTT head with bony oedema related to previous contusion or healing MTT fracture.

FINAL DIAGNOSIS
The final diagnosis is AVN of the first right MTT head.

TREATMENT
Conservative treatment was initiated with non-weight bearing exercises and analgesics. Paracetamol 1000 mg tablets and Ibuprofen 200 mg tablets were taken pro re nata. Non-weight bearing exercises were conducted with the use of bilateral elbow crutches for ambulation initially. Partial weight-bearing with single elbow crutch was commenced once pain symptoms have gradually reduced to a NRS level of < 5/10. Once patient was able to fully weight-bear with minimal pain (NRS 1-2/10), she was put on full weight-bearing protocol with no walking aids. Analgesics were continued to be given for pain relief during physical exercise and cross training. No deterioration or aggravation of pain symptoms occurred with this rehabilitation protocol.

OUTCOME AND FOLLOW-UP
The outcome of the follow-up is shown in Table 1.

At follow-up one week later, physical examination and CT scan both showed unchanged condition with continued pain and swelling. Overall features still implied either healing AVN or healing fracture. Conservative treatment was continued for another month when she complained of pain on her right toe. Patient was put on partial weight bear protocol with unilateral elbow crutch.

At 2 mo after attending our clinic, swelling had subsided and CT scan revealed no serial changes. The abnormal linear signal within the marrow cavity of the first MTT head remained. Although mild joint effusion of the first MTPJ remained, no observable progression or regression of the serpiginous line was seen. As a result, conservative treatment and analgesics were continued. Patient was able to fully weight bear at this...
Table 1 Follow-up on the patient’s treatment

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>First presentation (May 2017)</td>
<td>The patient first presented with right big toe pain. Physical examination revealed mild swelling of the first MTPJ with failed IPJ flexion, but intact FHL tendon. Clinical appearance of the feet, sensation and local perfusion of toes were normal</td>
</tr>
<tr>
<td></td>
<td>Pain NRS of 7-8/10 was noted. Patient was put on bilateral elbow crutches for walking aid</td>
</tr>
<tr>
<td>1 wk later (May 2017)</td>
<td>Physical examination and CT scan both showed unchanged condition with continued pain and swelling. Overall features still implied either diagnosis was healing AVN or healing fracture</td>
</tr>
<tr>
<td></td>
<td>Pain NRS of 3-4/10 was noted. Patient was stepped down to partial weight bearing protocol with unilateral elbow crutch</td>
</tr>
<tr>
<td>2 mo later (July 2017)</td>
<td>Swelling subsided. CT scan revealed no serial changes. The abnormal linear signal within the marrow cavity of the first MTT head remained. Although mild joint effusion of the first MTPJ remained, no observable progression or regression of serpiginous line was seen</td>
</tr>
<tr>
<td></td>
<td>Pain NRS of 1-2/10 was noted. Patient was allowed to conduct full weight bear</td>
</tr>
<tr>
<td>14 mo later (July 2018)</td>
<td>CT scan and MRI showed a reduction in bony oedema. The abnormal linear signal within marrow cavity of first MTT head, dorsal aspect of distal phalangeal base and proximal phalangeal head remained visible</td>
</tr>
<tr>
<td>18 mo later (November 2018)</td>
<td>Final follow-up: The patient reported slight improvement of her right toe pain, with slight tenderness observed upon palpation. Range of motion of the first MTPJ had improved with only a 10 degree deficit in flexion without swelling, redness or local heat</td>
</tr>
<tr>
<td></td>
<td>Characterisation of the improvement of anatomical morphology by radiological assessments (CT scan and MRI) remained the same. The patient reported that she was able to undergo cross-training during the past ten months. However, she was not able to return to rugby activities. Thus, advise was given to the patient to continue cross-training as tolerated. Anatomical investigation of the toe remained unchanged</td>
</tr>
<tr>
<td></td>
<td>Upon physical examination, tenderness continued to be experienced over the first MTT head. However, the patient was able to return to high-intensity training. She experienced no pain during rest or active flexion and extension, with only mild aching after training</td>
</tr>
<tr>
<td>Last follow-up (November 2018)</td>
<td>Mild tenderness remained, with full range of motion of first MTPJ achieved. Patient able to return to high-intensity training with mild aching after each session</td>
</tr>
</tbody>
</table>

MTPJ: Metatarsophalangeal joint; IPJ: Interphalangeal joint; FHL: Flexor Hallucis Longus; CT: Computed tomography; MTT: Metatarsal; MRI: Magnetic resonance imaging.

Figure 1 Initial foot magnetic resonance images. A: Anterior; B: Sagittal; C: Coronal images. The images showing serpiginous line with bony oedema at distal phalangeal base and proximal phalangeal head on T1-weighted magnetic resonance images.

At 14 mo follow-up, both CT scan and MRI showed a reduction in bony oedema. The abnormal linear signals within the marrow cavity of first MTT head, dorsal aspect of the distal phalangeal base and proximal phalangeal head remained similar (Figure 2).

In the following 4-mo, the patient reported slight improvement of her right first toe pain, with slight tenderness observed upon palpation. The range of motion of the first MTPJ had improved with only a 10 degree deficit in flexion without swelling, redness or local heat. Characterisation on the improvement of anatomical morphology by radiological assessments (CT scan and MRI) remained the same. Herein, the patient reported that she was able to undergo cross-training during the past 10-months.
DISCUSSION

Although no clear explanation can be given regarding the occurrence of AVN in our patient, it cannot be excluded based on possible previous history of trauma to the lesion site, owing to her high-intensity training as a recreational athlete. It is, however, interesting and perhaps perplexing, for a patient with such good health, young age and no history of corticosteroid or alcoholic use to have stagnant progress in recovery. As the age of AVN onset is more common between 30- to 50-year-olds, our young female patient (in her mid-twenties) is considered an exceptional case. Likewise, the occurrence of AVN in females are often associated with a background of SLE[9]; however, our patient is of good health with no history or clinical features suggestive of such.

To date, no current literature exist regarding the risk factors or prevalence of atypical site AVN. The classical approach is to diagnose AVN by MRI, noting the presence of diffuse oedema, a reactive interface line and serpiginous line. Yet, the presentation of such features is far from ascertaining the diagnosis of an atypical AVN. Hence, Smillie’s Classification for Freiberg’s Disease may likely be the best AVN classification protocol that could be adopted to assess the severity of our patient’s condition [10]. Adopting and drawing from this classification, we propose a five-stage model. Stage 1 represents a fracture in the epiphysis with sclerosis between the cancellous surfaces; stage 2 represents MTT head flattening as the dorsal aspect articular cartilage sinks; stage 3 represents structural compromise of the MTT head with further absorption and sinking of articular cartilage, with bony projections medially and laterally; stage 4 represents that restoration of the normal anatomy of MTT head has passed; and stage 5 represents arthrosis with flattening and deformities of the MTT head. Based on these criteria, our patient’s condition remains at the earlier classifications, either stage 1 or 2, indicative of receiving conservative measures instead of surgical treatment[11]. Due to the rareness of this condition, there is no obvious procedure for differentiation of its diagnosis. However, a number of conditions tend to exhibit a similar presentation and chief complaint, as in our patient. Differential diagnoses such as stress fracture, gouty arthritis, subchondral fracture with non-union, rheumatoid arthritis (RA), hallux rigidus arising from degenerative arthritis, and bone marrow oedema syndrome (BMES) are all compatible with the clinical presentation and imaging results of our patient.
Stress fracture is one of the more important differential diagnoses of this case. This condition, however, would not present with the characteristic appearances on imaging found in AVN. A fracture line, accompanied by periosteal and soft tissue oedema, can also be found in an MRI of a stress fracture, yet, a serpiginous line is unlikely to be present[8,12]. The differentiation between a stress fracture and AVN of first MTT is important, as the management approach for both are extremely different. The general approach to a stress fracture would be rest and prevention of weight-bearing activities[13].

A subchondral fracture refers to a stress fracture occurring below the joint cartilage, commonly seen in femoral head and knee joints, but also reported in MTT heads (most commonly the 2nd MTT). The condition is characterised by slow healing[14], a similar MRI presentation of a serpiginous line[15], and an associated narrow oedema-like pattern[16], which were present in our patient. Fracture non-union can be excluded due to the absence of blurred fracture margins and external callus formation on CT[17]. Further differentiation is possible, as the patient did not present with MTT head flattening[16]. The management approach to such pathology would resonate with a similar approach to that of a stress fracture.

Gouty arthritis commonly presents with pain, swelling, redness and warmth at the first MTP[18]. In any case of hallux pain, gout cannot be excluded without a prior serum uric acid test (normal: ≤ 6.0 mg/dL in women)[19]. Although being overweight is a risk factor[20], gout would seem unlikely for our premenopausal patient with no medication usage or chronic disease. Nevertheless, if the patient suffered from gouty arthritis, a purine-free or low protein diet, along with uric acid-lowering medication, must be implemented as part of the management plan during treatment.

Although Rheumatoid arthritis (RA) is also unlikely to occur in our young patient, it cannot be immediately excluded owing to a presentation of local pain, oedema, redness and limited range of motion[21]. Similarly, there is no gold standard for diagnosing RA. Based on the guidelines of the American College of Rheumatology, diagnosis is proposed through clinical presentation plus various serum results, such as presence of Rheumatoid factor, Anti-CCP antibodies, elevated C-reactive protein level and erythrocyte sedimentation rate. Laboratory assessment was not conducted on this patient owing to low suspicion of autoimmune related cases, yet, the diagnosis of RA must be considered if patient was to deteriorate with our given management plan. Further implications of RA include the presentation of bone erosion and bone oedema on imaging with joint space narrowing[22]. Imaging modalities can effectively reveal if the lesion is confined to first MTT head, rather than the MTP[23]. Although RA is unlikely to be the diagnosis in this case, it is worth noting the differences in the treatment approaches of a patient with AVN in comparison to a systemic disease, such as RA. For patients with RA, disease-modifying antirheumatic drugs are recommended as the mainstay of treatment[24].

Degenerative arthritis leading to hallux rigidus (HR) is another condition presenting with pain, stiffness and decreased range of motion[25]. HR, however, exhibits palpable exostosis[26] and radiographic evidence of MTT head flattening with subchondral sclerosis, in addition to joint space narrowing[27]. For these reasons, HR can be excluded in our patient. Management of HR would involve the use of orthotics and pads to restrict movement of the big toe, along with anti-inflammatory medications for pain relief[28].

Bone marrow oedema syndrome (BMES) may also be possible, due to radiographic evidence of oedema and localised debilitating pain[29]. Notably, BMES may occur concomitant to AVN and is not strictly a differential diagnosis[30]. BMES is characterised by high bone marrow signal intensity on fluid sensitive sequences on MRI. This is like what is seen on the MRI for our patient. Among all BMES, transient osteoporosis has been reported to be affecting only one skeletal site, similarly in our patient. However, it has also been cited to be associated with subclinical hypothyroidism, which is not the case in our patient[31]. One can also distinguish AVN from BMES by contrast-enhanced, three-dimensional spoiled gradient-echo sequence. As BMES possesses high plasma flow and low mean transit time in the subchondral area, AVN exhibits a small “rim” of high plasma flow[32]. Hence, BMES seems unlikely in our patient, as the condition is largely transient and self-limiting[30].

In general, osteotomy and joint debridement are possible options to manage AVN in our reported case. However, the mild severity of our patient’s symptoms suggest that such a drastic approach might not be necessary. Decompressive procedures, bone grafting and joint replacement exist as other treatment options of AVN. These treatments, however, are more commonly used in the management of the typical sites of AVN, rather than the first MTT head. It has been illustrated that pressure at the mid-forefoot beneath the second to fourth MTT head is higher than the mean
pressures of the medial and lateral aspects of the forefoot, namely the first and fifth MTT head respectively[33]. Thus, it is appropriate to initially treat this patient with nonoperative methods eliminating weight-bearing stress rather than adopting operative treatments to correct fractures or deficient blood supply as seen in AVN in typical sites.

Moreover, the main concern of our patient was not the deficit in range of motion, but the pain that resulted from cross-training. Therefore, this pain can be adequately controlled by Paracetamol and NSAIDs to allow the patient to return to play and also prevent unnecessary risks and possible complications from operative treatment. Even though the patient continued to worry about returning to her original intensity of training level, she displayed gradual improvements in her capacity of weight bearing and duration of play. As a result, the patient was placed on regular follow-up and conservative treatment with analgesics. In addition, a weight loss programme, orthotic footwear and restricted weight bearing can be considered. As her body mass index (BMI) was considered overweight (BMI = 25.2)[34], prescribing a weight loss programme may be beneficial in reducing stress on the hallux, which may enhance recovery.

CONCLUSION

In conclusion, an efficient and precise diagnosis of the patient’s case was important, especially considering her involvement in sports. Currently, patient shows promising progress in training level, she displayed gradual improvements in her capacity of weight bearing though the patient continued to worry about returning to her original intensity of traumatic injury with prolonged recovery time.

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Successful treatment of solitary bladder plasmacytoma: A case report

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Abstract

BACKGROUND
Plasmacytoma is a rare neoplastic disorder that arises from B-lymphocytes. Solitary bladder plasmacytoma, a type of solitary extramedullary plasmacytoma, is even rarer. Treatments for solitary extramedullary plasmacytoma include surgery, chemotherapy, and radiation. However, there are no clinical trials or guidelines specifying which treatment might represent the gold standard.

CASE SUMMARY
We herein report a case of a 51-year-old woman with solitary bladder plasmacytoma (SBP). There remains no consensus regarding the optimal treatment for SBP. However, we successfully treated her with transurethral resection of bladder tumor followed by postoperative radiotherapy (50 Gy/25 F). The patient remained free of tumor recurrence at a 7-mo follow-up.

CONCLUSION
Radiation is the potential main treatment for SBP. However, surgery is also necessary.

Key Words: Bone marrow; Local neoplasm recurrence; Multiple myeloma; M-proteins; Urinary bladder neoplasms; Case report

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Core Tip: Solitary bladder plasmacytoma is rare. At present, there is no consensus on the optimal treatment for this disease. Herein, we reviewed past case reports on SBP...
and suggested radiation as its main treatment based on our results. Furthermore, radiation combined with surgery may be better than radiation alone. In addition, close monitoring is as important as treatment, and monoclonal protein is significant to the prognosis of this disease.

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INTRODUCTION

There are three types of plasmacytomas: Extramedullary plasmacytomas (EMP), solitary plasmacytomas of bone, and multiple myeloma (MM)[1,2]. MM is a common hematological malignancy characterized by the proliferation of clonal plasma cells and the production of monoclonal proteins[3]. Single plasmacytoma and isolated EMP of bone belong to isolated plasmacytoma[1], which refers to localized plasmacytoma occurring in bone (isolated plasmacytoma of bone) or outside bone marrow (single EMP). Less than 5% of plasmacytomas might present as single lesions, whereas extramedullary soft-tissue plasmacytomas are rarer[4]. Most solitary EMP (SEPs)[3] are localized in the head and neck, especially the upper respiratory tract; the second most frequent site is the gastrointestinal tract. Conversely, few rare sites reported include the central nervous system, thyroid, breast, testes, parotid glands, and urinary bladder[5]. Bladder plasmacytoma (BP)[6] is extremely uncommon, with only 22 cases having been reported so far before 2010; 8 had a history of MM, while 5 had lymphadenopathy at presentation, and the most recent one[7] was an asymptomatic solitary bladder plasmacytoma (SBP).

However, solitary plasmacytoma[8,9] can develop into MM, as a more aggressive plasmacytoma associated with shorter progression-free survival and poorer prognosis. Based on the different treatments and prognoses of their malignancies, solitary plasmacytoma should be distinguished from MM.

The diagnostic criteria for isolated plasma cell tumors are: (1) Single extramedullary mass caused by clonal proliferation of plasma cells; (2) Normal morphological examination of bone marrow cells and bone marrow biopsy; (3) Normal skeletal survey including an X-ray examination of the long bones; (4) No anemia, hypercalcaemia, or renal failure due to plasma cell disease; and (5) Lack or low levels of monoclonal immunoglobulins in serum or urine. Magnetic resonance imaging and positron emission tomography-computed tomography (CT) are obviously helpful for determining whether SEP progresses to MM[3].

CASE PRESENTATION

Chief complaints
A 51-year-old woman presented with acute urination pain for 2 wk.

History of present illness
The patient was previously diagnosed with acute urethritis at another institution. After having been unsuccessfully treated, she was transferred to our hospital for further diagnosis and treatment.

History of past illness
The patient had no history of any other illness.

Personal and family history
Normal menstruation in the past, but she is menopausal now. She denied any family history.
**Physical examination**  
No abdominal mass was palpated, no pain was elicited upon pressing the bladder area, and no obvious positive findings were found.

**Laboratory examinations**  
The results such as routine hematological testing, blood sedimentation rate, serum carbohydrate antigen (CA)199, CA125, CA153, alpha-fetoprotein, and carcinoembryonic antigen and so on were normal.

**Imaging examinations**  
A renal color-Doppler ultrasonography detected solid bladder nodules localized at the inner surface of the urinary bladder close to the urethral orifice. Then, the patient was transferred to our hospital for more specialized treatment. We performed contrast-enhanced CT scan of both kidneys and the pelvis. It indicated posterior bladder occupation: A nodule on the posterior surface of the bladder, measuring about 15 mm × 11 mm. The CT attenuation value of plain scan was about 26 Hu, and the enhancement was obvious, showing progressive enhancement of about 80 Hu. Neoplastic lesions were considered, and bladder cancer was not excluded (Figure 1).

**FINAL DIAGNOSIS**  
Solitary bladder plasmacytoma.

**TREATMENT**  
The patient consented to undergo transurethral resection of bladder tumor. Pathological examination of the resected specimen suggested bladder tumor: Diffuse infiltration of tumor cells of the same size in the lamina propria were present, the nucleus was offset, and it looked like plasma cells. Mitosis was rare, and plasmacytoma was highly suspected. Immunohistochemistry results revealed: P63 (-), cytokeratin 20 (-), P53 (-), Ki67 (2%+), GATA binding protein 3 (-), and cytokeratin (-). B-cell lymphoma clonal gene rearrangement test results were: immunoglobulin heavy chain (+) and immunoglobulin light chain (+). Supplemental immunohistochemical results were: CD38 (+), CD138 (+), Kappa (+), and Lambda (-) (Figure 2).

Thereafter, as we recommended, the patient underwent postoperative radiation therapy of 50 Gy/25 F. Further bone marrow examination revealed that the ratio of bone marrow hematopoietic tissue to fat cells was about 4:6 under microscope; three lines of hematopoietic cells could be seen. In addition, the proportion of granulocytes and erythrocytes was also slightly elevated. Erythroblasts were the most identified cells in the erythroid. Myelocytes, metamyelocytes, and mature granulocytes were the most identified cells in the granulocyte series. No obvious abnormalities in the morphology and number of megakaryocytes were observed. No significant increase in the number of plasma cells was seen. Immunohistochemical results were: CD20 (Scattered decimal+), CD3 (Scattered decimal+), CD138 (Scattered+), CD38 (Scattered+), K (few+), L (Scattered+), epithelial membrane antigen (-), multiple myeloma oncogene 1 (-), CD56 (-), and myeloperoxidase (part+).

**OUTCOME AND FOLLOW-UP**  
Postoperative positron emission tomography-CT indicated: (1) Normal changes after resection of the posterior tumor of the bladder; a close follow-up was recommended; (2) The trunk axis bone metabolism was slightly increased diffusely; thus, it was necessary to pay attention to the possibility of developing myeloma, and bone marrow biopsy was recommended; (3) There were multiple slightly enlarged lymph nodes in level II of the bilateral neck space, and the metabolism was slightly increased, suggesting lymph node inflammatory hyperplasia; (4) The soft tissues around the shoulder joints were slightly thickened, and the metabolic symmetry was slightly increased indicating inflammatory changes; and (5) No clear abnormally high metabolic lesions in the rest of the body were detected. Laboratory test results including serum calcium and hemoglobin levels were normal. Levels of serum
immunoglobulins: Kappa and lambda and Bence-Jones protein were also normal. After completing postoperative radiotherapy of 50 Gy/25 F, a 7-mo follow-up showed no obvious symptoms.

DISCUSSION

Based on our findings, radiotherapy might be the main treatment of SBP. However, surgery is also necessary. Close collaboration between the hematology department, radiotherapy department, and surgeons is essential to formulate an appropriate treatment plan. Radical radiotherapy is recommended for SBP as the first choice. The tumor irradiation range should be at least 2 cm outside the edge detection of the magnetic resonance imaging view. The dose used was 40 Gy, given in 20 doses. When SEP is > 5 cm, the recommended dose should be 50 Gy, given in 25 divided doses. Evaluation of the response after radiotherapy depends on changes in monoclonal protein levels, progression or elimination of symptoms, and appearance of new lesions on imaging examinations. Patients whose monoclonal protein disappears after treatment indicate a high probability of cure. However, patients whose paraproteins persist after 1 year of treatment will progress to MM. The role of adjuvant chemotherapy has not yet been elucidated. Adding chemotherapy to radiotherapy has advantages in improving local control and preventing or delaying progression to MM. Patients with SBP need to be closely monitored for developing MM and should be followed up every 6 wk for 6 mo.[2]

Regarding prognosis, patients with systemic diseases have a poor prognosis, and 10% of patients experience local recurrence[7]. However, there is currently a lack of reports on specific long-term follow-up data of bladder plasmacytoma[10]. Therefore, we reviewed nine case reports of SBP and summarized them in Table 1.

Most of the cases reviewed were treated with radiotherapy, and some cases underwent adjuvant chemotherapy or surgery. Two of these 9 cases were reported dead. Only 1 case developed MM and died, and there were no signs of recurrence. Therefore, the recurrence rate of SBP is low, and prognosis is significantly better than
that of MM. However, SBP is still possible to progress to MM.

SBP is a very rare bladder malignancy. At present, there is still a lack of optimally sufficient treatment and prognostic data on SBP. Treatment of SBP is mainly based on the treatment of SEP. In terms of prognosis, the recurrence rate and survival rate of SBP are still unclear, and it may progress to MM. However, the overall prognosis of SBP is significantly better than that of MM.

**CONCLUSION**

Radiation is the potential main treatment of SBP. Moreover, radiation combined surgery may be better than radiation alone. In addition, close monitoring and follow-up are as important as treatment, and monoclonal protein is a significant laboratory examination for the prognosis of this disease.

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Successful management of solitary bladder plasmacytoma


Pseudomyxoma peritonei originating from intestinal duplication: A case report and review of the literature

Xue-Di Han, Nan Zhou, Yi-Yan Lu, Hong-Bin Xu, Jun Guo, Lei Liang

Abstract

BACKGROUND
Pseudomyxoma peritonei (PMP) is a rare mucinous neoplasm with a relatively low incidence of 1 to 2 per million individuals. It is typically characterized by a type of gelatinous ascites named “jelly belly”. Most cases of PMP occur in association with ruptured primary mucinous tumors of the appendix (90%). Periodically, PMP can originate from mucinous carcinomas at other sites, including the colorectum, gallbladder, and pancreas. However, unusual origin can occur, as noted in this case report.

CASE SUMMARY
A 52-year-old woman had an unusual derivation of PMP from intestinal duplication. The patient complained of abdominal distension and increasing abdominal girth. Abdominal contrast-enhanced computed tomography showed a mass in the greater omentum located on the left side of the abdomen, likely to be a cystic mass of peritoneal origin. A PMP diagnosis was presumed based on the specific signs of the mass with flocculent and stripe-like echoes in ultrasound images. Ultrasound-guided percutaneous aspiration suggested a high likelihood of PMP. Once the PMP diagnosis was recognized, identification of the origin of the primary tumor was indicated. Thus, an exploratory laparoscopy was performed. In the absence of a primary tumor of appendix origin, the diagnosis of a low-grade mucinous neoplasm of intestinal duplication origin was finally confirmed by histopathology.

CONCLUSION
PMP is secondary to mucinous carcinomas of the appendix mostly. This case resulted from an unusual derivation from intestinal duplication.
INTRODUCTION

Pseudomyxoma peritonei (PMP) is an uncommon disease with a relatively low incidence of 1 to 2 per million individuals[1,2]. PMP is often misdiagnosed clinically due to the lack of specific clinical presentation[3].

Classically, most PMP tumors are not primary, but secondary to ruptured mucinous tumors of other organs, especially the appendix[4]. Occasionally, PMP arises from adenocarcinomas of other sites within the gastrointestinal tract[5,6]. Typically, this disorder is characterized by an abundant accumulation of mucinous ascites developing from mucin secretion by a primary tumour[7-9]. The primary tumour ruptures and tumor cells then spread to implant throughout the peritoneal cavity, which results in the typical “jelly belly” appearance. Considering the rarity of the primary lesion of intestinal duplication, we report the current case with PMP seen in our hospital. This is an extremely rare origin of tumor disease.

CASE PRESENTATION

Chief complaints
A 52-year-old woman presented with the symptoms of abdominal distension and increasing abdominal girth.

History of present illness
Because of decreased appetite, the patient was referred to our hospital for further evaluation.

History of past illness
The patient had a rheumatoid arthritis history for 18 years. She also had a diagnosis of superficial gastritis for 2 mo.

Personal and family history
There was no family history.

Physical examination
Physical examination revealed the patient had a distended abdomen with a hard and non-tender mass. The mass was approximately 15 cm in diameters with ill-defined margins. Shifting dullness could not be found.
Laboratory examinations
Blood examination was performed. Normal levels of the tumor markers carcinoembryonic antigen (CEA), carbohydrate antigen 12-5 (CA12-5), CA19-9, and CA724 were observed. However, an increased CA242 level (25.87 U/mL) was found. Other physical examination results were as follows: Body temperature 37.0 degrees, pulse 80 beats per minute, respiratory rate 16 breaths per minute, blood pressure 120/70 mmHg, and abdominal gurgling sounds approximately three times per minute. No abnormalities were seen on the ultrasonic cardiogram or gastroscopy. The patient had a relatively unremarkable previous medical history apart from rheumatoid arthritis. She denied any other relevant, specific past medical or family medical history. The urinary and bowel elimination functions were reported to be good. She denied weight loss.

Imaging examinations
Contrast-enhanced abdominal computed tomography (CECT) (Figure 1) showed a mass in the greater omentum located on the left side of the abdomen, likely to be a cystic mass of peritoneal origin.
Ultrasound indicated that the mass in the left upper and middle abdomen was flocculent, with an internal stripe-like echo (Figure 2A). The mass could not be deformed by the probe pressing technique.[10,11] The space occupying lesion looked like a mucinous mass, on the basis of the flocculent and stripe-like echoes observed in the scan. Subsequently, ultrasound-guided percutaneous aspiration of the cystic lesion revealed hallmark yellow gelatinous material characteristic (Figure 2B). These findings, combined with the clinical presentation, suggested a clinical diagnosis of PMP.

Surgical operation
Once the PMP diagnosis was recognized, identification of the origin was indicated. Thus, an exploratory laparoscopy was performed. It showed a mass with cystic characteristics and jelly-like content located inside the greater omental cavity. Considering the jelly in the greater omentum, the suspicion of PMP increased in possibility.[12]
Nonetheless, complete microscopic tissue examination of the appendix was needed. Considering that appendiceal origin was most likely, appendectomy was performed with the permission of the family. Frozen sections of the excised appendiceal tissue were immediately analyzed during the operation. Hematoxylin-eosin (HE) staining showed chronic appendicitis obliterans of the tissue (Figure 3).

Women with PMP often have mucinous tumors involving both the appendix and the ovary.[13,14] Hence, the ovaries were carefully inspected in the patient, which showed negative results. Exploratory laparotomy therefore continued, in the absence of primary tumors from appendix and ovary. The location of jelly in the omental cavity necessitated total omentum removal. During radical greater omentectomy, an extremely sticky mucoid material was observed proximal to the splenic flexure of colon, which was a helpful feature likely signaling the primary origin of the cystic tumor. Besides, it was consistent with the location of the lesion on preoperative CECT imaging. Therefore, the sticky mucoid material was separated. And a mucinous tumor was found located on the anterior lobe of mesocolon on the left part of the splenic flexure of the transverse colon (Figure 4). Omentectomy was performed as the preferred option under this set of conditions.

FINAL DIAGNOSIS
There was a subsequent finding of mucoid material in the anterior lobe of the transverse mesocolon. Immunohistochemistry identified intestinal duplication origin. Low-grade mucinous epithelial cells were lining in the capsule wall of the cystic mass in the focal area. Extensive fibrosis and calcifications were found in the cystic wall. The smooth muscle layer could also be seen at some sites (Figure 5).

As shown in Figure 6, immunohistochemical staining of the mucinous tumor lesion demonstrated negative expression of cytokeratin (CK)-7, but strongly positive expression of CK-20, Villin, CDX-2, and Mucin 2 (MUC-2). PMP typically originates from MUC-2 over-expression of goblet cells.[15] CDX-2 plays a crucial role in cell proliferation and differentiation.[16] The finding of CDX-2 positive expression indicated that the tumor originated from the gastrointestinal (alimentary) system[17].
Figure 1 Abdominal contrast-enhanced computed tomography revealed a low density mass in the upper abdomen proximal to the spleen (arrow).

Figure 2 Ultrasound image and transabdominal ultrasound-guided percutaneous aspiration of the mass in the left upper abdomen. A: A large mass with flocculent and stripe-like echoes (arrow) was detected in the left middle and upper abdomen by ultrasound; B: Yellow gelatinous material was aspirated from the abdomen via transabdominal ultrasound-guided percutaneous aspiration.

Further pathology consultation with two other hospitals (Peking University Cancer Hospital and Peking Union Medical College Hospital) was performed to confirm the diagnosis. The two hospitals obtained the similar results that the presented case was PMP derived from intestinal duplication.

TREATMENT

Macroscopic tumor excision combined with heated intraperitoneal chemotherapy (HIPEC) has shown encouraging outcomes for extra-appendiceal PMP[2,18]. The patient was therefore treated with HIPEC, which consisted of 10 mg of mitomycin and 40 mg of cisplatin along with concurrent intravenous chemotherapy therapy of 5-FU (1 g). A 90-min thermal cycle was adopted.

OUTCOME AND FOLLOW-UP

The peritoneal cancer index[19] was estimated in the patient to assess the extent of PMP. The size of the lesion was scored: 0 = no tumor, 1 = tumor ≤ 0.5 cm, 2 = 0.5 cm < tumor ≤ 5.0 cm, and 3 = tumor > 5.0 cm. The cystic lesion was located behind the posterior wall of stomach, in the front of the pancreas, and on the inside of the spleen, which occupied regions of 3, 4, and 0. The scores of the three regions were all 3. The jelly like ascites in the uterus-rectum-fossa in region 6 was scored 1. Thus, the aggregative score of 13 abdominopelvic regions reached 10 in surgery. A complete cytoreduction was achieved after surgery. The degree of cytoreduction reached a grade of 0. Post-treatment CEA, CA12-5, CA19-9, CA724, and CA242 were all negative.
Figure 3 The obtained appendix specimen and its hematoxylin-eosin staining results. A: Gross pathology of appendix showed a length of 5.0 cm and width of 0.3-0.6 cm in diameter; B: Hematoxylin-eosin staining results of the specimen demonstrated appendicitis obliterans.

Figure 4 Intraoperative pictures. A: Characteristic cystic mass (arrow) presented in the anterior lobe of the transverse mesocolon in the left part of the splenic flexure; B: A yellow jelly-like mass existed inside.

Figure 5 Hematoxylin-eosin staining of the specimen found in the splenic flexure of the colon revealed a cystic mass emanating from the intestinal duplication, with low-grade mucinous epithelial cells lining in the capsule wall. A: × 40; B: × 200.

Additionally, no obvious abnormalities were observed on repeat abdominal computed tomography (CT). The patient had no tumor recurrence in follow-up visits until May, 2020 (5 years after the initial operation).
DISCUSSION

The diagnosis of PMP, a rare clinical syndrome, is difficult[20,21]. Commonly, the presenting symptom is increasing abdominal girth. As symptoms are typically non-specific, an initial misdiagnosis of other conditions occurs frequently. Usually a suspected diagnosis may be made by ultrasonography. Ultrasonography, CT, and other examinations, followed by histopathologic verification of extensively sampled tumor, are the preferred ways to confirm a diagnosis of PMP[22]. The feature of flocculent and stripe-like echoes could be detected by an experienced observer[10,23], which is helpful for the diagnosis of PMP. Detection of yellow gelatinous material[24] via transabdominal ultrasound-guided percutaneous aspiration strengthens the probability of PMP diagnosis.

Once the PMP diagnosis is recognized, the source should be identified. The great majority of PMP cases are associated with the spread of a primary mucin-producing tumor of the appendix, accounting for approximately 90% of cases. According to the clinical experience of our center, more than 86% (904/1050) of the center’s PMP cases originated from appendix. A primary PMP tumor can arise from elsewhere in the gastrointestinal tract as well. Since most PMP cases are due to appendiceal tumors, the appendiceal region should be closely inspected. Studies[25,26] have reported that it might be impossible to identify an appendiceal origin of PMP at surgery because the residual appendix may be small or fibrosed after rupture. Thus, it is preferred to perform an appendectomy. The appendix should be sent for serial sections for definitive histopathology examination before another primary site is considered[27].

The coexistence of ovarian and appendiceal mucinous tumors is commonly encountered[4]. Substantial research discusses long-held controversies regarding origin from either the appendix or the ovary in mucinous tumor cases of PMP in women. Several studies[28-31] have suggested that most cases of PMP in women are of intestinal origin with secondary ovarian involvement. The removal of the ovaries is routinely advised in patients with colonic origin of carcinomatosis and menopause, as there is a high chance of ovarian metastasis.

Since there was an abnormal omental mass indicated by preoperative CT in this case, careful inspection of the anatomic region of the peritoneal cavity where extremely sticky mucoid material occurred was required. Finally, a mucinous tumor in the anterior lobe of the transverse mesocolon was observed on exploratory laparoscopy, though peritoneal tumors were difficult to identify. The subsequent pathology test of the lesion revealed a low-grade mucinous adenocarcinoma, originating from intestinal duplication.

Figure 6 Histologic presentation of low-grade mucinous neoplasm. A: Hematoxylin-eosin staining of the primary tumor; B-F: Immunohistochemical staining found that the primary tumor was CK-7(-) (B), CK-20(+) (C), Villin(+) (D), CDX-2(+) (E), and MUC-2(+) (F).
In terms of severity of the disease, PMP is classified into either low-grade or high-grade mucinous adenocarcinomas. The distinction between low-grade and high-grade carcinomas is of prognostic significance. Patients with low-grade tumors generally have a good 5-year survival of 63%-86% comparatively, whereas high-grade tumors generally indicate a survival of only 28%-44%. It is noteworthy that adult intestinal duplication is quite rare. In the current case, the intestinal duplication was characterized by well-developed smooth muscle. Additionally, a low-grade mucinous epithelium and smooth muscular layers in the intestinal tumor focal area were present. Typically, intestinal duplication arises from the mesenteric border of the bowel. But the abnormal changes in the mesentry or mesocolon could not be detected by ultrasound or CT due to the anatomical complexity of the region.

It is hypothesized that the case was caused by the metaplasia of mucous epithelial cells in duplication of the intestine. Mucinous tumor cells produced progressive amounts of mucinous materials and then penetrated through the intestinal wall, eventually spread to the peritoneal cavity in the form of gelatinous deposits. Increased abdominal girth then occurred, but the mechanism for this process needed further study. PMP tumors are mostly CK-20 positive and CK-7 negative. The positive expression of CDX-2 in this case indicated an origin from the gastrointestinal system.

CONCLUSION

In conclusion, PMP is a rare condition characterized by the deposition of mucinous material on peritoneal surfaces. Most of the tumors are not primary, but secondary to ruptured mucinous tumors of other organs. The appendix is by far the most common primary site. It is noteworthy that intestinal duplication could also be the origin of PMP, which was also reported by Lemahieu et al. and Letarte et al.

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Agranulocytosis following injection of inactivated Japanese encephalitis vaccine (Vero cell): A case report

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Author contributions: Wang L reviewed the literature and drafted the manuscript; Zhang X was responsible for the revision of the manuscript for important intellectual content; Liu YT reviewed the literature and contributed to manuscript drafting; all authors issued final approval for the version to be submitted.

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BACKGROUND

Japanese encephalitis virus (JEV), a mosquito borne flavivirus, is the leading cause of viral encephalitis in Asia, in terms of frequency and severity. JEV infection is thought to confer lifelong immunity. With the near eradication of poliomyelitis, JEV is now the continent’s leading cause of childhood viral neurologic infection and disability. The most common clinical manifestation of JEV infection is acute encephalitis, and currently there is no specific antiviral therapy. Japanese Encephalitis Vaccine (JE-VC) is an effective prevention measure, including JE-VC, Live (JE-MB), and Inactivated JE-VC.

CASE SUMMARY

A 9-mo-old girl received injection of Inactivated JE-VC (Vero cell) (Liaoning Chengda, batch number 201611B17) on August 31, 2017. On that night, she developed a fever with the body temperature up to 38.5 °C, for which Ibuprofen Suspension Drops 1.25 mL was given as antipyretic treatment. On September 1, the patient developed apoleisis, and her parents noticed herpes in her oral cavity. The patient was sent to our hospital on September 3. Physical examination led to a
diagnosis of herpetic stomatitis, for which Stomatitis Spray 1 puff, tid, Kangfuxin Liquid 2 mL, tid, and vitamin B, 0.5 tablet, tid, were prescribed. Routine blood tests for low fever on September 6, 2017 revealed an absolute neutrophil count (ANC) of 0.62 \times 10^9/L, hemoglobin (Hb) of 109 g/L, and platelet count (PLT) of 308 \times 10^12/L, and the tests were monitored regularly thereafter. The patient was followed until July 26, 2020, when routine blood tests revealed ANC 1.72 \times 10^9/L, Hb 138 g/L, and PLT 309 \times 10^12/L, indicating that the neutropenia count had normalized.

**CONCLUSION**

This report attempts to bring to clinical attention that Inactivated JE-VC (Vero cell) might cause prolonged granulocytopenia or even agranulocytosis.

**Key Words:** Inactivated Japanese Encephalitis Vaccine (Vero cell); Neutropenia; Agranulocytosis; Japanese Encephalitis virus; Case report

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**Core Tip:** So far, there has been no report of vaccine-induced neutropenia that persisted for 2 years until recovery. Japanese Encephalitis virus, a mosquito borne flavivirus, is the leading cause of viral encephalitis in Asia, in terms of frequency and severity. This report attempts to bring to clinical attention that Inactivated Japanese Encephalitis Vaccine (Vero cell) might cause prolonged neutropenia or even agranulocytosis.

**INTRODUCTION**

Japanese Encephalitis virus (JEV), a mosquito borne flavivirus, is the leading cause of viral encephalitis in Asia, in terms of frequency and severity[1].

JEV infection is thought to confer lifelong immunity. With the near eradication of poliomyelitis, JEV is now the continent’s leading cause of childhood viral neurologic infection and disability[2]. The most common clinical manifestation of JEV infection is acute encephalitis, and currently there is no specific antiviral therapy. Japanese Encephalitis Vaccine (JE-VC) is an effective prevention measure, including JE-VC, Live (JE-MB), and Inactivated JE-VC[2]. Inactivated Vero cell culture-derived JE-VC is the only JE vaccine licensed and available in the United States. In 2009, the U.S. Food and Drug Administration licensed JE-VC for use in persons aged > 17 years. In 2013, licensure was extended to include children aged > 2 mo. The studies on adverse events with JE-VC have reported fever (≥ 38 °C) within 7 d after the first dose or second dose [3].

**CASE PRESENTATION**

**Chief complaints**

A 9-mo-old girl received injection of Inactivated JE-VC (Vero cell) on August 31, 2017. On that night, she developed a fever with the body temperature up to 38.5 °C.

**History of past illness**

No special history of past illness.

**Physical examination**

Physical examination led to a diagnosis of herpetic stomatitis.
Laboratory examinations
Routine blood tests for low fever on September 6, 2017 revealed an absolute neutrophil count (ANC) of 0.62 × 10⁹/L, hemoglobin (Hb) of 109 g/L, and platelet count (PLT) of 308 × 10¹²/L, and the tests were monitored regularly thereafter (Table 1). The patient was followed until July 26, 2020, when routine blood tests revealed ANC 1.72 × 10⁹/L, Hb 138 g/L, and PLT 309 × 10¹²/L, indicating that the neutrophil count had normalized. Routine blood tests revealed ANC 2.18 × 10⁹/L before injection of Inactivated JE-VC (Vero cell) on May 24, 2017 and ANC 2.12 × 10⁹/L on July 3, 2017, indicating a normal neutrophil count.

FINAL DIAGNOSIS
Neutropenia.

TREATMENT
No treatment was given for neutropenia, but treatment for complications such as fever was administered.

OUTCOME AND FOLLOW-UP
The patient developed neutropenia. After September 2017, regular tests were performed to monitor the neutrophil values, as shown in Table 1. The blood test showed that the lowest of ANC was 0.06 × 10⁹/L, indicating neutropenia developed agranulocytosis. The patient was followed until July 26, 2020, when routine blood tests revealed ANC 1.72 × 10⁹/L, Hb 138 g/L, and PLT 309 × 10¹²/L, indicating that the neutrophil count had normalized.

DISCUSSION
It is important to evaluate the safety profile of new vaccines. Abnormal hematological values, such as neutropenia, are often reported. We should not only identify potentially important safety signals but also understand their implications and clinical relevance.

In many cases, neutropenia occurs in people of African descent because they have a lower ANC compared to other ethnic groups. Neutropenia is not listed as a potential adverse reaction in the package insert of Inactivated JE-VC (Vero cell), nor have there been literature reports on neutropenia induced by inoculating such vaccine. There have been few literature reports on vaccine-induced neutropenia. Only one article on randomized, controlled clinical trials and systematic review[4] suggests that several cases of neutropenia were reported as post-inoculation adverse events within the first 2 wk after inoculation. However, such cases of neutropenia were generally transient, and expected to have favorable clinical outcome after receiving various novel or widely recognized licensed vaccines. Furthermore, vaccine recipients with neutropenia typically have a lower baseline ANC than those without neutropenia. Neutropenia is usually caused by a variety of diseases, including infections, drug treatments, autoimmune diseases, nutritional deficiencies, or hematological malignancies, but there is also genetic conditions such as benign ethnic neutropenia (BEN). Those of African descent are particularly affected by BEN which is believed to be caused by the regulatory variation of the chemokine gene Duffy Antigen Receptor and has no connection with the increase in the incidence of infection.

CONCLUSION
So far, there has been no report of vaccine-induced neutropenia that has persisted for 2 years until recovery. This report attempts to bring to clinical attention that Inactivated JE-VC (Vero cell) might cause prolonged neutropenia or even agranulocytosis.
Table 1 Results of blood tests

<table>
<thead>
<tr>
<th>Date</th>
<th>ANC ($\times 10^9$/L)</th>
<th>Hb (g/L)</th>
<th>PLT ($\times 10^{12}$/L)</th>
</tr>
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<tbody>
<tr>
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<td>0.52</td>
<td>113</td>
<td>459</td>
</tr>
<tr>
<td>September 16, 2017</td>
<td>0.13</td>
<td>118</td>
<td>460</td>
</tr>
<tr>
<td>October 7, 2017</td>
<td>0.06</td>
<td>120</td>
<td>335</td>
</tr>
<tr>
<td>October 27, 2017</td>
<td>0.34</td>
<td>110</td>
<td>311</td>
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<tr>
<td>November 28, 2017</td>
<td>0.15</td>
<td>113</td>
<td>353</td>
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<tr>
<td>January 2, 2018</td>
<td>0.35</td>
<td>116</td>
<td>375</td>
</tr>
<tr>
<td>February 12, 2018</td>
<td>0.21</td>
<td>115</td>
<td>365</td>
</tr>
<tr>
<td>April 22, 2018</td>
<td>0.11</td>
<td>118</td>
<td>313</td>
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<tr>
<td>May 25, 2018</td>
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<td>124</td>
<td>252</td>
</tr>
<tr>
<td>November 15, 2019</td>
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<td>129</td>
<td>287</td>
</tr>
<tr>
<td>June 2, 2020</td>
<td>1.49</td>
<td>131</td>
<td>297</td>
</tr>
<tr>
<td>July 26, 2020</td>
<td>1.72</td>
<td>138</td>
<td>309</td>
</tr>
</tbody>
</table>

ANC: Absolute neutrophil count; Hb: Hemoglobin; PLT: Platelet count.

ACKNOWLEDGEMENTS

Heartfelt thanks to Miss DeAnn.

REFERENCES


Importance of clinical suspicion and multidisciplinary management for early diagnosis of a cardiac laminopathy patient: A case report

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Author contributions: All authors played a key-role in the diagnostic and therapeutic workup of the patient, contributed to the writing of the manuscript, and approved the final version to be submitted.

Informed consent statement: The patient provided oral and written informed consent prior to study enrolment.

Conflict-of-interest statement: No conflicts of interest to declare.

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BACKGROUND

Laminopathies are rare diseases, whose cardiac manifestations are heterogeneous and, especially in their initial stage, similar to those of more common conditions, such as ischemic heart disease. Early diagnosis is essential, as these conditions can first manifest themselves with sudden cardiac death. Electrical complications usually appear before structural complications; therefore, it is important to take into consideration these rare genetic disorders for the differential diagnosis of brady and tachyarrhythmias, even when left ventricle systolic function is still preserved.

CASE SUMMARY

A 60-year-old man, without history of previous disorders, presented in September 2019 to the emergency department because of the onset of syncope associated with hypotension. The patient was diagnosed with a high-grade atrioventricular block. A dual chamber pacemaker was implanted, but after the onset of a sustained ventricular tachycardia during physical exertion, a drug eluting stent was implanted on an intermediate stenosis on the left anterior descending artery, which had previously been considered non-haemodynamically significant. During the follow-up, the treating cardiologist, suspicious of the overall clinical picture, recommended a genetic test for the diagnosis of cardiomyopathies, which tested positive for a pathogenetic mutation of the lamin A/C gene. While awaiting the result of the genetic test and, later, the pacemaker to be upgraded to a biventricular defibrillator, a remote monitoring device was given to the patient in

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order to minimize in-person clinical evaluations during the coronavirus disease 2019-related lockdown.

**CONCLUSION**

This case aims to raise awareness of the cardiological manifestations of laminopathies, which can be dangerously misdiagnosed as other, more common conditions.

**Key Words:** Lamin A/C-mutation; Cardiolaminopathy; Ventricular tachyarrhythmias; Remote-monitoring; COVID-19; Case report

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**Core Tip:** Cardiolaminopathy diagnosis, especially in its initial stage, is challenging. In presence of misleading factors, such as coronary stenosis, and limiting factors, such as the coronavirus disease 2019-related lockdown, the difficulties increase. Remote monitoring for assessing arrhythmic burden and clinical suspicion make it possible to safely diagnose this rare disease.

---

**INTRODUCTION**

The lamin A/C (*LMNA*) gene, located on the long arm of chromosome 1 (1q22), codes Lamins A and C by means of alternative splicing. These two intermediate filament proteins belong to the nuclear lamina that underlies and supports the nuclear membrane of eukaryotic cells. *LMNA* gene mutations have been shown to cause several pathological conditions (generally known as laminopathies), such as lipodystrophies, restrictive dermopathies, premature ageing syndromes, peripheral neuropathies, and different types of muscular dystrophy[1]. *LMNA* defects have the worst repercussions on specific tissues, such as neuronal, adipose, epithelial, and striated muscular tissues. With regard to the latter, the possible involvement of the myocardium deserves special mention, as this can lead to cardiac phenotypes characterized by the coexistence of both electrical and mechanical manifestations. Electrical manifestations, which usually appear before mechanical ones, by several years, consist of atrio- and intraventricular conduction abnormalities and atrial and ventricular tachyarrhythmias that can cause sudden cardiac death. On the other hand, cardiolaminopathies are commonly the cause of dilated cardiomyopathy (DCM), and progressive systolic left ventricular dysfunction is associated with heart failure signs and symptoms[2]. However, the initial manifestation of the disease with electrical complications in structurally healthy hearts, their low prevalence in the general population, and their onset in middle age make the diagnosis of genetic cardiopathy challenging. For this reason, the diagnostic workup and the therapeutic process are often delayed, to the point of being fatal due to sudden cardiac death or other complications.

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**CASE PRESENTATION**

**Chief complaints**

Our patient was a 60-year-old Caucasian male who presented in September 2019 with syncope associated with hypotension.
History of present illness
The patient had no previous symptoms and syncope was indeed the first clinical manifestation.

History of past illness
The patient had no history of previous disease and he was not taking any medications.

Personal and family history
The only red flags were the known congenital bicuspid aortic valve and family history of congestive heart failure (sister).

Physical examination
When he came to the emergency department, he presented hypotensive, with tachyarrhythmic peripheral pulse. A paroxysmal atrial fibrillation (AF) episode was diagnosed, which regressed after a few hours.

Laboratory examinations
Routine laboratory tests (complete blood count, kidney function, electrolytes, liver and heart enzymes) were all in the normal ranges.

Imaging examinations
Transthoracic echocardiography showed no pathological findings.

Further diagnostic work-up
The 24-h electrocardiogram Holter monitoring recorded frequent episodes of high-grade atrioventricular block with no further AF episodes. Upon suspicion of an ischemic aetiology, he was admitted to the cardiology unit and underwent coronaryography, which indicated intermediate stenosis (50%) in the left anterior descending artery. This stenosis was not considered hemodynamically significant. Thus, the decision was to implant a dual chamber anti-bradycardia pacemaker. Given the single and short AF episode and the CHA2DS2-VASc score of 0, no anticoagulation treatment was initiated. In December 2019, he underwent a scintigraphy stress–rest test, during which he presented loss of consciousness due to the onset of sustained ventricular tachycardia (VT) (Figure 1), which was successfully treated with cardiopulmonary resuscitation manoeuvres and lidocaine infusion. The arrhythmia was considered to be of ischaemic origin. Therefore, the patient underwent percutaneous transluminal coronary angioplasty with drug-eluting stent (DES) implantation at the known coronary stenosis. During and after hospitalization, numerous non-sustained VTs were recorded, for which he was given amiodarone, with clinical benefit. After a few weeks, a treadmill stress test was also performed under antiarrhythmic therapy, which was negative for both myocardial ischemia and VTs. During the follow-up examinations, considering the patient’s clinical picture, encompassing VT, atrioventricular block, family history, and echocardiographic findings showing accentuated right ventricular apex trabeculation, the treating cardiologist decided to reassess the clinical case. He recommended that the patient undergo cardiac magnetic resonance and molecular analysis performed with a panel of 128 genes known to be associated with cardiomyopathies and channelopathies. Both tests were performed in February 2020 (6 wk after DES implantation, as indicated in the manufacturer’s data sheet). The former showed a left ventricular ejection fraction (LVEF) of 50% without any areas of late enhancement or myocardial fibrosis (Figure 2).

The results of the genetic testing took 3 mo to be validated, during which outpatient appointments with patients were suddenly stopped due to the severe acute respiratory syndrome coronavirus 2-related pandemic. Considering the need to supervise the patient during this time for the possible onset of life-threatening ventricular tachyarrhythmia (LTVT) and AF, without the possibility of a periodic in person interrogation of the PM arrhythmias registry, as was usually done, it was decided to give the patient a remote monitoring device (Medtronic Carelink Network®). The device was configured to transmit the data it recorded, automatically every week. At the same time, both LTVT and AF were set up as “care alerts”, which meant that an automatic alert would have been sent immediately after identification, as long as the potential LTVT or AF onset would have required a prompt and potentially lifesaving intervention, either the upgrading the PM to an implantable cardioverter defibrillator (ICD) or the initiation of a life-long anticoagulant therapy, respectively. Fortunately, no arrhythmias were detected during that time.
Sustained ventricular tachycardia during ergometric stress. Cardiomyopathy electrical complications often anticipate mechanical ones: Life-threatening ventricular tachyarrhythmias may be the first clinical manifestation of the disease.

Cardiac magnetic resonance imaging. It showed an initial decrease in the left ventricular ejection fraction (50%), without any area of late enhancement or myocardial fibrosis.

**FINAL DIAGNOSIS**

The genetic test reported a heterozygous missense mutation (c.949G>A; p.Glu317Lys) in exon 6 of the *LMNA* gene, which is known to be a pathogenic variant. A further LVEF reduction of 43% was observed. Therefore, the patient was diagnosed with cardiac manifestation of laminopathy.

**TREATMENT**

Based on the new diagnosis, it was decided to hospitalize the patient to upgrade the PM to a biventricular ICD.

**OUTCOME AND FOLLOW-UP**

The patient is currently asymptomatic for heart failure. No further LTVT has occurred. He is still using the remote monitoring device in order to promptly identify any new AF episode that would potentially require life-long anticoagulant therapy. The patient is continuing follow-up with both clinical and echocardiographic re-evaluation associated with an electronic check of the ICD.
DISCUSSION

The decision to protect the patient from LTVT was made in accordance with current guidelines\cite{3,4}, which recommend device implantation (class of recommendation IIa) in patients with LMNA gene mutations in the presence of at least two of the following risk factors: (1) Non-sustained VT; (2) LVEF < 45%; (3) Male sex; and (4) Non-missense mutations. However, Wahbi \textit{et al.}\cite{5} recently proposed a new risk score that also takes into account the history of atrioventricular block. The latter has been shown to have a greater accuracy in the risk prediction of LTVT, for which our patient was 41.6%. Based on the 2016 heart failure ESC guidelines\cite{6} (class of recommendation I), we opted for a biventricular ICD in light of the high percentage of pacing (99.4%) and of the concomitant rapid reduction in left ventricular systolic function after PM implantation (LVEF from 60% in December 2019 to 50% in February 2020 to 43% in June 2020), which could also be explained by the more aggressive clinical course of LMNA-related DCM compared with other forms\cite{7}.

CONCLUSION

Laminopathies have a heterogeneous spectrum of cardiological manifestations ranging from supraventricular and ventricular tachyarrhythmias to atrio- and intraventricular conduction disorders and left ventricular dysfunction\cite{1,8}. Moreover, clinical manifestations of cardiac phenotypes tend to occur in an age-related way, starting in the fourth decade of life and reaching 90%-95% of subjects by the seventh decade\cite{1,8}, which corresponds to the timing of the presentation of coronary atherosclerotic disease and idiopathic senile degeneration of cardiac conduction tissue. However, since the latter aetiologies are considerably more frequent than the genetic ones, it is easy to attribute cardiological disorders to them. This was applicable to our patient, in whom the electrical laminopathy manifestations were erroneously confused with manifestations of coronary disease. This belief was supported by the incidental finding of an intermediate lesion on coronaryography, which led the treating physician to implant a probably unnecessary DES and consequently start dual antiplatelet therapy, a treatment that brings an obvious increase in the ischaemic and haemorrhagic risks. The choice to carry out genetic testing in our patient was mainly driven by the overall clinical picture, although it did not fully respect the indications of the Heart Rhythm Society/European Heart Rhythm Association consensus statement\cite{9}, which instead recommends genetic testing in patients with atrioventricular block and DCM. In fact, at the time of genetic testing, echocardiography did not yet show signs of chamber dilation. The initial presentation with electrical complications in structurally healthy hearts is quite common since the structural cardiac manifestations usually arise after the electrical ones\cite{10}. However, in LMNA-related DCM patients, who are at high arrhythmic risk, delaying the diagnosis and waiting for the onset of late mechanical manifestations, in order to follow the guidelines for genetic testing, can also lead to delayed treatment and defibrillator implantation, with possible fatal consequences.

Our case testifies to several findings: (1) How difficult it is to diagnose cardio-laminopathies, especially in their initial stages; (2) How the occurrence of other, more common pathological conditions can be misleading and delay the diagnostic and therapeutic workup; (3) How useful remote monitoring can be, especially during the coronavirus disease 2019-related lockdown, at assessing the arrhythmic burden in patients with suspected laminopathies; and (4) How sudden cardiac death prediction is hard in these subjects.

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REFERENCES


First case of forearm crisscross injury in children: A case report

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Author contributions: Jiang YK, Wu DK, and Wang YB reviewed the literature and contributed to manuscript drafting; Peng CG and Qu J contributed to manuscript drafting; Jiang YK made critical revisions related to important intellectual content, and analyzed and interpreted the imaging findings; all authors issued final approval for the version to be submitted.

Informed consent statement: Written informed consent was obtained from the patient’s parents for publication of this case report and accompanying images.

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Background
Forearm crisscross injury is rare in children; there is no relevant literature so far. Surgeons lack experience and knowledge in treating this type of crisscross injury. We report a case of forearm crisscross injury in a child for the first time and analyze its mechanism.

Case Summary
An 8-year-old boy experienced pain in his left forearm when he accidentally fell while skateboarding. Physical examination revealed swelling and deformity of the left forearm. We performed imaging and the results revealed left radial head dislocation, left distal radial epiphyseal separation from the shaft, and interruption of the continuity of the dorsal cortex of the left distal ulna. Anteroposterior and lateral X-ray films showed that the radius and ulna were crisscrossed. A diagnosis of superior radioulnar joint dislocation, left distal radial epiphyseal injury, and left distal ulnar fracture was made. After unsuccessful manual reduction, we adopted a minimally invasive procedure and succeeded. After a 14-wk period of follow-up, the patient had good left upper limb function, no complaints of pain or limited range of motion, and good follow-up results.

Conclusion
This is the first report of a child with a forearm crisscross injury in which the mechanism and the differences from adult crisscross injury are analyzed. Minimally invasive surgery with intramedullary fixation can achieve a good therapeutic effect. This case provides a reference for the treatment of similar patients in the future.

Key Words: Children; Forearm; Cross injury; Fracture; Case report

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INTRODUCTION

Forearm crisscross injury is rare due to its special mechanism; less than ten cases have been reported in the existing literature. Among current reports, all forearm crisscross injuries occurred in adult patients, and there have been no reports on pediatric patients. We report the first pediatric case of a forearm crisscross injury and analyze its differences in the mechanism from injury in adult patients, which could improve the understanding of forearm crisscross injury in children. Minimally invasive surgery led to the patient’s smooth recovery at follow-up week 14. This case provided a reference for diagnosis and treatment of forearm crisscross injuries in children.

CASE PRESENTATION

Chief complaints

An 8-year-old patient experienced pain and deformity in his left forearm due to an accidental fall. He was admitted to our hospital 2 h after semi-restriction of movement.

History of present illness

A detailed medical history inquiry revealed that the patient accidentally fell while skateboarding; his palm touched the ground, causing excessive external rotation of his forearm and resulting in injury.

Physical examination

Physical examination revealed ecchymosis, deformity of the left wrist, and limited range of motion due to pain. The left forearm showed no obvious swelling, and there was no paresthesia of the left upper extremity, and no vascular or nerve injuries.

Imaging examinations

We performed X-ray and 3-dimensional computed tomography, which showed that the left elbow humeroradial joint was poorly aligned and the radial head was dislocated forward (Figure 1). The left distal radial epiphysis was separated from the shaft, indicating a Salter-Harris type II epiphyseal injury. The cortical continuity of the left distal ulna was interrupted. Anterior and lateral radiographs showed that the ulna and radius were crisscrossed.

FINAL DIAGNOSIS

A diagnosis of superior radioulnar joint dislocation, left distal radial epiphyseal injury, and left distal ulnar fracture was made.

TREATMENT

None of the examinations suggested any obvious contraindications; hence, manual reduction was performed under anesthesia. Unfortunately, manual reduction failed and open reduction surgery was planned. After anesthesia induction, a 5-cm longit-
Figure 1 Preoperative imaging examination showing that the distal radius and ulna were fractured. A: Anteroposterior X-ray of the wrist showing epiphysis injury of the distal radius with the distal fracture displaced to the radial side; B: Lateral X-ray of the wrist showing that the distal fracture was displaced to the back side; C: Anteroposterior X-ray of the elbow showing that the radial head was dislocated laterally; D: Lateral X-ray of the elbow showing that the radial head was dislocated anteriorly; E: Three-dimensional computed tomography of the forearm showing radial head dislocation with distal radial epiphysis injury; F: The relative position of the radius and ulna is crisscross.

A longitudinal incision was made on the radial side of the palmar side of the left wrist to expose the distal radius. The anterior spiral muscle was embedded in the distal radius fracture. The embedded soft tissue was removed and the distal radius fracture was fully reduced under direct vision. Crossed K-wire fixation was performed. When the distal ulnar and radial anatomical structures were restored, the original anatomical position of the superior radioulnar joint was also automatically restored. Afterward, the distal ulnar fracture was fixed using a 2.0-mm elastic intramedullary needle.

OUTCOME AND FOLLOW-UP

Postoperatively, the left elbow was flexed to 90° and the forearm was in a neutral position (Figure 2). After 6 wk of plaster cast immobilization, X-ray examination showed that the fracture fully healed and the disabilities of the arm, shoulder, and hand (DASH) score was 16 points. Hence, the plaster and internal fixation were removed and functional exercises were started (Figure 3). At follow-up week 14, the patient had good left upper extremity function without complaints of pain or limited range of motion (Figure 4). The DASH upper extremity function score was 9 points, with good follow-up results.
DISCUSSION

Forearm crisscross injury is rare. Due to the special mechanism, less than ten cases have been reported worldwide; all cases involved adult patients[1,2]. To date, this special injury has not been reported in children; its pathogenesis, treatment, and prognosis remain unclear. Leung et al[2] first reported the definition and diagnostic criteria of crisscross injury in 2002. A currently recognized crisscross injury refers to simultaneous upper and lower radioulnar joint dislocation with intact interstitial membrane, accompanied by fractures of the radial head and the ulnar styloid process, but not accompanied by ipsilateral ulnar and radial shaft fractures. Lateral and anteroposterior radiographic findings of the forearm revealed radioulnar crisscross. According to Leung et al[2], crisscross injuries can be classified into two types: Type I

Figure 2 Postoperative imaging examination. The forearm returned to its normal anatomical position and internal fixation functioned well. A: Postoperative anteroposterior X-ray showing that the fracture was reduced and the humeroradial joint returned to normal; B: Postoperative lateral X-ray showing that the fracture was reduced and the humeroradial joint returned to normal.

Figure 3 The fracture healed smoothly at postoperative week 6. A: Anteroposterior X-ray examination at 6 wk following removal of the internal fixation; B: Lateral X-ray examination at 6 wk following removal of the internal fixation.
Figure 4 The patient's forearm function returned to normal without complaints of pain or limited range of motion at postoperative week 14. A: Stretching movement of the wrist; B: External rotation of the forearm; C: Stretching movement of the elbow; D: Buckling movement of the wrist; E: Internal rotation of the forearm; F: Buckling movement of the elbow.

refers to forward radial and ulnar head dislocations; type II refers to posterior dislocation of the radial and ulnar heads. The former is due to forearm overpronation, while the latter is caused by supination (with the intact interosseous membrane serving as a fulcrum that participates in the mechanism of the forearm crisscross injury)\[3\]. Our patient’s imaging data showed that the ulna and radius were crisscrossed in the anterior and lateral X-ray images. Although we did not perform magnetic resonance imaging to prove that the interosseous membrane of the forearm was intact, the patient’s forearm was not swollen. When the anatomical structure of the distal ulna and radius recovered, the superior radioulnar joint was automatically restored without any additional intervention. These results indirectly proved that the interosseous membrane was intact. In our case, strictly speaking, only the superior radioulnar joint was dislocated. The distal radius epiphysis was fractured and some distal joints were still connected to the ulna; hence, the inferior radioulnar joint did not comprise a true dislocation. Since the ligament strength in children is greater than that of the epiphyseal plate, epiphyseal injury occurs in the distal radius without inferior radioulnar separation. We believe that this is a special manifestation of crisscross injury in children.

In the diagnosis of crisscross injury in adults, simultaneous dislocation of the superior and inferior radioulnar joints without combined ipsilateral ulnar and radial shaft fractures is a universally accepted diagnostic criterion. Current reports include no description of fractures other than the radioulnar joint dislocation\[2,4,5\]. During adolescence, tendons, ligaments, and joint capsules are two to five times stronger than epiphyses plates\[6\]. Therefore, when radioulnar joint dislocations occur in children, their forearms are extremely pronated or supinated, and injuries to the epiphyseal plate” are possible. In our case, the patient’s forearm was extremely externally rotated and the shearing force of the epiphysis and ligament of the distal radius increased. Epiphyseal fracture occurred due to the different strengths of the epiphyses and ligaments. The child’s single ulna was unable to support the weight of the body and fracture. Our case was different from those reported in the existing literature, possibly due to the differences in the strength of bones and ligaments of children from those of adults. Our patient’s imaging manifestation is fully consistent with the diagnosis of a type I crisscross injury, ignoring the impact of distal radial epiphyseal fractures and considering the palm and ulna as a whole. For fracture in children, we generally do not perform CT examination before operation. However, this is a rare and unique case. In order to observe the relative position of the ulna and radius after injury, we chose three-dimensional CT examination. In the process of CT examination, we have made full radiation protection to the non-examined parts of the children, so the amount of radiation received by the children is not much.
Cases of crisscross injuries reported in the existing literature have been successfully treated by closed reduction, manipulation, plaster, or external fixation, and no complications of joint instability or pain occurred. In a patient reported by Potter et al [4], closed reduction failed multiple times due to deformities of the radial head, and scar reduction was ultimately successful. In our case, multiple manual reductions failed and the patient had an open epiphyseal fracture. Therefore, epiphyseal fractures must be properly treated as early as possible, focusing on anatomical reduction; otherwise, late deformities can easily occur due to premature epiphyseal closure. We performed intramedullary fixation to treat the fracture, reducing the patient’s traumatic stress, while achieving anatomical reduction. The patient fully recovered and returned to his normal life 3 mo postoperatively.

**CONCLUSION**

We report a case of forearm crisscross injury in children for the first time and analyze the mechanism and differences from adults. Minimally invasive surgery with intramedullary fixation for a forearm crisscross fracture can achieve good results. This case provides a reference for future diagnosis and treatment of similar patients.

**REFERENCES**


CASE REPORT

Octreotide-induced acute life-threatening gallstones after vicarious contrast medium excretion: A case report

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Author contributions: Han ZH and Wang CY conceived and designed the research; He ZM and Chen WH acquired data; Han ZH and Wang Q prepared and revised the manuscript; Chen WH provided helpful suggestions about the study; All authors issued final approval of the version for submission.

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Core Tip: Octreotide is widely used for the treatment of acromegaly, neuroendocrine tumors, and secretory diarrhea. However, long-term octreotide treatment can increase the incidence of gallstones. Vicarious contrast medium excretion (VCME) through the hepatobiliary system is well known. However, few studies have reported octreotide-induced acute gallstones following VCME.

Abstract

BACKGROUND
Octreotide is widely used for the treatment of acromegaly, neuroendocrine tumors, and secretory diarrhea. However, long-term octreotide treatment can increase the incidence of gallstones. Vicarious contrast medium excretion (VCME) through the hepatobiliary system is well known. However, few studies have reported octreotide-induced acute gallstones following VCME.

CASE SUMMARY
A 69-year-old man presented with left lower back pain and hematuria caused by a fall. The patient had a history of polycystic kidney disease. VCME occurred following renal artery embolization for a ruptured polycystic kidney. After 5 d of treatment with octreotide, the patient developed acute gallstones and intrahepatic cholestasis which further induced pancreatitis and cholangitis. He was discharged after hemodialysis, antibiotics, and supportive treatments.

CONCLUSION
For patients with a high-risk of VCME, octreotide should be cautiously administered and carefully monitored.

Key Words: Octreotide; Gallstones; Contrast medium; Case report
Han ZH et al. Octreotide-induced gallstones after VCME

INTRODUCTION

Contrast medium (CM) is widely used in intravenous pyelography, computed tomography (CT), and angiography examinations. The incidence of adverse reactions due to CM is low, especially when using modern non-ionic CMs. Vicarious CM excretion (VCME) is a well-recognized entity, of which excretion through the hepatobiliary system accounts for the majority of cases, and is asymptomatic [1]. Octreotide is widely used for the treatment of acromegaly, neuroendocrine tumors, and secretory diarrhea, and long-term treatment significantly increases the incidence of gallstones, most of which are asymptomatic [2].

We report a patient who developed acute gallstones following treatment with octreotide after VCME.

CASE PRESENTATION

Chief complaints

A 69-year-old Chinese male complained of yellow discoloration of the skin and urine with abdominal distension.

History of present illness

The patient was admitted to the emergency department of our hospital in the afternoon of June 11, 2020 complaining of left lower back pain and hematuria caused by a fall 6 h previously. His blood pressure was 81/46 mmHg at admission, and laboratory tests revealed a hemoglobin level of 80 g/L, blood urea nitrogen of 7.9 mmol/L, creatinine of 105 μmol/L, and pH 7.30. Ultrasonography (US) and contrast-enhanced CT (60 mL, 270 mg of iodine/mL; Yangtze River Pharmaceutical Group, Taizhou, China) revealed bilateral polycystic kidney with rupture of the left kidney, a huge hematoma, and multiple liver cysts. The gallbladder and pancreas were normal. Emergency renal artery embolization (RAE, 150 mL iodixanol) was performed, after which his blood pressure promptly returned to normal and hematuria decreased. On the second day after RAE (d1-post-RAE), the patient complained of abdominal distension with absence of both flatus and stool. Paralytic intestinal obstruction was diagnosed together with absence of bowel sounds. He was treated with fasting, gastrointestinal decompression, fluid replacement, and octreotide (100 mg, once daily; Novartis Pharma Schweiz AG, Risch-Rotkreuz, Switzerland). On d5-post-RAE, the patient resumed passage of both flatus and stool, and the above treatments were discontinued.

History of past illness

He had a history of polycystic kidney disease for 40 years, but had no other illnesses.

Personal and family history

He denied a history of similar diseases in close relatives.

Physical examination

Physical examination revealed that the skin and sclera were slightly jaundiced, and a mass 16 cm × 12 cm in size on the left flank was observed, which was soft and tender with percussion pain in the left renal region. There were no abnormal liver and
Laboratory examinations
On d6-post-RAE, the patient’s sclera and skin were slightly yellow, and was worse the following day. Laboratory tests showed that the levels of bilirubin, alkaline phosphatase (AKP) and gamma-glutamyl transpeptidase (γ-GT) were significantly increased (Table 1), but transaminases were normal. Urinalysis showed that urinary bilirubin was positive and urobilinogen was negative.

Imaging examinations
On d3-post-RAE, non-contrast CT showed high density in the gallbladder and colon, which was considered to be due to VCME, while in the upper pole of the left kidney CM had spilled out of the renal artery (Figure 1A). On d7-post-RAE, repeat US revealed a large amount of sludge in the gallbladder, but no dilation of intrahepatic and extrahepatic bile ducts.

Final Diagnosis
Final diagnoses were octreotide-induced acute gallstones and VCME.

Treatment
On the evening of d7-post-RAE, the patient complained of upper abdominal pain. Laboratory tests revealed an amylase level of 640 U/L and lipase level of 1198 U/L, resulting in a diagnosis of acute pancreatitis, which dropped to normal following treatment for 5 d. However, the levels of bilirubin, AKP and γ-GT continuously increased (Table 1). On d8-post-RAE, endoscopic retrograde cholangiopancreatography (ERCP) (10 mL ioversol, 320 mg of iodine/mL; Hengrui Medicine, Jiangsu, China) was conducted and revealed that the duodenal papilla was plump, and brown-black bile and sludge were observed, a nasobiliary catheter was then placed for the drainage of bile. A non-contrast CT on d10-post-RAE showed that the liver was normal except for multiple cysts, while the CM still remained in the gallbladder and colon. Tests for hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, hemolysis and autoimmune hepatitis were negative, and upper abdominal magnetic resonance imaging was normal except for multiple cysts and sludge in the gallbladder (Figure 1B). Antibiotics were upgraded to imipenem-cilastatin sodium as bile culture showed multi-drug resistant Escherichia coli. However, dynamic monitoring of the levels of bilirubin, AKP and γ-GT continued to increase with skin and sclera becoming more yellow (Table 1). The patient developed transient lethargy at night on d16-post-RAE, and then recovered after treatment with the double plasma molecular adsorption system (DPMAS) for 4 h the following day. Dynamic laboratory tests showed that the levels of bilirubin, AKP and γ-GT had declined, but increased again the next day (Table 1). DPMAS was performed again to reduce bilirubin on d19-post-RAE, and to achieve the previous similar changes in laboratory tests (Table 1). Repeat bile culture showed multi-drug resistant Klebsiella pneumoniae subsp, and the antibiotics were changed to sulbactam-cefoperazone followed by a multidisciplinary consultation. Surprisingly, dynamic laboratory tests showed that the levels of bilirubin, AKP, γ-GT, and the white blood cell count gradually began to decrease (Table 1) together with a decrease in the patient’s fever, and yellowing of the sclera and skin.

Outcome and Follow-up
The patient recovered and was discharged after 2 wk of treatment. After 1 and 3 mo, repeated laboratory tests showed that blood cell counts, liver and kidney function were all within normal limits (Table 1).

Discussion
VCME refers to the excretion of water-soluble CM through a route other than renal
Table 1 Levels of bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase during treatment and follow-up

<table>
<thead>
<tr>
<th>Date</th>
<th>TB μmol/L</th>
<th>DB μmol/L</th>
<th>AKP μ/L</th>
<th>γ-GT μ/L</th>
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<tr>
<td>6.12</td>
<td>13.4</td>
<td>6.1</td>
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<tr>
<td>D1</td>
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<td>5.1</td>
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</tr>
<tr>
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<td>92</td>
<td>37.5</td>
</tr>
<tr>
<td>M3</td>
<td>13.6</td>
<td>5.4</td>
<td>51</td>
<td>22.3</td>
</tr>
</tbody>
</table>

1D1 represents the first day after renal artery embolization, and so on.
2M1 represents 1 mo after discharge, and so forth. AKP: Alkaline phosphatase; DB: Direct bilirubin; γ-GT: Gamma-glutamyl transpeptidase; TB: Total bilirubin.

secretion, and is a well-known phenomenon, although the exact mechanism is still not fully understood. According to previous studies, these authors believed that possible factors promoting the heterotopic biliary (vicarious) excretion of CM included prolonged recirculation of the CM due to impaired renal function, hypovolemia and hypotension, and increased protein binding of CM in the presence of acidosis.[1,3]. Higher doses, higher molecular weight and lower osmotic pressure of CM are also thought to be factors contributing to VCME[1,3]. Although VCME can also occur in patients with normal renal function, studies have shown that patients with renal insufficiency have a higher incidence of VCME[1]. An analysis of our patient showed that some of the above-mentioned high-risk factors were present, which may have led to VCME.
Long-term treatment with octreotide can lead to a significant increase in the incidence of gallstones, which is reported to be 10%-63%, but these patients are often asymptomatic[2]. Many previous studies have shown that octreotide not only inhibits meal-stimulated cholecystokinin release from the small intestine and gallbladder contraction, but it also directly promotes gallbladder absorption, which may act synergistically to increase the concentration of prolithogenic factors in bile and facilitate nucleation and stone growth[4]. Moreover, octreotide induces lithogenic changes in bile composition and physical chemistry such as supersaturated bile, excess biliary cholesterol transport in vesicles, a high vesicular cholesterol: phospholipids molar ratio, and abnormally rapid nucleation of cholesterol microcrystals[5]. Some studies have shown that octreotide prolonged intestinal transit leads to increased deoxycholic acid absorption from the colon and thereby the risk of gallstone formation [6,7], which was consistent with the long-term retention of CM in the gallbladder and colon in this case. In addition, octreotide inhibits the usual prandial relaxation of the sphincter of Oddi, thus creating physical conditions favoring microcrystal precipitation and stone formation[6]. The development of stones occurs after an average period of 3 years, and increases with the dose of medication and duration of treatment [8]. In this patient, the gallbladder sediment-like stones developed after treatment with octreotide for only 5 d, which was inconsistent with previous studies. Parasher et al[9] demonstrated that ERCP CMs have crystals that can mimic calcium bilirubinate granules (pseudomicrolithiasis). In our patient, we speculate that the cause of intrahepatic cholestasis was calculi in the intrahepatic biliary tract induced by octreotide after VCME through the hepatobiliary system, as autoimmune liver disease, hemolytic and hepatocellular jaundice were excluded, and the intrahepatic bile duct did not dilate. When the CM was excreted into the hepatobiliary system, which was retained for a long time and concentrated by octreotide, this may have changed the physicochemical properties of bile and decreased nucleation time, resulting in the formation of acute gallstones. Similar changes might have occurred simultaneously in the intrahepatic biliary tree, which was the cause of poor bile excretion, and led to intrahepatic cholestasis and jaundice. When these gallstones were eliminated and passed through the duodenal papilla, they were embedded and induced acute pancreatitis. Ju et al[10] demonstrated that the growth of gallbladder endothelial cells was significantly inhibited by CM and was positively correlated with osmotic pressure. Unfortunately, analysis of gallstones composition was not performed. In our patient, the causes of cholangitis may have been cholestasis, long-term indwelling nasobiliary catheter, and CM damage to the bile duct epithelium. Gallstones, cholestasis, and cholangitis caused severe jaundice, which can induce bilirubin encephalopathy.

CONCLUSION

Although symptomatic VCME and octreotide-induced gallstones are relatively rare, with the widespread use of CM, the frequency of this rare complication is expected to increase and careful observation of patients is required in order not to miss the opportunity of treatment especially when the patient is at high risk of ectopic
excretion. As we did not have data on the composition of the gallstones to confirm our hypothesis, future research is required.

REFERENCES


Acute deep venous thrombosis induced by May-Thurner syndrome after spondylolisthesis surgery: A case report and review of literature

Lei Yue, Hao-Yong Fu, Hao-Lin Sun

BACKGROUND
Deep venous thrombosis (DVT) is a serious complication of lumbar spine surgery. Current guidelines recommend pharmacomechanical prophylaxis for patients at high risk of DVT after spine surgery. May-Thurner syndrome (MTS), a venous anatomical variation that may require invasive intervention, is an often overlooked cause of DVT. To date, no case reports of symptomatic MTS caused by isthmic spondylolisthesis or subsequent acute DVT after posterior lumbar surgery have been published.

CASE SUMMARY
We here present a case of a patient who developed acute DVT 4 h after spondylolisthesis surgery, and MTS was only considered after surgery, during a review of a gynecological enhanced computed tomography image taken before the procedure.

CONCLUSION
In conclusion, clinicians should consider MTS in the presence of a dangerous triad: spondylolisthesis, elevated D-dimer levels, and sonographically indicated unilateral deep vein dilation. Consultation with a vascular surgeon is also essential to MTS management.

Key Words: Spondylolisthesis; Spine surgery; Deep venous thrombosis; May-Thurner syndrome; Complication; Case report
INTRODUCTION
Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is one of the most serious complications of spine surgery, with an incidence of 0.1% to 2.09%\[1-3\]. There are multiple quantitative VTE risk assessment models (RAMs) available for use in clinical practice. The one that is most widely validated in surgery populations is the Caprini score (version 2005). Despite their comprehensiveness, the RAMs used might not account for additional VTE risk factors such as potential anatomical variations\[4\]. May-Thurner syndrome (MTS), also known as iliac vein compression syndrome, is a rare vascular condition in which the left common iliac vein (LCIV) is mechanically compressed by the overriding right common iliac artery (RCIA), leading to venous congestion. MTS can be asymptomatic with partial venous obstruction, but progression with symptoms related to chronic venous hypertension or acute DVT can occur[5]. Although MTS accounts for only 2% to 5% of all DVT patients, multiple cadaveric and radiographic studies have shown that the actual prevalence in the general population is as high as 14% to 32%[6,7]. The present study reports a patient with MTS induced by isthmic spondylolisthesis who developed subsequent acute DVT after posterior spine surgery.

CASE PRESENTATION

Chief complaints
A 40-year-old Chinese woman was hospitalized with a chief complaint of severe back pain without neurological symptoms for 3 mo. She had exhausted conservative measures and elected to proceed with surgery. Her baseline pain severity was 90 mm on a 100-mm visual analogue scale (VAS).

History of present illness
The patient had a past history of cervical squamous cell carcinoma with metastasis to T10 vertebrae and the lung. She had undergone chemoradiation but not surgery, and her most recent radiotherapy and chemotherapy were 6 mo and 5 mo prior to admission, respectively. She denied any recent travel, surgeries, or immobilization. Her body mass index was 27.3 kg/m².

History of past illness
There was no other obvious abnormality or any past illness other than cervical cancer.

Personal and family history
There was no special history or personal history. The patient had no known family history of DVT.

Physical examination
No abnormality other than low-back tenderness were noticed on physical exam-
ination. No sign of swollen lower limbs was noticed.

**Laboratory examinations**
The routine blood and blood biochemical parameters of the patient were within normal limits. Her D-dimer level was 0.55 mg/mL, and her fibrinogen degradation product (FDP) level was 4.5 mg/mL.

**Imaging examinations**
X-ray and computed tomography (CT) showed grade 1 bilateral isthmic L5 spondylolisthesis. Dura sac/nerve root compression was not found on magnetic resonance imaging (Figure 1). Doppler ultrasound indicated mild left femoral vein dilatation and detectable blood flow in the distal part of the leg without thrombosis (Figure 2).

**VTE risk assessment**
Preoperative thrombosis risk factor assessment indicated a high risk of DVT with a Caprini score of 6 because of obesity, history of chemoradiation, malignancy, and major surgery)\(^8\). The thromboembolic prophylaxis plan was thrombosis prophylaxis hosiery immediately after the surgery and application of low-molecular-weight heparin (LMWH) as soon as the bleeding risk became low enough for that to be acceptable.

**Surgical procedure**
The procedure included L5-S1 decompression, lumbar spondylolisthesis reset, L5-S1 pedicle screw fixation, and posterior-lateral lumbar fusion. The entire surgery lasted 135 min, and the estimated blood loss was only 50 mL.

**Postoperative DVT**
Compression stockings were applied as planned. However, swelling and pain were noted in her left lower limb 4 h after the surgery. Laboratory tests and Doppler ultrasound were performed, and results showed elevated D-dimer level (2.15 mg/L), elevated FDP (12.5 mg/L) level, and left common femoral and deep femoral venous thrombosis. DVT was confirmed; the patient was immobilized and antithrombotic and thrombolytic therapy (LMWH and warfarin) were immediately administered. On review of preoperative examinations, an enhanced pelvis CT scan taken 2 wk before the operation for tumor follow-up showed that the LCIV was sandwiched between the RCIA and slipped vertebrae. MTS was therefore considered (Figure 2A-C).

**FINAL DIAGNOSIS**
The diagnosis was left common femoral and deep femoral venous thrombosis, MTS, isthmic spondylolisthesis, and metastatic cervical cancer.

**TREATMENT**
After a 2-wk immobilization and systemic anticoagulation, the left leg swelling gradually subsided, and embolism was undetectable on ultrasonography.

**OUTCOME AND FOLLOW-UP**
At the 1 mo postoperative follow-up, her VAS score of back pain decreased to 20 mm without further complications (Figure 1C). Neither DVT nor PE occurred during 1-year of follow-up. It should be noted that the patient also manifested acute progressive renal failure postoperatively because of bilateral radiotherapy-induced urethral stricture. The symptoms were relieved after percutaneous nephrostomy and insertion of two double-J tubes.
DISCUSSION

MTS is described as venous compression by the iliac artery against the spine that may or may not present with symptoms of venous obstruction. This syndrome was first described in 1908 when McMurrich[9] noted that the incidence of congenital adhesions in the common iliac veins contributed to DVTs. In 1957, May and Thurner[10] reported that the presence of intraluminal fibrous bands, caused by external compression by the RCIA, directly led to extensive DVT of the left lower extremity in 22% of 430 cadavers, and they named the condition MTS. Although most cases of MTS follow the classic left-sided description (Figure 2E), right-sided MTS has also been reported[11,12]. Risk factors for MTS include female gender, scoliosis, dehydration, hypercoagulable disorders, and radiation exposure[5].

To the best of our knowledge, this is the first case report of MTS secondary to isthmic spondylolisthesis, and it highlights the need to suspect this variant of MTS under certain conditions. MTS is mostly asymptomatic for partial venous obstruction, but progression may present acutely as DVT/PE or chronically as varicose veins, venous ulcerations, or recurrent superficial venous thrombophlebitis[13,14]. Awareness of MTS should be raised especially among neurosurgeons, because spinal diseases or procedures can be responsible for MTS, while MTS can also manifest as sciatic neuralgia or cauda equina syndrome[15-19] (Table 1).

The overall prevalence of MTS and its contribution to DVT have been underestimated, as cadaveric studies have shown that venous spurs on the LCIV were present in 50% to 66.7% patients with left-sided iliofemoral DVT[20,21]. MTS typically progresses in three stages, asymptomatic iliac vein compression, development of venous spurs, and thrombus formation[15,22]. Timely diagnosis of MTS is challenging because MTS is usually overshadowed by other more easily recognized risk factors of DVT[7]. Despite its superior accuracy in diagnosing MTS, the use of contrast venography is usually limited in disease screening by its invasive nature. Although CT, magnetic resonance venography, and intravascular ultrasound (IVUS) have also been proven to be effective, they cannot be used for routine preoperative examinations.
Table 1 Literature review of May-Thurner syndrome in spinal settings

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<tr>
<th>Ref.</th>
<th>Country</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Gender/age in yr</th>
<th>Length of onset</th>
<th>Means of diagnosis</th>
<th>Cause of MTS/MTS consequences</th>
<th>Treatment</th>
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<td>United States</td>
<td>Case report</td>
<td>1</td>
<td>Female/60</td>
<td>8 mo</td>
<td>CT, Venogram and IVUS</td>
<td>Spondylolisthesis</td>
<td>Wait and see strategy</td>
</tr>
<tr>
<td>Kim et al [15], 2020</td>
<td>Korea</td>
<td>Case report</td>
<td>1</td>
<td>Female/28</td>
<td>15 d</td>
<td>CT</td>
<td>Spinal heterotopic ossification</td>
<td>Wait and see strategy</td>
</tr>
<tr>
<td>Diaz et al [31], 2019</td>
<td>Spain</td>
<td>Case report</td>
<td>1</td>
<td>Female/40</td>
<td>6 h</td>
<td>MRI, venography</td>
<td>MTS induced back pain and radicular pain</td>
<td>Catheter-directed thrombolysis, cava venal filter and stenting</td>
</tr>
<tr>
<td>Khalid et al [32], 2019</td>
<td>United States</td>
<td>Case report</td>
<td>1</td>
<td>Female/66</td>
<td>3 mo</td>
<td>CT, Venogram, IVUS</td>
<td>Degenerative disc</td>
<td>Ballooning and stenting</td>
</tr>
<tr>
<td>Xu et al [16], 2019</td>
<td>China</td>
<td>Case report</td>
<td>1</td>
<td>Female/39</td>
<td>1 mo</td>
<td>CT, MRI and venography</td>
<td>Lumbar disc anterior herniation</td>
<td>Disc radiofrequency thrombocoeagulation</td>
</tr>
<tr>
<td>Yamamoto et al [18], 2018</td>
<td>Japan</td>
<td>Case report</td>
<td>1</td>
<td>Male/53</td>
<td>3 mo</td>
<td>CT, MRI and venography</td>
<td>MTS induced sciatic neuralgia</td>
<td>Stenting</td>
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<tr>
<td>McKean et al [33], 2017</td>
<td>UK</td>
<td>Case report</td>
<td>1</td>
<td>Female/64</td>
<td>Several wk</td>
<td>CT</td>
<td>Degenerative spondylolisthesis</td>
<td>Anticoagulation therapy</td>
</tr>
<tr>
<td>Rachailah et al [17], 2016</td>
<td>India</td>
<td>Case report</td>
<td>1</td>
<td>Female/63</td>
<td>3 d</td>
<td>Venogram</td>
<td>Vertebral transpedicular screw</td>
<td>Catheter-directed thrombolysis and oral anticoagulation therapy</td>
</tr>
<tr>
<td>Ou-Yang and Lu [34], 2016</td>
<td>China</td>
<td>Cross-sectional study</td>
<td>33</td>
<td>NM/63.5 ± 10.6</td>
<td>22.5 ± 7.6 d</td>
<td>CT</td>
<td>Intervertebral discs (17/33), osteophytes (16/33), and degenerative lumbar spondylolisthesis (8/33)</td>
<td>Catheter-directed thrombolysis, thromb-broken aspiration, ballooning and stenting</td>
</tr>
<tr>
<td>Woo et al [35], 2016</td>
<td>United States</td>
<td>Case report</td>
<td>1</td>
<td>Female/65</td>
<td>NM</td>
<td>MRA, venography</td>
<td>Pedicle screw perforation</td>
<td>Ballooning and stenting</td>
</tr>
<tr>
<td>Reddy et al [36], 2015</td>
<td>United States</td>
<td>Case report</td>
<td>1</td>
<td>Female/33</td>
<td>8 d after spine surgery</td>
<td>CT, venography</td>
<td>NM</td>
<td>Catheter-directed thrombolysis, stenting and oral anticoagulation therapy</td>
</tr>
<tr>
<td>Oteros et al [37], 2008</td>
<td>Spain</td>
<td>Case report</td>
<td>1</td>
<td>Female/13</td>
<td>During scoliosis surgery</td>
<td>CT, venography</td>
<td>Scoliosis</td>
<td>Wait and see strategy</td>
</tr>
</tbody>
</table>

CT: Computed tomography; IVUS: Intravenous ultrasound; MRA: Magnetic resonance angiography; MRI: Magnetic resonance imaging; NM: Not mentioned.

CT: Computed tomography; IVUS: Intravenous ultrasound; MRA: Magnetic resonance angiography; MRI: Magnetic resonance imaging; NM: Not mentioned.

in practice[23]. Doppler ultrasound is convenient and is useful in the detection of lower limb DVT but not MTS because of technological challenges. In our case, although preoperative ultrasound of the lower limb showed mild dilation of the left femoral vein, MTS was only confirmed by enhanced pelvic CT. As suggested by Harbin and Lutsey[7], the patient’s preoperative elevation of D-dimer could have indicated hypercoagulability and possible MTS. Therefore, based on this case, we conclude that MTS should be suspected when the following dangerous triad is observable: spondylolisthesis, elevated D-dimer levels, and unilateral deep vein dilatation on sonography. The specific risks of thrombosis in this patient were obesity, history of chemoradiation, malignancy, and major surgery. All the factors could have been responsible for the thrombosis event, and MTS would have gone undetected if not for the review of the patient’s gynecological CT imaging.

Several RAMs have been developed for postoperative VTE estimation and prevention, and the Caprini risk score is the one that has been the most extensively used and validated[8,24-26]. However, the commonly used RAMs do not take such variant factors as MTS into account and may cause clinicians to underestimate the risk of venous thrombosis complications. Bartlett et al[4] recommended exercising caution in relying on RAMs to determine the optimal prophylaxis strategy. The Caprini score of this patient was 6 with recommended prevention of pharmacological and mechanical prophylaxis, which is clearly inappropriate in the setting of MTS because it does not address the underlying pathology. Standard care for MTS is endovascular...
treatment, which involves catheter-directed pharmacological thrombolysis, mechanical thrombectomy, and stenting of the iliac vein with or without a caval filter. Recanalization in difficult cases can be performed under IVUS guidance\textsuperscript{[27]}. Surgery, including vein repair with thrombus removal, relocation of the artery, and placement of a venous bypass graft, are only indicated when endovascular approaches have failed\textsuperscript{[28]}. However, invasive intervention is not always necessary when MTS is asymptomatic\textsuperscript{[29]}. For this patient, endovascular intervention was not suitable because of the accompanying acute progressive renal failure and hyperkalemia. Antithrombotic and thrombolytic therapy were effective for her. We here further presume the repair of the spondylolisthesis anatomically addressed the compression of left common femoral vein and indirectly relieved MTS.

CONCLUSION

In summary, our case showed that MTS may occur in patients with isthmic spondylolisthesis. MTS should be suspected if the patient shows a dangerous triad. Besides, consultation with a vascular surgeon is essential to MTS management in patients undergoing spine surgery.

REFERENCES


Successful treatment of refractory lung adenocarcinoma harboring a germline BRCA2 mutation with olaparib: A case report

Li Zhang, Jing Wang, Ling-Zhi Cui, Kai Wang, Ming-Ming Yuan, Rong-Rong Chen, Li-Jiao Zhang

Abstract

BACKGROUND
In recent years, targeted therapy and immunotherapy have become important treatment strategies for patients with non-small cell lung cancer (NSCLC). However, the clinical evidence for successful off-label use of targeted drugs for patients with NSCLC following progression on multiple lines of treatment is still lacking.

CASE SUMMARY
We describe a 62-year-old male patient with a right lung adenocarcinoma who harbored an EGFR exon 19 deletion mutation. He received gefitinib combined with six cycles of vinorelbine, cisplatin, and recombinant human endostatin as the first-line therapy. Then gefitinib was administered in combination with recombinant human endostatin as maintenance therapy, resulting in a progression-free survival (PFS) of 14 mo. Chemoradiotherapy was added following progression (enlarged brain metastases) on maintenance treatment. Unfortunately, the brain lesions were highly refractory and progressed again after 15 mo, at which time next-generation sequencing (NGS) of 1021 cancer-related genes was performed using peripheral blood to identify potential actionable mutations. NGS revealed that the patient harbored a BRCA2 germline mutation, the EGFR exon 19 deletion mutation disappeared, and no additional targetable genetic variant was detected. Therefore, the patient received olaparib combined with gefitinib and recombinant human endostatin, with a rapid and long-lasting clinical response (PFS = 13.5 mo).

CONCLUSION
This is a rare case of lung adenocarcinoma in a patient with a BRCA2 germline mutation who had long-term benefit from olaparib combination treatment, suggesting that NGS-based genetic testing may render the possibility of long-term survival in NSCLC patients after disease progression.
revised according to the CARE Checklist (2016).

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Core Tip: The clinical evidence for successful off-label use of targeted drugs for lung adenocarcinoma patients following progression on multiple lines of treatment is still lacking. Herein, we describe the identification of a germline BRCA2 mutation in a lung adenocarcinoma patient. The patient had multiple refractory brain metastases and received olaparib combined with gefitinib and recombinant human endostatin following progression on multiple lines of treatment, with a progression-free survival of 13.5 mo. This case provides unequivocal clinical evidence for the off-label use of olaparib in lung adenocarcinoma patients with a BRCA2 mutation after disease progression.

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DOI: https://dx.doi.org/10.12998/wjcc.v9.i25.7498

INTRODUCTION

Lung cancer is one of the most common malignancies with high morbidity and mortality rates worldwide. In recent years, immunotherapy and targeted therapy have made great progress in non-small cell lung cancer (NSCLC), which is the most common type of lung cancer. However, post-progression effective therapy for NSCLC is still lacking. One highly potential strategy is to identify alternative therapeutic options. Next-generation sequencing (NGS)-based genetic testing, which provides abundant genetic information on cancer including both germline and somatic gene mutations, has resulted in more individualized therapeutic strategies for NSCLC.

BRCA2 is a tumor suppressor gene that encodes a protein involved in the DNA homologous recombination repair (HRR) pathway to maintain genome stability. A BRCA2 germline mutation increases the risks of a variety of malignancies, including a 50%-60% increased risk of breast cancer and a 30% increased risk of ovarian cancer[1]. It is also associated with an increased risk of breast cancer and prostate cancer in males [2,3]. In addition, studies have shown that the HRR genes including BRCA2 may be involved in the tumorigenesis of lung cancer[4]. Multiple clinical studies have confirmed that patients with BRCA1/2-mutated cancer, including breast cancer, ovarian cancer, and prostate cancer, may be sensitive to poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors[5-7]. PARP inhibitors are a novel class of anticancer drugs, which take advantage of synthetic lethality and induce cell death by exploiting a defect in DNA repair. Currently, the US Food and Drug Administration has approved four PARP inhibitors for various indications: Olaparib for ovarian cancer, metastatic breast cancer, fallopian tube cancer, and primary peritoneal cancer, niraparib and rucaparib for ovarian cancer, fallopian tube cancer, and primary peritoneal cancer, and talazoparib for metastatic breast cancer. However, the efficacy of PARP inhibitors in patients with tumors that are not commonly associated with germline BRCA1/2 mutations remains to be explored. The results from multiple basket trials suggested that patients harboring the same molecular abnormalities may benefit from targeted therapy independent of tumor origin[8]. Although some studies have suggested that the PARP inhibitors talazoparib and olaparib both had synergistic activity with gemcitabine in lung cancer cell lines[9], and that BRCA2-mutant lung cancer organoids responded to olaparib[10], there is still a lack of clear clinical evidence to support that NSCLC patients with a BRCA2 gene mutation respond to targeted therapies. In this paper, we present a case of BRCA2 germline mutation positive, refractory lung adenocarcinoma with durable response and tolerable toxicities to olaparib combined with gefitinib and recombinant human endostatin, with a progression-free survival (PFS) up to 13.5 mo.
CASE PRESENTATION

Chief complaints
In September 2019, a 62-year-old Chinese man presented to hospital for treatment because of multiple progression of brain metastases from lung adenocarcinoma without an effective therapy.

History of present illness
In March 2017, the patient presented with cough and blood-tinged sputum. He underwent bronchoscopy at another hospital and was diagnosed with lung adenocarcinoma. In order to seek further treatment, he came to our hospital and was diagnosed with a T2N0M1 (stage IV) adenocarcinoma of the right lung with focal squamous cell differentiation, and multiple brain metastases. An *EGFR* exon 19 deletion mutation was identified. Therefore, the patient received gefitinib 250 mg/d, and was given six courses of chemotherapy with the vinorelbine plus cisplatin (NP) regimen and recombinant human endostatin, and achieved a partial response. Then gefitinib was given in combination with recombinant human endostatin as maintenance therapy. Bilateral frontal lobe and temporal lobe metastases were observed after 14 mo, and 4 mo later, the bilateral frontal lobe metastases were enlarged. The patient was given oral temozolomide for four courses on the basis of maintenance therapy, but had progressive disease. Magnetic resonance imaging (MRI) showed supratentorial and infratentorial brain metastases. To identify potentially actionable mutations, NGS-based genetic testing of 1021 cancer-related genes was performed using peripheral blood. A germline mutation in *BRCA2* was found (NM_000059.3, c.6816_6820del AAGAG, p.G2274Afs*17), and the *EGFR* exon 19 deletion mutation disappeared. The patient was then treated with intensity-modulated radiation therapy, and the supratentorial and infratentorial brain metastases were reduced.

History of past illness
No past illnesses were documented.

Personal and family history
The patient had no known comorbidities or family history and had a 30-year smoking history.

Physical examination
No abnormal indicators were observed on physical examination. His Eastern Cooperative Oncology Group performance status score was 2.

Laboratory examinations
Examinations of serum tumor markers showed that carcinoembryonic antigen, neuron-specific enolase, cytokeratin fragment antigen 21-1, progastrin-releasing peptide, and cancer antigen 125 were 1.96 μg/L (reference range: < 3 μg/L), 5.31 μg/L (reference range: < 12 μg/L), 0.75 ng/mL (reference range: < 4 ng/mL), 9.46 pg/mL (reference range: < 45 pg/mL), and 3.18 U/mL (reference range: < 30 U/mL), respectively.

Imaging examinations
On September 6, 2019, the patient underwent MRI. The long T1 and long T2 signals from nodules of various sizes were found in the supratentorial and infratentorial brain parenchyma, and the largest lesion was located in the left frontal lobe with a diameter of approximately 1.0 cm (Figure 1A). Small patchy and slightly longer T1 and slightly longer T2 signals were observed in bilateral paraventricles and bilateral basal ganglia. The sulcus was not widened and the ventricular system was not dilated.

Further diagnostic work-up
To determine potential therapeutic methods, the patient underwent genetic testing of 1021 cancer-related genes using peripheral blood (Geneplus-Beijing, Beijing, China) for the second time, and a somatic *ASXL1* mutation and the previous germline *BRCA2* mutation were identified (Table 1).
Table 1 Somatic mutation and germline mutation detected by next-generation sequencing

<table>
<thead>
<tr>
<th>Somatic mutation</th>
<th>Gene</th>
<th>Transcript</th>
<th>c.HGVS</th>
<th>p.HGVS</th>
<th>Allele frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASXL1</td>
<td>NM_015338.5</td>
<td>c.2247C[4&gt;3]</td>
<td>p.V751LfsX21</td>
<td>0.6%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Germline mutation</th>
<th>Gene</th>
<th>Transcript</th>
<th>c.HGVS</th>
<th>p.HGVS</th>
<th>Homozygous/heterozygous</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA2</td>
<td>NM_000059.3</td>
<td>c.6816_6820delAAGAG</td>
<td>p.G2274AfsX17</td>
<td>Heterozygous</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 Changes in brain metastases after olaparib treatment. A: The lesion before olaparib treatment; B: 7 mo after treatment; C: At 13.5 mo after treatment; D: At 13.5 mo after treatment.

FINAL DIAGNOSIS
A germline BRCA2-mutated right lung adenocarcinoma with focal squamous cell differentiation and multiple brain metastases.

TREATMENT
Since September 24, 2019, the patient has been receiving oral olaparib at a dosage of 300 mg twice daily, on the basis of maintenance therapy with gefitinib plus recombinant human endostatin.

OUTCOME AND FOLLOW-UP
In the course of treatment, the brain metastases were under control and maintained the
same size as 2 mo previously. At the end of March 2020, MRI showed a slight reduction of the left frontal lobe metastases, with the largest being approximately 0.8 cm in diameter. There was also a cavity in the middle of the metastases (Figure 1B). Furthermore, his Eastern Cooperative Oncology Group performance status score changed from 2 to 1. From April to May 2020, the patient was unable to purchase the drug due to the impact of the coronavirus disease 2019 outbreak and opted to be treated only with gefitinib. From June 2020, he was treated with oral olaparib and gefitinib plus recombinant human endostatin. In late August 2020, his brain metastases appeared to be enlarged; thus, temozolomide was added to the treatment regimen. In early November 2020, imaging revealed enlargement of bilateral cerebral hemisphere metastases and the appearance of new metastases. The largest lesion was located near the left posterior horn of the ventricle and was about 1.1 cm × 0.9 cm in size (Figure 1C and D), which was evaluated as progression, and PFS on olaparib combined with gefitinib and recombinant human endostatin was 13.5 mo. In addition, the patient’s primary lung cancer has remained consistently well-controlled since diagnosis. No adverse events associated with the use of olaparib were observed.

DISCUSSION

Olaparib, a PARP inhibitor, has been proven to be effective in patients with BRCA-mutant breast, ovarian, prostate, and pancreatic cancers[5–7,11]. The STUDY19 trial showed that patients with BRCA-mutated ovarian cancer gained great benefit from olaparib[5]. Among patients with HER2-negative metastatic breast cancer and a germ-line BRCA mutation, olaparib monotherapy provided significant benefit over standard therapy[6]. Another study showed that of 16 prostate cancer patients with mutations in DNA damage repair genes, 14 (88%) had a response to olaparib, including all 7 patients with loss of DNA damage repair genes[7]. A study also confirmed that BRCA2-mutant lung cancer organoids responded to olaparib[10]. In the present report, the patient with an adenocarcinoma of the right lung harboring an EGFR exon 19 deletion mutation received olaparib plus gefitinib and recombinant human endostatin following progression after multiple lines of treatment, as NGS revealed a BRCA2 germline mutation. Brain metastases in this refractory lung adenocarcinoma patient were successfully controlled.

In this study, the BRCA2-mutated lung adenocarcinoma patient benefited from olaparib combined with gefitinib and recombinant human endostatin with a relatively long survival following progression on multiple lines of treatment. One study found [12] that niraparib (a PARP inhibitor) combined with bevacizumab (an anti-angiogenic drug) significantly improved PFS compared with niraparib alone [median PFS 11.9 mo vs 5.5 mo; adjusted hazard ratio 0.35 (95% confidence interval: 0.21-0.57), $P < 0.0001$] for platinum-sensitive recurrent ovarian cancer, suggesting that PARP inhibitors combined with anti-angiogenic drugs may increase sensitivity to PARP inhibitors. In this study, the combination of olaparib and an anti-angiogenic drug also led to a good outcome. We observed that the patient had a cavity in the middle of the brain metastases after initiation of olaparib treatment. We suspected that the metastatic lesions were killed and the tumor tissue expelled, or insufficient neovascularization led to necrosis due to insufficient blood supply, resulting in cavitation. As this tumor cavity was formed after the use of olaparib, it may have been related to olaparib treatment, or the synergistic effect of olaparib and other drugs.

CONCLUSION

We present a lung adenocarcinoma patient with a BRCA2 mutation who had long-lasting benefit following treatment with olaparib plus gefitinib and recombinant human endostatin. This case provides unequivocal clinical evidence for the off-label use of the PARP inhibitor olaparib in lung adenocarcinoma patients with BRCA mutations after disease progression.

ACKNOWLEDGEMENTS

We would like to thank the patient and his family.
REFERENCES


Effective treatment of polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes syndrome with congestive heart failure: A case report

Ling-Yao Fu, Hong-Bin Zhang

BACKGROUND
Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome is a rare paraneoplastic syndrome caused by a plasma cell proliferative disorder. The syndrome is characterized by elevated plasma cells, platelets, and vascular endothelial growth factor levels. Although heart disease rarely occurs in POEMS syndrome, the death rate increases sharply after heart failure. We report a patient who initially presented with an endocrine disease and developed congestive heart failure related to POEMS syndrome 9 years later.

CASE SUMMARY
A 23-year-old woman with no history of menstruation and a 9-year history of type 1 diabetes reported feeling breathless after activities. She could not lie down and rest at night. Three months prior, she experienced pain and increased tension in her left thigh accompanied by tenderness and edema in both lower extremities. The chief complaint upon hospital admission was that blood sugar has increased for more than 9 years, pain in the left thigh, and edema in both legs for more than 2 mo. After a multisystem evaluation, she was diagnosed with POEMS syndrome. Her echocardiogram showed left ventricular dilation with systolic dysfunction, and the left ventricular ejection fraction was only 38% with severely elevated brain natriuretic peptide. She received a combination of dexamethasone and thalidomide for 1 mo, but her symptoms did not improve. Therefore, we added a two-per-week bortezomib injection. After 2 wk, the patient’s heart function had improved significantly.

CONCLUSION
This case provides information about the treatment of POEMS syndrome with complications and highlights the challenges of developing a standardized treatment.
INTRODUCTION
Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome is a rare paraneoplastic syndrome caused by a plasma cell proliferative disorder that is most commonly lambda restricted. This complex multisystem disease may involve angiogenesis and proinflammatory cytokines. For example, upregulation of various proinflammatory cytokines and growth factors [tumor necrosis factor-alpha, interleukin (IL)-1, IL-6, and above all, vascular endothelial growth factor (VEGF)] plays a crucial role in the pathogenesis of POEMS syndrome, contributing to vascular leakage and polyneuropathy. Cases of POEMS syndrome with heart failure are rare. Given the limited experiences with early diagnoses and follow-up treatments, no clinically standardized treatment is available. However, reports have described effective treatment methods as well as methods of observing heart disease in patients with POEMS syndrome. This case report describes a patient with POEMS syndrome and heart failure who has not yet received high-dose chemotherapy with peripheral blood stem cell transplantation (PBSCT), dexamethasone, or thalidomide.

CASE PRESENTATION
Chief complaints
A 23-year-old Chinese woman with overall poor physical development was admitted to the hospital because her blood sugar had increased over 9 years. In addition, her left thigh was swollen and painful, and her lower extremities showed edema.

History of present illness
The patient had been diagnosed with type I diabetes 9 years before she came to the hospital. However, she was not treated with regular insulin injections outside the hospital, and her blood sugar was not well controlled. One year ago, she felt tired after exercise and could not lie down at night; she also felt squeezing in her chest area during defecation. She felt pain in her left thigh pain and increased tension that had occurred more than 3 mo earlier accompanied by tenderness, edema in both lower extremities, paleness, swelling, and ulceration. Initially, she could walk autonomously but gradually became unstable while standing, even finding it difficult to squat during
bowel movements.

History of past illness
“Cataractectomy” was performed 1 year ago.

Personal and family history
Menarche had not occurred to date, and she was diagnosed with a naive uterus outside our hospital. The family history was unremarkable.

Physical examination
The parameters of vital signs were as follows: Heart rate, 107 beats/min; BP 110/78 mmHg; height, 145 cm; and weight, 45 kg. The skin and mucous membranes of the whole body were pale. There was no pubic or axillary hair, and multiple areas of the skin were damaged and crusted. On auscultation, the breath sounds in both upper lungs were thick and weak, and moist rales were heard in both lower lungs. The abdomen was distended. The liver and spleen were unaffected and moved upon respiration. There was positive dullness and pitting edema of both lower limbs. There were no other obvious abnormalities.

Laboratory examinations
The patient’s laboratory results are listed in Table 1. Endocrine examination revealed hypothyroidism and hypogonadotropic hypogonadism. The patient’s brain natriuretic peptide (BNP) was severely elevated.

Imaging examinations
Electromyography showed that the conduction velocity of both upper limbs was slowed and accompanied by low amplitude M and F waves; edema of both lower limbs could not be detected. Computed tomography (CT) showed enlarged liver, spleen, and multiple lymph nodes with pleural effusion and ascites. We did not find monoclonal plasma cell proliferation by lymph node biopsy, bone biopsy, or flow cytometry. A 12-lead electrocardiogram showed sinus tachycardia (Figure 1). It is worth noting that echocardiography showed left ventricular dilation with systolic dysfunction, and the left ventricular ejection fraction (LVEF) was only 38% (Figure 2). Cardiac magnetic resonance imaging (MRI) showed interstitial edema of the myocardium, myocardial native T1 values globally increased, and late gadolinium enhancement could represent definite myocardial necrosis (Figure 3).

FINAL DIAGNOSIS
The patient had multiple neuropathy, organ enlargement, endocrine diseases, skin changes, and other manifestations, coupled with an increase of VEGF. She was finally diagnosed as having POEMS syndrome with congestive heart failure.

TREATMENT
We started her on an insulin pump (continuously adjusting the dose) with some oral medicines that were targeted to improve heart function. These drugs were digoxin (0.125 mg/d), sacubitril valsartan sodium tablets (50 mg/d), and furosemide (60 mg/d). To actively control blood sugar and improve heart function symptoms, 50 mg/d oral dexamethasone (4 consecutive days, repeated every 14 d) combined with 100 mg/d thalidomide (increased to 200 mg after 14 d) was administered. One month later, the patient’s weight, cardiac ejection fraction, BNP, LVEF, and other indicators suggested that the patient’s lower limb edema and cardiac function had not significantly improved. Therefore, we changed the treatment plan based on the 1 mo of treatment, and the patient was administered intravenously with 20 mg/d dexamethasone (for 4 consecutive days/2 wk) and 50 mg/d oral thalidomide combined with 1.3 mg/m² bortezomib (injected twice a week for 2 consecutive weeks).
### Table 1 Laboratory findings on admission

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Serum chemistry</th>
<th>Endocrinology</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (7.71 × 10⁹/L)</td>
<td>α1 (8.5%)</td>
<td>LH (0.02 mIU/mL)</td>
</tr>
<tr>
<td>Neu (65.4%)</td>
<td>γ (30.9%)</td>
<td>FSH (0.95 mIU/mL)</td>
</tr>
<tr>
<td>RBC (2.88 × 10¹² /L)</td>
<td>Alb (22 g/L)</td>
<td>GH (11.69 ng/mL)</td>
</tr>
<tr>
<td>HB (85 g/dL)</td>
<td>cTnT (0.188 μg/L)</td>
<td>T3 (0.54 nmol/L)</td>
</tr>
<tr>
<td>Hct (28%)</td>
<td>Mb (272.8 ng/mL)</td>
<td>T4 (5.26 nmol/L)</td>
</tr>
<tr>
<td>PLT (360 × 10⁹/L)</td>
<td>CK-MB (12.7 U/L)</td>
<td>TSH (17.634 mU/L)</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>BNP (5487 pg/mL)</td>
<td>PTH (51.6 ng/L)</td>
</tr>
<tr>
<td>PT (16.5 s)</td>
<td></td>
<td>IGF-1 (&lt; 25.0 ng/mL)</td>
</tr>
<tr>
<td>PTR (1.43)</td>
<td></td>
<td>VEGF (9800 pg/mL)</td>
</tr>
<tr>
<td>Protein (1921 μmol/dL)</td>
<td>INR (1.45)</td>
<td>IgG (23.90 g/L)</td>
</tr>
<tr>
<td>M protein (0.27 g/L)</td>
<td>Fbg (3.95 g/L)</td>
<td>IgA (5.04 g/L)</td>
</tr>
<tr>
<td>KET (+++)</td>
<td>ALB (26 g/L)</td>
<td>HbA1c (8.10%)</td>
</tr>
<tr>
<td>AST (30 U/L)</td>
<td>ALT (25 U/L)</td>
<td></td>
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<tr>
<td>ALT (25 U/L)</td>
<td>BUN (7.4 mmol/L)</td>
<td></td>
</tr>
<tr>
<td>CRE (50 μmol/L)</td>
<td>UA (408 μmol/L)</td>
<td></td>
</tr>
<tr>
<td>Na (135 mmol/L)</td>
<td>K (4.8 mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Cl (104 mmol/L)</td>
<td></td>
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</tbody>
</table>


**Figure 1** Electrocardiograph showing sinus tachycardia.

**OUTCOME AND FOLLOW-UP**

The patient showed significant improvement in cardiac function at the 6th week after all treatments. For example, the LVEF increased to 45%, and a 5-kg weight loss was observed. A CT scan showed reduced hepatosplenomegaly, and serum VEGF levels
Figure 2 Echocardiography showed diffuse hypokinesis of the left ventricle with a 38% ejection fraction. LV: Left ventricle; RV: Right ventricle; RA: Right atrium; LA: Left atrium.

Figure 3 T2-weighted images, late gadolinium enhancement, and T1 and T2 mapping in this patient. Mapping of the native T1 values of the left ventricle showed a diffusely enhanced T1 value of approximately 1380 msec. T2 = 45 ms. A: Edema ratio; B: Late gadolinium enhancement; C: T1; D: T2.

decreased rapidly. In the process of continuing the treatment plan, we recommended that the patient undergo autologous stem cell transplantation to obtain a better prognosis and informed the patient of the adverse consequences of the treatment. The patient refused this treatment. In the current treatment plan, thalidomide was well tolerated, and there was no neurotoxicity with bortezomib. If oral medication is necessary, we can only give long-term medication as far as possible without affecting the patient’s future stem cell collection.
DISCUSSION

In most patients diagnosed with POEMS syndrome, neuropathy is the first clinical feature and may even be the only feature at the initial diagnosis[3]. However, based on all the examination results, this patient was diagnosed with multiple serous effusions with multisystem damage and multiple endocrine diseases; the cause of the heart function decline was unknown. There were no abnormally relevant immunological indicators of systemic lupus erythematosus and dermatomyositis during diagnosis and treatment; thus, rheumatic immune disease could not explain the patient's polynuropathy. Studies have shown that monoclonal lambda sclerosing plasma-cytoma or bone marrow infiltration can be detected in greater than 95% of patients[4], but we could not detect monoclonal plasma cell proliferation in this patient. A large amount of clinical data is needed to reassess whether single clonal plasma cell proliferative disease can become the main criterion for the diagnosis of POEMS syndrome [1]. Case reports of POEMS and retrospective studies have indicated that although the treatment of POEMS syndrome has not yet been standardized, current treatment methods have progressed from steroid monotherapy to more effective drugs and methods, such as radiotherapy, chemotherapy, hematopoietic stem cell transplantation, and other strategies. Radiotherapy is mainly aimed at patients with POEMS syndrome without bone marrow infiltration and bone lesions. In addition, systemic therapy is the most reasonable choice[3]. Available chemotherapy drugs include lenalidomide, thalidomide, bortezomib, bevacizumab, and others[6-11]. The successful treatment of POEMS syndrome is related to the treatment of potential clonal plasma cell disorder[12]. At present, autologous hematopoietic stem cell transplantation under high-dose chemotherapy may be the best treatment for POEMS syndrome. After this treatment, we observed immunological improvement, nervous system response recovery, good survival rates, and other improvements[13]. However, for POEMS syndrome with different complications after a clear diagnosis, more case reports on how to choose treatment methods and how to judge the indications for PBSCT are needed. Pulmonary hypertension is more common in POEMS syndrome involving the cardiovascular system[14,15], but the syndrome rarely affects the heart. In addition, the performance of the heart is also different in these reported cases[2]. To date, only eight cases have been reported[1,16-20]. The case reported in this article represents the ninth case of POEMS syndrome with heart failure. The patient's left ventricle was enlarged and exhibited decreased systolic function. Its pathogenesis may involve increased serum VEGF levels in POEMS syndrome. VEGF promotes vascular endothelial cell migration and increases vascular permeability. VEGF overexpression can cause extracellular edema of myocardial cells, increasing the distances between capillaries and myocardial fibers in the interstitium, affecting myocardial blood supply, and leading to contractile dysfunction[2]. However, it is still necessary to accumulate many cases to clarify the pathogenesis of POEMS with concurrent heart disease. According to reports by Daichi et al[1,7], thalidomide, which has been successfully used in the treatment of multiple myeloma (MM), is effective in treating POEMS syndrome with severe congestive heart failure[11]. However, chemotherapy is also effective. There are great risks, such as damage to the hematopoietic system, cardiovascular system, and nervous system, but few adverse reactions have been reported after treatment. The curative effect can be observed through various factors, such as LVEF, BNP, plasma VEGF, electromyography, and endocrine markers[1,12]. However, individual differences in treatment response are possible. The patient's response to dexamethasone and thalidomide was poor in this case. Given that no standardized treatment has been established, this poor response may be related to the dosage and method of medication administration, but some of them have not been used to treat heart failure. After using bortezomib as a basic treatment for patients with POEMS syndrome, disease activity is effectively controlled[21]. In this case, the patient's heart function improved significantly after the addition of bortezomib. The current research on proteasome inhibitors for the treatment of MM is more in-depth. We believe that both diseases are caused by abnormal plasma cells. When treating POEMS syndrome-related complications, we can still refer to the standardized treatment plan for MM first, and more clinical cases are still pending. According to reports, elevated BNP levels are associated with a poor prognosis in POEMS syndrome patients with pulmonary hypertension complications[22]. This finding suggests that once POEMS syndrome patients develop heart failure, the treatment effect is poor, and the mortality rate sharply increases. Therefore, early identification of heart disease and its causes and timely follow-up treatment of the heart are critical to the treatment of POEMS syndrome. In this case, it was necessary to exclude other organic heart diseases and abnormalities found by coronary angiography. For patients with POEMS syndrome, disease activity is effectively controlled.
syndrome and congestive heart failure caused by myocardial edema or diabetic cardiomyopathy, it is necessary to identify these conditions by cardiac MRI[2]. If necessary, an endocardial myocardial biopsy is feasible. Cardiac MRI can also evaluate POEMS-related heart disease management by detecting the volume of extracellular fluid. For this patient, although no monoclonal plasma cell proliferation was noted in the bone marrow, it seems that PBSCT could still be chosen[1]. In this case, this treatment may have been used to eliminate VEGF and other possible pathogenic cytokines in the body. The therapeutic effect can also be feedback through serum VEGF levels[7], but more postoperative case results are needed to support this principle. The postoperative results of the cases that have been treated with PBSCT suggest that surgical treatment may lead to high morbidity[4] due to various issues, such as multiple organ failure and even possible conversion to chronic myeloid leukemia. This article reports that whether patients should continue to undergo PBSCT treatment after drug treatment remains to be evaluated. The results and indications of surgery have not been well defined, and there is no established treatment method for preventing heart disease in POEMS patients with no heart failure.

CONCLUSION

In this case, the response to treatment with dexamethasone and thalidomide was poor. Given the lack of standardized treatment, the poor response may have been related to the dosage, method, and individual differences. However, the patient's heart function improved significantly after the addition of bortezomib. Current research on proteasome inhibitors for the treatment of MM has been relatively in-depth. We believe that these two diseases are both caused by abnormal plasma cells. The standardized treatment for MM should serve as the first reference for the treatment of POEMS syndrome-related complications.

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Awake craniotomy for auditory brainstem implant in patients with neurofibromatosis type 2: Four case reports

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Abstract

BACKGROUND

The auditory brainstem implant (ABI) is a significant treatment to restore hearing sensations for neurofibromatosis type 2 (NF2) patients. However, there is no ideal method in assisting the placement of ABIs. In this case series, intraoperative cochlear nucleus mapping was performed in awake craniotomy to help guide the placement of the electrode array.

CASE SUMMARY

We applied the asleep-awake-asleep technique for awake craniotomy and hearing test via the retrosigmoid approach for acoustic neuroma resections and ABIs, using mechanical ventilation with a laryngeal mask during the asleep phases, utilizing a ropivacaine-based regional anesthesia, and sevoflurane combined with propofol/remifentanil as the sedative/analgesic agents in four NF2 patients. ABI electrode arrays were placed in the awake phase with successful intraoperative hearing tests in three patients. There was one uncooperative patient whose awake hearing test needed to be aborted. In all cases, tumor resection and ABI were performed safely. Satisfactory electrode effectiveness was achieved in awake ABI placement.

CONCLUSION

This case series suggests that awake craniotomy with an intraoperative hearing test for ABI placement is safe and well tolerated. Awake craniotomy is beneficial for improving the accuracy of ABI electrode placement and meanwhile reduces non-auditory side effects.

Key Words: Awake craniotomy; Neurofibromatosis type 2; Auditory brainstem implant; Hearing test; Case report

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INTRODUCTION

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder characterized by the development of bilateral vestibular nerve schwannomas. Progressive growth or neurosurgical removal of bilateral tumors often damages the cochlear nerve, causing hearing impairment. The auditory brainstem implant (ABI) guided by evoked auditory brainstem responses (EABRs) was developed to restore hearing sensations for NF2 patients. However, since the postoperative effect of ABIs is variable and complicated, the value of the EABRs as a tool for assisting placement of ABIs becomes disputable[1]. In this report, awake craniotomy was performed after acoustic neuroma removal so that cochlear nucleus mapping could be pursued to secure the accuracy of electrode array placement.

CASE PRESENTATION

Chief complaints

Case 1: A 43-year-old female presented with a chief complaint of tinnitus in left ear for 3 years (Table 1).

Case 2: A 31-year-old male presented with a chief complaint of visual obscuration for 1 mo.

Case 3: A 38-year-old male presented with a chief complaint of tinnitus in left ear for 12 years, hearing loss in left ear for 4 years, and hearing loss in right ear for 1 year.

Case 4: A 24-year-old female presented with a chief complaint of ptosis in right eye and hearing loss in both ears for 6 years.

History of present illness

Case 1: Patient’s symptom started 3 years ago and had not been a good attention. Her mother was diagnosed with NF2 3 mo ago and the patient performed Magnetic resonance image (MRI) scan showed bilateral vestibular nerve schwannomas.

Case 2: Fundus examination was performed by an outside hospital and showed papilloedema. MRI demonstrated bilateral vestibular nerve schwannomas and left-sided lesions at the C3-C4 and C6-C7 intervertebral foraminal areas. The patient was diagnosed with NF2 and visited our hospital for surgical treatment.

Case 3: 12 years ago, the patient went to another hospital due to tinnitus in left ear. He was diagnosed with neurogenic tinnitus and was administered neurotrophic treatment without improvement. He developed progressive hearing loss in left ear 4 years ago and hearing loss in right ear 1 year ago. He was diagnosed with NF2 based on an MRI grade of E (Poor): 0, D (Fair): 0, C (Good): C, B (Very good): B, B, and A (Excellent): 0.

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

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Core Tip: The auditory brainstem implant (ABI) is a significantly beneficial treatment to restore hearing sensations for neurofibromatosis type 2 (NF2) patients. However, there is no ideal method in assisting the placement of ABI. The asleep-awake-asleep technique was applied for awake craniotomy and hearing test via the retrosigmoid approach for acoustic neuromas resections and ABI in four NF2 patients. ABI electrode arrays were placed in the awake phase with successful intraoperative hearing tests in three patients. There was one uncooperative patient whose awake hearing test needed to be aborted due to her restlessness. In all cases, tumor resection and ABI were performed safely. The awake craniotomy is beneficial to improve the accuracy of electrode placement in the ABI and meanwhile reduces non-auditory side effects.
Table 1 Patient characteristics and demographic data

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>BMI (kg/m²)</th>
<th>Preoperative hearing status</th>
<th>Comorbidities</th>
<th>Surgical side</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>F</td>
<td>20</td>
<td>Severe hearing loss in left and mild in right</td>
<td>None</td>
<td>Left</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>M</td>
<td>26</td>
<td>Complete hearing loss in left ear and profound hearing loss in right</td>
<td>Left-sided lesions at the C3-C4 and C6-C7 intervertebral foraminal areas, 14 years after resection of cervical spinal schwannomas</td>
<td>Left</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>M</td>
<td>25</td>
<td>Bilateral total deafness</td>
<td>Total deafness</td>
<td>Left</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>F</td>
<td>17</td>
<td>Complete hearing loss in right ear and severe hearing loss in right ear</td>
<td>Anxiety</td>
<td>Right</td>
</tr>
</tbody>
</table>

BMI: Body mass index.

Case 4: Patient’s symptoms started 6 years ago. MRI was performed by an outside hospital and showed bilateral vestibular nerve schwannomas. The patient was diagnosed with NF2. She accepted MRI examination at intervals without treatment. Hearing loss had been worsening gradually.

History of past illness
Cases 1, 3, and 4: The patient had a free previous medical history.
Case 2: The patient underwent resection of cervical spinal schwannomas 14 years ago.

Personal and family history
Case 1: The patient admitted a family history of NF2 associated with mother.
Case 2: The patient’s maternal grandfather, mother and two aunts on my mother’s side were diagnosed NF2 successively.
Cases 3 and 4: The patient denied a family history of NF2.

Physical examination
Case 1: The patient had severe hearing loss in left ear and mild in right ear (Table 1).
Case 2: The patient had complete hearing loss in left ear and profound hearing loss in right ear.
Case 3: The patient had complete hearing loss in both ears
Case 4: The patient had total hearing loss in right ear and severe hearing loss in right ear and suffered from anxiety.

Laboratory examinations
Routine laboratory tests revealed no remarkable abnormality in the four patients.

Imaging examinations
MRI showed bilateral vestibular nerve schwannomas in four patients (Figure 1).

Final Diagnosis
Cases 1-4: All patients were diagnosed with NF2.

Treatment
The procedures for the surgery and hearing tests in this case series have been published previously[2]. In this report, we present further details on anesthesia management. During preoperative consultation, we clearly outlined for the patient what to
Figure 1 Magnetic resonance images before surgery of 4 patients demonstrate bilateral vestibular nerve schwannomas (orange arrow). A1 and A2: Case 1; B1 and B2: Case 2; C1 and C2: Case 3; D1 and D2: Case 4.

expect during the procedure, including the varying states of sedation and awareness, the positioning, the possible discomfort, and the testing process. A trustful, solid relationship between the patients and anesthesiologists had been established prior to the procedure.

The first awake phase
After the patient entered the operating room, electrocardiography, noninvasive blood pressure, body temperature, oxygen saturation and bispectral index (BIS) were monitored. General anesthesia was induced with propofol using a targeted controlled infusion technique. Subsequently, a laryngeal mask airway (LMA) was inserted followed by mechanical ventilation and maintenance with 0.5-0.7 minimum alveolar concentration (MAC) sevoflurane combined with propofol 0.5-1.5 μg/mL and remifentanil 0.02-0.10 μg/kg/min. Ropivacaine (0.5%) was used for auriculotemporal nerve and cervical plexus block along the side to be operated on. Pin sites were infiltrated with 0.5% ropivacaine. Patients were positioned laterally at 90 degrees and secured in a Mayfield head holder without jaw adduction (Figure 2). The Bair Hugger warming units were used intraoperatively to maintain a comfortable body temperature in the range of 36-37 °C. Ropivacaine (0.5%) was infiltrated in the incision. Cottonoids soaked with 1% lidocaine were applied to cover the dura flap. Three to four hours later, when the tumor was almost resected, inhalant sevoflurane was discontinued, and the propofol infusion rate was increased to 2.0-2.5 μg/mL.

The awake phase
Once adequate hemostasis was achieved and the electrode array was placed, all the anesthetic agents were discontinued. LMA was removed when the patient’s respiration recovered. Sevoflurane was washed out (end tidal concentration < 0.1). When the patient was fully awake and engaged in cooperation, a wake-up hearing test was performed. The target blood concentration of propofol at that time was 0.5-0.6 μg/mL (Table 2). Propofol was continuously infused at this concentration to maintain an appropriate level of consciousness for ongoing hearing tests in the awake phase.

Awake craniotomy with well-placed electrodes and a successful intraoperative hearing test was achieved in 3 patients (Cases 1, 2, and 3). It took 41-65 min (mean, 55 min) for the patients to regain consciousness and 47-70 min (mean, 61 min) for them to fully cooperate after anesthetics were discontinued (Table 2). Case 4 was considered uncooperative and in a state of agitation when the plasma concentration of propofol decreased to 0.5 μg/mL and the BIS increased to 85. The patient’s status was not improved after sufentanil 3 μg was administered. Thus, the awake procedure was aborted to ensure the safety of this patient. The ABI electrode was placed with the
Table 2 Summary of intraoperative anesthetic management of awake craniotomy

<table>
<thead>
<tr>
<th>Case</th>
<th>Duration of the first phase (min)</th>
<th>The interval of time between discontinuation and eye opening (min)</th>
<th>The interval of time between discontinuation and full cooperation (min)</th>
<th>The plasma propofol awakening concentration (μg/mL)</th>
<th>Duration of hearing test (min)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>336</td>
<td>41</td>
<td>47</td>
<td>0.6</td>
<td>56</td>
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<tr>
<td>2</td>
<td>354</td>
<td>60</td>
<td>65</td>
<td>0.6</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>367</td>
<td>65</td>
<td>70</td>
<td>0.5</td>
<td>62</td>
</tr>
</tbody>
</table>

Figure 2 Intraoperative position and the incision line of case 3.

The second asleep stage
At the end of the hearing test, general anesthesia was induced. The LMA was inserted followed by mechanical ventilation. Anesthesia was maintained with propofol 2.5-3 μg/mL and remifentanil 0.05-0.1 μg/kg/min. Four patients recovered smoothly after the surgery and were transferred to the intensive care unit.

OUTCOME AND FOLLOW-UP
The median duration of surgery in the first asleep stage was 347 min (330-367 min) (Table 2). There were no cardiovascular or respiratory adverse events in any of the 4 patients. No instances of intraoperative seizures, brain swelling or bleeding were observed during the awake phase. Case 3 reported nausea and received ondansetron 4mg and methylprednisolone 40mg without improvement (Table 3). The hearing test showed that the placement of the ABI electrode array over the cochlear nucleus was suboptimal. The position of the electrode was therefore adjusted, and the patient reported no further discomfort. Case 2 reported neck pain, which was considered to be caused by the tumor and surgical history of the cervical spinal cord (Table 3). The pain was relieved with flurbiprofen 50 mg.

Case 1: ABI implanted was not switched on because she had functional hearing in her right ear. Cases 2 and 3: They used ABI daily and showed an obvious improvement in speech recognition scores in lip reading combined with ABIs after 1 year. Case 4: ABI implanted was not switched on because she had functional hearing in her left ear.

DISCUSSION
We successfully performed an asleep-awake-asleep technique for ABI surgery following acoustic neuroma resections via the retrosigmoid approach in three NF2
patients. Awake craniotomy is usually performed to maximize resection of tumors near the eloquent area[3,4]. It can reduce anesthetic interference with brain mapping [5]. Awake craniotomy for posterior fossa surgery reminds a number of significant challenges for the anesthesiologist. Posterior fossa procedure is more commonly performed in the three-quarter prone or prone with jaw adduction and head rotation position, which provide superior surgical exposure. However, it is difficult to get access to the airway and to communicate with patient in this position. Furthermore, sudden alterations of the cardiovascular and respiratory systems may occur during or after brainstem manipulation with surgery in the posterior fossa surgery. Moreover, patients must keep quiet completely during brainstem manipulation.

Shinoura et al[6] published a report in relation to awake craniotomy during vestibular schwannoma surgery to preserve hearing in 2017. There are several noteworthy differences between the present report and Shinoura’s report regarding surgery and anesthesia technique usage. First, an awake hearing test was performed after the removal of the tumor. Consequently, the duration of the first asleep phase was far longer than awake tumor resection and the total consumption of analgesics and sedatives increased dramatically. Second, NF2 patient usually encounters different degrees of hearing loss, which increases the difficulty of patient’s cooperation. For the patient who had no useful hearing, a communication method was designed preoperatively for use during in the awake phase; for example, this method included patting the patient’s face slightly as a signal to open the eyes and writing notes for the patient to read when awake. Moreover, suboptimal placement of the electrode array may result in the stimulation of non-auditory structures in the brainstem, causing non-auditory side effects (NASEs), such as dizziness, tingling sensations, nausea and vomiting. In our report, patients were positioned laterally at 90° during surgery, instead of in the park-bench position, which facilitated airway management and made it convenient for anesthesiologists to observe and deal with various events, especially when NASEs or other complications occurred.

Local anesthesia is the cornerstone of the awake craniotomy technique. The incision for acoustic neuroma resection and ABI surgery was entirely different from an incision for supratentorial tumor resection. On the operative side, the auriculotemporal nerve and cervical plexus were blocked with 0.5% ropivacaine. The anesthesia protocol for the pin sites, the incision, and the dura was similar to the protocol used in awake craniotomy for supratentorial mass lesions[7]. There was no increase in heart rate or blood pressure in any of the four patients during painful phases, and none of the patients experienced headache during the awake hearing test. No signs of cardiovascular or central nervous system toxicity were observed in any of the four patients.

A combination of propofol, remifentanil, and sevoflurane was used for general anesthesia in the first asleep phase. The facial, glossopharyngeal and trigeminal nerves were monitored throughout the procedure to assist in the placement of the electrode array and avoid nerve injuries during acoustic neuroma resection. Sevoflurane was limited to 0.5 MAC during tumor resection in all 4 patients[8]. Cranial nerve EMG activity was recorded effectively in all patients.

In this case series, the interval between the discontinuation of the IV infusion and the moment of consciousness recovery was much longer than previously reported in awake craniotomy for supratentorial masses [55 min (41-65 min) vs 14 ± 6 min][9]. This was probably related to the fact that the duration of the first asleep phase was far longer [347 min (330-367 min) vs 98 ± 25 min][9]. The plasma propofol concentration upon awakening would be lower after long-term infusion than after short-term infusion[10]. This was consistent with what we observed in the present case series. The blood propofol concentration at awakening was 0.5-0.6 μg/mL in this case series. However, the mean target propofol concentration was 1.3 ± 0.4 μg/mL for a fully cooperative patient who underwent awake craniotomy for supratentorial tumors[9].

Table 3 Intraoperative adverse events

<table>
<thead>
<tr>
<th>Case</th>
<th>Adverse events during wake-up hearing test</th>
<th>Treatment measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No event</td>
<td>No event</td>
</tr>
<tr>
<td>2</td>
<td>Neck pain</td>
<td>Flurbiprofen 50 mg</td>
</tr>
<tr>
<td>3</td>
<td>Nausea and vomiting</td>
<td>Ondansetron 4 mg, methylprednisolone 40 mg and adjusting the position of electrode array</td>
</tr>
<tr>
<td>4</td>
<td>Agitation</td>
<td>Aborting the awake surgery</td>
</tr>
</tbody>
</table>
Despite receiving prophylactic anti-emetics, case 3 suffered from nausea and vomiting. Under this circumstance, it is worth mentioning that the hearing test showed that the placement of the ABI electrode array over the cochlear nucleus was suboptimal. The patient did not report any discomfort when the position of the electrode was adjusted. As a result, nausea and vomiting might be symptoms of NASEs in this patient.

Case 4 was uncooperative and agitated when she woke up from general anesthesia. This patient suffered from anxiety before surgery, although great efforts had been made to establish mutual trust. Anxiety might be the main reason for agitation in the awake phase[11]. Since awake craniotomy patients are liable to become anxious and stimulated, their attention and vigilance are critical to the success of the surgery. Therefore, to guarantee safety, the surgeon and anesthesiologist should seriously consider the risk of failure before planning an awake craniotomy for a patient with a severe anxiety disorder[12].

This case series demonstrated that the awake hearing test in ABI might increase the availability of electrodes and decrease patients’ NASEs[2]. Two patients (cases 2 and 3) who used ABI daily showed an obvious improvement in speech recognition scores in lip reading combined with ABIs after 1 year, which was comparable to previously literature[13]. The other two patients (cases 1 and 4) still with functional hearing in the contralateral ear. ABI implanted was not switched on until hearing was lost in the contralateral ear. It has been reported in a previous study that for most patients, hearing will continuously improve after implantation[14]. More studies with long-term follow-up are expected to further investigate the potential benefits of awake craniotomy.

CONCLUSION

Our experiences suggested that awake craniotomy during ABI placement for NF2 patients was safe and mostly tolerated, and no obvious extra surgical risk was found due to awake craniotomy. This technique can potentially improve the accuracy of electrode positioning in the cochlear nucleus and reduce NASEs during surgery.

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Coexistence of tuberculosis and squamous cell carcinoma in the right main bronchus: A case report

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Abstract

BACKGROUND
Lung cancer with pulmonary tuberculosis (TB) refers to the occurrence of lesions simultaneously or sequentially in the lung(s) of the same patient, and the pathological examination and sputum TB examination diagnose them as lung cancer and TB, respectively. The occurrence of endobronchial TB (EBTB) with endobronchial tumor sequentially in the same bronchus lesion of the same patient is relatively rare.

CASE SUMMARY
A 62-year-old female patient was admitted to a local hospital on June 18, 2019 after a 3-mo history of dyspnea. She was a farmer and had no history of smoking and alcohol misuse. The patient had neither family nor work contact indicating exposure to TB. Emergency chest computed tomography (CT) examination showed that the right main bronchus was occupied and malignant tumor was possible. Histopathologic examination of a bronchial biopsy showed granulomatous inflammation with caseification and the presence of acid fast bacilli (AFB). However, after 6 mo of antitubercular treatment, repeat bronchoscopy and biopsy histological examination showed squamous cell carcinoma. The patient has started on systemic chemotherapy with carboplatin. After another two cycles of therapy, chest CT showed complete resolution of the lesions. Bronchoalveolar lavage and bronchial aspirate were negative for AFB and cancer cells.

CONCLUSION
It is not only more likely that a patient presenting with what appears to be TB will concurrently have a pulmonary malignancy than someone who does not have a TB infection, but also that it is of greater urgency to make an expedited diagnosis of the malignancy.
Key Words: Tumorous endobronchial tuberculosis; Bronchial squamous cell cancer; Diagnosis; Treatment; Case report

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Core Tip: In the correct clinical setting, lesions such as those seen during bronchoscopy should alert the physician to the possibility of active tuberculosis (TB). With the advancement of diagnostic techniques, the screening of high-risk populations of patients with lung cancer, and the prolongation of postoperative survival rates, and the close follow-up of lung cancer patients with TB, it is expected that TB can be detected in an early stage with a good prognosis after treatment.

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INTRODUCTION
Lung cancer with pulmonary tuberculosis (TB) refers to the occurrence of lesions simultaneously or sequentially in the lung(s) of the same patient, and the pathological examination and sputum TB examination diagnose them as lung cancer and TB, respectively. The pulmonary TB can be active or inactive.

The coexistence of lung cancer and TB has previously been reported and some studies suggest that TB lesion is an independent prognostic factor for lung cancer. The risk of lung cancer in TB patients was three times that in patients without TB. Paulin et al[1] demonstrated that malignancies intensify immune disorder, which may raise the probability of TB and latent TB recurrence.

Unlike other cases of TB, reports of the association between endobronchial TB (EBTB) and bronchial cancer are rare. Pulmonary TB together with bronchus squamous cell carcinoma occurs extremely rarely. We hereby report a rare case of coexistence of tumorous EBTB and bronchus squamous cell cancer.

CASE PRESENTATION

Chief complaints
A 62-year-old female patient was admitted to a local hospital on June 18 2019 after a 3-mo history of dyspnea.

History of past illness
The patient was healthy.

Personal and family history
The patient was a farmer and had no history of smoking and alcohol misuse. She had no history of tuberculosis or other previous chronic disease. The patient had neither family nor work contact indicating exposure to TB.

Physical examination
Physical examination disclosed no abnormalities. The patient had a body mass index of 29.6. She denied losing weight in the past 6 mo.

Laboratory examinations
Tumor markers, TB antibody test, tuberculin skin test, and interferon gamma release assay were also negative. Sputum smear was negative for acid fast bacilli (AFB). Considering the possibility of bronchus cancer with lymph node metastasis, biopsy was suggested. On bronchoscopy, a tumorous growth obstructing around 90% of the right main bronchus was seen (Figure 1). The remaining bronchi were passable,
without lesions. Reviewing the chest CT images, we found that the mass in the right main bronchus was easy to see, but the histology of mass was hard to identify on CT images. And this was also the reason why bronchoscopy was required.

No distant metastasis or abdominal lymph node metastasis was found on CT examination. Tumorous mass resection via bronchoscopy under general anesthesia was performed, and the wound was ligated by use of a high frequency snare and cleaned up with an endotherm knife. Biopsy of the tumorous mass was performed for histological and cytological examinations. Histopathologic examination revealed well-defined caseating granuloma, and the biopsy was positive for AFB (Figure 2), and Xpert Mycobacterium tuberculosis (MTB)/rifampicin assay of the biopsy sample was weakly positive.

**Imaging examinations**
Emergency chest computed tomography (CT) examination showed that the right main bronchus was occupied (1.2 cm × 1.0 cm) and a malignant tumor was suspected (Figure 3).

**FINAL DIAGNOSIS**
Endobronchial MTB infection.

**TREATMENT**
The patient was given standard anti-tuberculosis treatment with isoniazid, rifampicin, ethambutol, and pyrazinamide as per the national standard treatment guidelines.

**OUTCOME AND FOLLOW-UP**
Chest CT after 6 mo of therapy (December 23, 2019) showed that bronchial narrowing and airspace consolidation in the right main bronchus (5 mm × 4 mm) (Figure 4), but the size of mass was smaller than that at the first admission, without bronchial wall thickening, and lymphadenopathy in the mediastinal was considered to be mediastinal lymph node metastasis.

Laboratory examination revealed elevated tumor markers including CEA (4 ng/mL), CA125 (2 U/mL), NSE (3 ng/mL), SCC antigen (14 mg/L), CYFRA211 (41.2 ng/mL), and ProGRP (4 pg/mL). On bronchoscopy, a shiny black vesicular lesion was found in the right main bronchus (Figure 5). Mucosal punch biopsies were then obtained from the lesion. Poorly differentiated SCC was cytologically and histologically verified. Immunohistochemistry staining showed that the tumor cells were positive for P63, P40, CK7, CK(Pan), Ki67, and p53, but negative for TTF-1, NapsinA, SOX2, SALL4, and CD34 (Figure 6). Although the tumor was tiny, it invaded the main trachea, was very close to the carina, and was staged as IIIB (T4N2M0). Owing to the anatomic location of the tumor, surgical resection was not advised. Oncologists had
Figure 2 Bronchial biopsy. A: Granulomatous inflammation with caseification, which is consistent with tuberculosis (Hematoxylin and eosin stain, × 200); B: Biopsy staining showed positivity for acid-fast bacilli (Ziehl-Nielsen staining, × 1000).

Figure 3 Imaging changes of the mass before treatment. A: Reconstructed thoracic computed tomography (CT) image; B: Enhanced chest CT in mediastinal window; C: Axial CT in lung window showing narrowing of the main bronchus and airspace consolidation in the right bronchus, without parenchymal infiltration or pneumonia.

Figure 4 Chest computed tomography images (December 23, 2019) showing a 5 mm × 4 mm lung mass in the right main bronchus. A: Lung window; B: Mediastinal window.

suggested anticancer chemotherapy combined with anti-tuberculosis treatment so as not to increase the occurrence of complications or result in a negative outcome. On the basis of clinical studies, the NCCN guidelines recommend that cisplatin combined with gemcitabine be preferred for squamous cell NSCLC. The patient had started on systemic chemotherapy with cisplatin combined with gemcitabine. After 3 mo of therapy (March 20, 2020), chest CT showed complete resolution of the lesion.
Figure 5 Bronchoscopy (December 23, 2019). A and B: A black mucosa was found in the right main bronchus.

Figure 6 Histological and immunohistochemical examinations. A: The right main bronchus mass was squamous cell carcinoma (hematoxylin and eosin staining, × 200); B: The tumor cells were positive for P63, P40, CK7, CK(Pan), Ki67, and p53 but negative for TTF-1, NapsinA, SOX2, SALL4, and CD34 (× 200).

(Figure 7). Bronchoalveolar lavage and bronchial aspirate were negative for AFB and cancer cells. The patient has been followed for 9 mo so far. She is currently on antituberculosis medication combined with anticancer chemotherapy.

DISCUSSION

In 1810, the coexistence of pulmonary TB and lung cancer was first described, which poses significant challenges for their diagnosis and treatment[2]. Among the exposures associated with the risk for lung cancer, a history of chronic pulmonary disease, especially tuberculosis, is one potentially important factor[3].

Several case series and case-control studies on this association have been well-documented, but the association between lung TB and lung carcinoma is still controversial[4]. Studies have proposed that chronic inflammation in the lungs due to TB could cause clastogenic activity in the DNA of bronchial epithelium. Another hypothesis is lateral gene transfer. Since MTB is an intracellular organism, bacterial DNA could integrate into bronchial epithelial cells to induce neoplastic transformation [5,6]. In addition, lung carcinogenesis (LC) during the course of chronic TB was more pronounced in animals with severe lung tissue damage mediated by TB susceptibility locus[7].

Several studies have shown a significantly increased lung cancer risk associated with preexisting TB, and the association of preexisting TB with adenocarcinoma was significant. In a case series of LC in Ankara, SCC was the most common cancer, and LC had a more peripheral origin and was squamous cell carcinoma histopathologically [8]. In this patient, it is significant that EBTB was diagnosed before SCC, and the main cancer lesion was tiny; however, the lesions of SCC and EBTB were located in the same bronchial region. Therefore, we should not exclude the possibility that the histological...
Figure 7 Chest computed tomography images (March 20, 2020) showing complete resolution of the lesion in the right main bronchus. A: Lung window; B: Mediastinal window.

CONCLUSION

In the correct clinical setting, lesions such as those seen during bronchoscopy should alert the physician to the possibility of an active MTB infection\cite{ref9}. With the advancement of diagnostic techniques, the screening of high-risk populations for lung cancer, and the prolongation of postoperative survival and close follow-up of lung cancer patients with tuberculosis, it is expected that TB can be detected in an early stage with a good prognosis after treatment.

REFERENCES

Is simultaneous presence of IgG4-positive plasma cells and giant-cell hepatitis a coincidence in autoimmune hepatitis? A case report

You-Wen Tan, Jia-Min Wang, Li Chen

BACKGROUND
The immune-mediated invasion of IgG4-positive plasma cells in the liver is found in some autoimmune hepatitis. Giant-cell hepatitis (GCH) is a very rare pathological feature in adults, and the clinical characteristics of the simultaneous appearance of the two pathological phenomena are not clear.

CASE SUMMARY
A 68-year-old woman was hospitalized with fatigue, poor appetite, and yellow urine for 20 d. Liver function tests and immunological indexes were significantly abnormal and accompanied by elevated serum IgG4 levels. Liver pathology revealed severe inflammation of the interface between the portal tract and hepatocytes, portal area inflammation, plasma cell infiltration, formation of rosette cells, IgG4-positive plasma cells > 10/high-power field, IgG4/IgG > 40%, and multinucleated liver cell swelling. IgG4-related autoimmune hepatitis (AIH) combined with GCH was diagnosed, and methylprednisolone was administered at 40 mg/day. Two weeks later, the clinical symptoms disappeared, and the liver function and immunological indicators were significantly improved. Methylprednisolone was reduced at a rate of 4–8 mg per week to 8 mg/day for maintenance. A second liver biopsy 48 wk later indicated that liver inflammation and fibrosis were significantly improved. IgG4-positive plasma cells and GCH were not detected. A literature search was conducted to analyze articles reporting similar pathological phenomena.

CONCLUSION
AIH with simultaneous IgG4-positive plasma cell infiltration and GCH, liver inflammation, and fibrosis is possibly more severe than typical AIH but sensitive to corticosteroids.

Key Words: IgG4; Autoimmune hepatitis; Giant-cell hepatitis; Case report
A 68-year-old woman was hospitalized for liver function tests. Her immunological indices differed significantly from normal, and were accompanied by elevated serum IgG4 levels. Liver pathology revealed severe inflammation at the interface between the portal tract and hepatocytes, plasma cell infiltration, formation of rosette cells, IgG4-positive plasma cells > 10/high-power field, IgG4/IgG > 40%, and multinucleated liver cell swelling. The patient was diagnosed as having IgG4-autoimmune hepatitis combined with giant-cell hepatitis (GCH), and 40 mg/day methylprednisolone was administered. A second liver biopsy 48 wk later indicated significant amelioration of liver inflammation and fibrosis. IgG4-positive plasma cells and GCHs were not detected. A literature search was conducted to analyze reports of similar pathological phenomena.

**INTRODUCTION**

IgG4-related disease (IgG4-RD) is a new autoimmune disease mediated by immunity [1]. This kind of disease is closely related to IgG4 lymphocytes, with increased serum IgG4 levels and IgG4-positive plasma cells infiltrating many organs and tissues. The most common organs involved include the pancreas and salivary gland, followed by the bile duct, kidney, liver, lung, and lacrimal glands. It has been recently reported that in the diagnosis of IgG4-autoimmune hepatitis (IgG4-AIH) [2,3], whether IgG4-AIH has independent subclass characteristics of classical AIH remains controversial. Giant-cell hepatitis (GCH) or post-infantile GCH is an inflammatory disease of the liver characterized by the presence of large, thin-walled multinucleated (4-5 or more nuclei) liver cells. GCH is common in infants and young children but is very rare in adult liver diseases. In the past 30 years, scarcely more than 100 cases have been reported in the literature with an incidence of 0.1%-0.25%[4]. Therefore, the disease characteristics when the simultaneous presence of IgG4-positive plasma cells and GCH in liver tissue is accompanied by elevated serum IgG4 levels in patients with AIH are still unknown. We herein report a case of AIH with such characteristics and present the entire diagnosis and treatment process.

**CASE PRESENTATION**

**Chief complaints**

A 68-year-old woman was hospitalized with symptoms of asthenia, poor appetite, and yellow urine lasting more than 20 d.

**History of present illness**

The patient had no nausea, vomiting, epigastric pain, or other symptoms of discomfort, including fever and joint pain.

**History of past illness**

The patient had no history of hepatitis, blood transfusions, contact with schistosomiasis contaminated water, alcohol abuse, or use of liver-damaging drugs. The patient reported no hypertension, diabetes, coronary heart disease, or other chronic diseases.

**Personal and family history**

The patient’s parents had no liver disease, and her siblings displayed no signs of liver disease.
**Physical examination**

Physical examination revealed the following: Blood pressure, 106/88 mmHg; heart rate, 71 beats/min; and body temperature, 36.8 °C. The skin and sclera were slightly yellow, and no liver palms or spider nevi were found. The abdomen was flat and soft, and there was no tenderness or rebound pain throughout the abdomen, no palpation under the sternum or right ribs, no palpation under the left ribcage, no percussion pain in the liver area, negative mobility dullness, and no edema in either lower limb.

**Laboratory examinations**

A liver function test revealed the following: Total bilirubin (TBIL) 65.21 µmol/L; direct bilirubin 45.19 µmol/L; alanine aminotransferase (ALT) 441.2 U/L; aspartate aminotransferase (AST) 466.6 U/L; alkaline phosphatase (ALP) 330.4 U/L; γ-glutamyl transpeptidase (GGT) 489.6 U/L; lactate dehydrogenase 222.6 U/L; total cholesterol 6.43 mmol/L; albumin 31.2 g/L; globulin 38.6 g/L; and prealbumin 102.3 mg/L. A blood test panel revealed the following: White blood cells 3.61 × 10^9/L; red blood cells 3.38 × 10^12/L; hemoglobin 89 g/L; platelets 75 × 10^9/L; neutrophil count 1.97 × 10^9/L; and neutrophil percentage 55.4%. Antinuclear antibody (85 U/L; < 10 U/L, enzyme-linked immunosorbent assay), anti-smooth muscle antibody, anti-liver/kidney microsomal antibody type 1, anti-nuclear glycoprotein antibody, anti-soluble acid nucleoprotein antibody, anti-hepatocyte cytoplasmic antigen type 1 antibody, anti-soluble liver antigen/hepatopancreatic antigen antibody, and other test results were negative. IgG, IgG4, and IgM levels were 29.4 g/L (< 17.1 g/L), 2.93 g/L (< 2.01 g/L), and 4.33 g/L (< 4 g/L), respectively. Viral hepatitis (A–E), Epstein–Barr virus (EBV), and cytomegalovirus (CMV) infections were ruled out.

**Imaging examinations**

Enhanced upper abdominal computed tomography, magnetic resonance imaging, and magnetic resonance cholangiopancreatography revealed splenomegaly but no lesions of the pancreas, bile duct, or other lesions.

**FINAL DIAGNOSIS**

A liver biopsy was performed, and the pathology showed extensive proliferation of fibrous tissue (Ishak’s fibrosis score, 5), moderate and severe interface hepatitis, bridging necrosis and fibrosis, edema of hepatocytes as evidenced by rosette formation, multinucleated hepatocytes in each portal area (Figure 1A and B), extensive monocyte lymph infiltration, dense plasma cells in the portal area, and positive plasma cells stained with IgG4 (≥ 10/high-power field, HPF; Figure 1C and D), and IgG4/IgG > 40%. The pathological diagnosis was IgG4-related AIH and GCH.

**TREATMENT**

Methylprednisolone (40 mg/d) was administered.

**OUTCOME AND FOLLOW-UP**

Two weeks after initial treatment, liver function moderately improved [TBIL, 45.3 µmol/L; ALT, 113 U/L; ALP, 143 U/L; GGT, 332 U/L], and immunological indices began to decline (IgG, 21.4 g/L; IgG4, 2.21 g/L). After 4 wk, methylprednisolone was reduced by 4–8 mg per week, to reach a stably maintained dose of 8 mg/d. Liver function and immunological indicators were monitored every 4–12 wk (Figure 2). A second liver biopsy was performed after 48 wk. Liver pathology indicated significant improvement in liver inflammation and necrosis, no lobular inflammation, mild inflammation in the portal area (Figure 3A), and significantly ameliorated fibrosis (from stage 5 to stage 2 according to Ishak’s fibrosis scoring system, Figure 3B and C), and scattered plasma cells. IgG4-positive immunohistochemical staining was negative, and GCH was no longer detected (Figure 3A).
FIGURE 1 Histological characteristics of the first liver biopsy. A: Severe portal inflammation and interface inflammation (arrow) are visible. Hematoxylin-eosin (HE) staining, 200 × magnification; B: Giant-cell hepatitis (arrow). HE, 400 × magnification; C: Plasma cell infiltration (arrow). HE, 400 × magnification; D: IgG4-positive plasma cell infiltration (arrow). IgG4 immunohistochemical staining, 200 × magnification.

FIGURE 2 Changes of main liver function and immunological indexes in the patient. MP: Methylprednisolone; LB: Liver biopsy; TBIL: Total bilirubin; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase.

DISCUSSION

Umemura et al [2] described the clinicopathological features of IgG4-related liver disease for the first time. A variety of histological manifestations was observed in 17 patients with autoimmune pancreatitis (AIP), including portal vein inflammation (35%), interface hepatitis (24%), lobular hepatitis (29%), bile duct injury (59%), and tubular cholestasis (53%). These pathological results strongly suggest that about 20%–30% of patients with AIP have pathological manifestations similar to those of classic AIH.

Umemura et al [5] reported the first case of IgG4-AIH in 2007. Abnormal ALT, AST, and ALP levels and other abnormalities of the liver function were observed, as well as elevated serum IgG and IgG4. Typical pathological features of AIH were found in the
IgG4-AIH and GCH

Figure 3 Characteristic pathological changes of liver tissue. A: The portal area and interface inflammation have improved significantly (arrow) in the second liver biopsy. HE, 200 × magnification; B: The portal area was enlarged and the hepatic lobules were surrounded by fibers in the first liver biopsy. Masson staining, 100 × magnification; C: The fiber spacing is also thinner and improved than before in the second liver biopsy. Masson staining, 100 × magnification.

liver biopsy histology, such as interface hepatitis, plasma cell infiltration, and formation of rosette cells. According to the diagnostic criteria of the International Autoimmune Hepatitis Group[6], our case was consistent with AIH. According to the simple AIH scoring standard introduced in 2008, we diagnosed the patient with AIH based on the following eight-point criteria: ANA+, 2 points; IgG, 2 points; typical pathological characteristics, 2 points; viral hepatitis exclusion, 2 points.

IgG4-AIH has only been reported in a few studies[7-11]. In these studies, the proportion of IgG4-AIH ranges from 3.3% to 34.6% in AIH. IgG4-AIH and AIH are not significantly different in terms of clinical characteristics, biochemistry, and immunology, including the efficacy of corticosteroids. However, the criterion for IgG4-positive plasma cells differs in the diagnosis of IgG4-AIH. Chung et al[7] and Amarapurkar et al[9] used IgG4+/HPF > 5, whereas Umemura et al[8], Canivet et al[10], and Aydemir et al[12] used IgG4+ > 10 as the diagnostic criterion. In 2016, a study summarized and analyzed published data that met the diagnostic criteria for IgG4-RD, and proposed diagnostic recommendations for IgG4-AIH[12] as follows: (1) Serum IgG4 ≥ 1.35 g/L; (2) IgG4-plasma cells/HPF in liver tissue ≥ 10 and the ratio of IgG4-positive plasma cells to plasma cells infiltrated > 40%; (3) Chronic hepatitis with banding and bridging necrosis or apparent parenchymal collapse; and (4) Incorporation of other IgG4-RD. Complying with all four items is defined as confirmed IgG4-AIH, and complying with the first three items as highly likely IgG4-AIH, whereas complying with any two items as possible IgG4-AIH. Diagnostic recommendations are still subject to clinical testing.

However, the diagnosis of IgG4-AIH is still not accepted. IgG4-AIH is not recognized as a diagnostic category in the AIH guideline specification[13]. IgG4-RD is an immune disease of the systemic system, and its pathological features include non-infectious and non-neoplastic inflammation and fibrosis[1]. Therefore, it is reasonable to believe that the liver is not an organ that can avoid injury.

However, a newly published study found that 10 (11.9%) out of 84 patients with AIH had IgG4-AIH[14]. Although the biochemical characteristics of IgG4-AIH were similar to those of classical AIH, the pathological manifestations of IgG4-AIH were more severe interface hepatitis and lobular hepatitis and more progressive fibrosis than those of AIH. After a median of 139 mo of long-term observation, the recurrence rate of IgG4-AIH was lower than that of classical AIH. Xue et al[15] observed 152 patients with AIH. They analyzed 111 patients with AIH in the low IgG4 group (< 135 mg/mL) and 41 patients in the high IgG4 group (> 135 mg/mL) and found that those in the high IgG4 group presented a higher proportion of cirrhosis than those in the low IgG4 group. In our case, severe inflammation and fibrosis were also observed during the first histological examination. After 1 year of corticosteroid treatment, the second histological examination showed that the inflammation and fibrosis of the liver improved significantly, and the liver function remained normal.

Phillips et al[16] identified GCH in the early 1990s. They found that in 10 cases of GCH, individual hepatocytes had 30 nuclei, 5 out of 10 patients died, and 5 received liver transplantation, showing a very poor prognosis of the disease. Paramyxovirus antigens were detected in the cytoplasm of two patients, suggesting that GCH may be related to a viral infection.

GCH is a rare pathological feature of the liver. A total of 36726 liver biopsies sampled across 25 years from a single center showed 50 (0.14%) cases of GCH[17]. The reasons for its appearance may include infection (hepatitis A, B, C, EBV, CMV,
paramyxovirus, human immunodeficiency virus, HPS pulmonary syndrome, and human papillomavirus), autoimmune disease (AIH, ulcerative colitis, primary sclerosing cholangitis, primary biliary cholangitis, systemic lupus erythematosus, and rheumatoid arthritis), drugs (polyarteritis nodosa, methotrexate, mercaptopurine, amitriptyline, p-aminosalicylic acid, vinyl chloride, chropromazine, and methotre- xate), hematologic diseases (chronic lymphocytic leukemia, lymphoma, sickle cell disease, hypereosinophilia, and autoimmune hemolytic anemia), endocrine disease (hypoparathyroidism), or infiltrative disease (sarcoidosis). Among more than 2000 liver biopsies conducted in our center, two GCH cases were related to AIH.

The mechanism of GCH generation is not clear, and two explanations are accepted: One is the expression of immature cells[18], in which nuclear proliferation is not accompanied by cell membrane mitosis, resulting in nuclear accumulation[19]; the other is the nuclear overreaction of liver cells under abnormal stimulation[20,21].

To search for similar articles from the PubMed/Medline database, the time set was January 1, 1960 to December 31, 2020 and the keywords set as “IgG4 or AIH and GCH”. Three cases involving the coexistence of IgG4-AIH and GCH have been reported[5,8]. Umemura et al[8] reported 70 consecutive patients with type 1 AIH from a single center between June 1985 and December 2006. GCH was found in two cases of IgG4-AIH in 58 cases of typical AIH. In addition to elevated IgG4 in serum and IgG4-positive plasma cell expression in liver tissue, these two patients had more serious portal inflammation (> 2/3 of perportal areas), interface hepatitis (> 2/3 of perportal areas), lobular hepatitis (zonal hepatitis), plasma cells (> 20/HPF), and bridging fibrosis compared with those with classic AIH. In one case, after 5 years of treatment and follow-up, ALP and GGT levels continued to rise to 622 and 936 IU/L, respectively. The disease eventually developed into IgG4-related sclerosing cholangitis. The second case was a 42-year-old male patient with a serum IgG4 level of 642 mg/dL and a large number of IgG4-plasma cells expressed in liver tissue. After treatment with prednisone at 60 mg/day for 4 wk, the serum IgG4 level was reduced to 452 mg/dL and became normal after 7 mo. A second liver biopsy was performed and the pathology showed that although portal sclerosis was still present, portal inflammation and lobular inflammation improved markedly, and the GCH disappeared. The patient was followed for 13 years, and prednisone administration (5.0 mg/day) was maintained. Another case was reported as the first one of IgG4-AIH[5]. The authors did not emphasize the presence of GCH, but a large number of GCH hepatocytes were observed in the pathology images. The patient was sensitive to prednisone, and after 4 wk, the dose was reduced to 5 mg/day. The serum IgG4 and ALT levels were normal.

From the reported three cases of IgG4-AIH accompanied with GCH together with our case, some common features were observed: (1) The pathological lesions including inflammation, necrosis, and fibrosis are more serious than the pathological characteristics of classical AIH; (2) The disease is sensitive to corticosteroids. Except for one case that developed PSC, the other several cases had good histological improvement and biochemical response; and (3) Lastly, the more significant feature is that GCH disappears after corticosteroid therapy.

It is still difficult to explain the relationship between these two mechanisms. It can be assumed that: (1) The infection is the initiator; the evidence of not only the infection was found in GCH[16] but also the initiator of IgG4-RD. Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs) are important receptors that mediate immune recognition of pathogenic microorganisms and are widely distributed on the surfaces of immune cells. Microbial antigens activating TLR and NLR on the surfaces of monocytes may promote the production of IgG4 by the B cell activating factor signaling pathway[22]; and (2) Large number of cytokines, such as IL-4, IL-5, IL-10, IL-13, and IL-21, which regulate the growth of various cells, and the transforming growth factor-[23][24] are involved in the occurrence of IgG4-RD. Overexpression of these factors promotes the overdifferentiation of plasma cells and overproliferation of liver nuclei[27].

CONCLUSION

In conclusion, in our case and those from the literature, the simultaneous occurrence of IgG4 and GCH in AIH may reflect severe inflammation, necrosis, and fibrosis of liver injury, which may be sensitive to corticosteroid therapy, and the disappearance of GCH is evidence of pathological repair.
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Surgical treatment of delayed cervical infection and incomplete quadriplegia with fish-bone ingestion: A case report

Suo-Yuan Li, Ye Miao, Liang Cheng, Ye-Feng Wang, Zhi-Qiang Li, Yu-Bo Liu, Tian-Ming Zou, Jun Shen

BACKGROUND
The most commonly ingested foreign body in Asians is fish bone. The vast majority of patients have obvious symptoms and can be timely diagnosed and treated. Cases of pyogenic cervical spondylitis and diskitis with retropharyngeal and epidural abscess resulting in incomplete quadriplegia due to foreign body ingestion have been rarely reported. The absence of pharyngeal or esophageal discomfort and negative computed tomography (CT) findings of fish bone have not been reported. We report the case of an elderly female patient with delayed cervical infection and incomplete quadriplegia who had a history of fish bone ingestion.

CASE SUMMARY
A 73-year-old woman presented with right neck pain and weakness of four limbs for a week, and had a history of fish bone ingestion and negative findings on laryngoscopic examination one month previously. She did not complain of any pharyngeal or esophageal discomfort. Cervical magnetic resonance imaging showed C4/C5 spondylitis and diskitis with retropharyngeal and ventral epidural abscesses. No sign of fish bone was detected on lateral cervical radiography and CT scans. The muscle strength of the patient’s right lower limb receded to grade 1 and other limbs to grade 2 suddenly on the 10th day of hospitalization. Emergency surgery was performed to drain the abscess and decompress the spinal cord by removing the anterior inflammatory necrotic tissue. Simultaneously, flexible esophagogastroduodenoscopy was carried out and a hole in the posterior pharyngeal wall was found. The motor weakness of the right lower limb improved to grade 3 and the other limbs to grade 4 within 2 d postoperatively.

CONCLUSION
This rare case highlights the awareness of the posterior pharyngeal or esophageal wall perforation in patients with cervical pyogenic spondylitis along with a
history of fish bone ingestion, even though local discomfort symptoms are absent and the radiological examinations are negative.

Key Words: Fish bone; Cervical infection; Pyogenic spondylitis; Retropharyngeal abscess; Epidural abscess; Case report

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Core Tip: We report a rare case of an elderly female patient with delayed cervical infection and incomplete quadriplegia who had a history of fish bone ingestion. We recommend clinicians be aware of this rare condition that can occur without positive computed tomography findings and mediastinitis. In addition, local complete debridement, sufficient use of antibiotics and placement of a gastric tube for nasal feeding played a vital role in infection control and healing of the laryngopharyngeal wall perforation.

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INTRODUCTION
In Asians, the most commonly ingested foreign body is fish bone[1]. The vast majority of patients have obvious symptoms and can be timely diagnosed and treated[2,3]. Few cases may develop pharyngeal or esophageal wall perforation[4]. As far as we know, this is the first reported case of an ingested fish-bone with no obvious clinical manifestation found until the occurrence of severe cervical infection of C4/C5 and incomplete quadriplegia one month later.

CASE PRESENTATION

Chief complaints
A 73-year-old woman was referred to our hospital due to right neck pain and weakness of all four limbs for one week, urine retention and occasional high fever for three days.

History of present illness
She had a history of fish bone ingestion one month ago, and laryngoscopic examination did not show positive findings. The patient did not complain of any pharyngeal or esophageal discomfort.

History of past illness
She had an 8-year history of diabetes and poor glycemic control.

Personal and family history
The patient had unremarkable personal and familial medical history, including psycho-social history.

Physical examination
On admission, her body temperature was 36.5℃. Physical examination showed sensitive percussion over the cervical spinous processes and marked restriction of neck motion. Lhermitte’s sign was positive. The strength of the right upper and lower extremities was grade 3 and of the left upper and lower extremities was grade 4. No sensory deficit was observed. The bilateral pathologic reflexes were positive.
The muscle strength of the right lower limb receded to grade 1 and other limbs to grade 2 suddenly on the 10th day of hospitalization.

**Laboratory examinations**
Laboratory examinations revealed leukocytosis at 12360/μL with 92% neutrophils, and C-reactive protein (CRP) of 121.47 mg/dL.

**Imaging examinations**
Cervical radiography and computed tomography (CT) did not find the fish bone or other foreign bodies (Figure 1). Cervical magnetic resonance imaging (MRI) demonstrated spondylitis and diskitis of C4/C5, so the patient received intravenous Biapenem 0.3 g every 8 h immediately.

The emergency MRI revealed a great amount of septic fluid collection in the spatium retropharyngeum spreading into the spinal canal through C4/C5 disc space (Figure 2A), forming a ventral epidural abscess extending from C6 to the foramen magnum (Figure 2B).

**FINAL DIAGNOSIS**
Final diagnosis of the presented case was delayed cervical infection and incomplete quadriplegia.

**TREATMENT**
Following emergency MRI examination, emergency surgery was performed to decompress the spinal cord by removing the anterior inflammatory necrotic tissue and draining the epidural abscess. Simultaneously, flexible esophagogastroduodenoscopy found an underlying abscess and esophageal perforation, which were exposed and treated with irrigation and careful debridement (Figure 3). Enteral nutrition through an indwelling nasogastric tube was conducted, and the esophageal perforation was treated conservatively. After surgery, the fish bone was found in the irrigation fluid (Figure 4). Culture of the epidural abscess suggested *Staphylococcus aureus* infection.

**OUTCOME AND FOLLOW-UP**
The patient’s symptoms significantly improved postoperatively. On the second day after surgery, muscle strength of the right lower limb was improved to grade 3, and muscle strength of the other limbs was improved to grade 4. On the 15th day after surgery, MRI examination showed that the abscess in the posterior pharyngeal wall and epidural was significantly smaller than that before surgery (Figure 5). The cervical spine was stabilized with a Minerva cervicothoracic orthosis for 8 wk. Postoperative enteral nutrition through an indwelling nasogastric tube was conducted for 6 wk. Intravenous Linezolid 600 mg every 12 h was administered for 15 d until the erythrocyte sedimentation rate and CRP declined to normal levels. On the fifth week after surgery, no foreign body was found in the cervical X-ray examination (Figure 6).

One-year follow-up showed that the patient’s limb muscle strength had completely returned to normal.

**DISCUSSION**
Cervical epidural abscess developing from a retropharyngeal abscess and spondylitis due to upper digestive tract wall injury and perforation is extremely rare\[5\]. All the reported perforation cases caused by foreign body ingestion have pharyngeal or esophageal discomfort\[1,6-8\]. Our patient did not complain of any symptoms, including dysphagia, odynophagia, hematemesis, dyspnea, etc. CT has a sensitivity of 90%-100% in detecting impacted fish bones\[9-11\], which is obviously superior to 32% by plain radiography\[6\]. However, in the present case, both plain radiography and CT did not identify the impacted fish bone. Physicians should be aware of the posterior pharyngeal or esophageal wall perforation in patients with cervical pyogenic
Figure 1 Preoperative computed tomography scan. No fish bone was detected. Note the narrowing of the disc space at C4/C5 (arrow).

Figure 2 Preoperative magnetic resonance images. A: Sagittal T2-weighted fat-suppressed image shows a marked fluid collection in the spatium retropharyngeum (arrow) spreading into the spinal canal through the C4/C5 disc space; B: Sagittal gadolinium-enhanced image demonstrates a well-delineated peripherally enhancing ventral epidural abscess (arrow) extending from C6 to the foramen magnum.

spondylitis with a certain or uncertain history of foreign body ingestion, even though local discomfort symptoms are absent and the radiological examinations are negative.

Urgent management in the first 24 h is critical for the prognosis of foreign body ingestion. If the patient is subjected to delayed management for more than 2 days, the state of the local injury may develop into a fatal condition[12], especially the foreign body lodging at the esophagus entrance, which is surrounded by the cricopharyngeus muscle[13]. In the present case, symptoms due to spinal cord compression developed one month after fish bone ingestion, which missed a timely early intervention and increased the likelihood of severe complications.

Endoscopy is the most frequently used technique in clinical practice, which is recommended as the first-line therapeutic option for foreign body extraction[14]. Fish bone is one of the main ingested esophageal foreign bodies. Perforation of the esophagus caused by fish bone usually leads to mediastinitis[15-18]. In the present case, the patient developed spondylitis without mediastinitis. Endoscopy after
admission revealed that the posterior wall of the laryngopharynx was ruptured and a fish bone was found in the irrigation fluid after surgery. During the diagnostic process, clinicians need to pay sufficient attention to patients with a history of fish bone ingestion, even if the immediate laryngoscopy results are negative. It is suggested that in patients without mediastinitis, esophageal perforation caused by a foreign body is mostly located in the posterior wall. In terms of treatment, we adopted local complete debridement, sufficient and effective use of antibiotics and placement of a gastric tube for nasal feeding to avoid secondary infection. These measures played a vital role in infection control and healing of the laryngopharyngeal wall perforation.

**CONCLUSION**

This case was our first encounter with a delayed cervical infection and incomplete quadriplegia with fish-bone ingestion and reminds us to consider the possibility of foreign body in the differential diagnosis for patients with neck pain and weakness of four limbs. It is necessary for clinicians to consider and recognize cervical infection and incomplete quadriplegia due to fish-bone ingestion in patients with atypical clinical manifestations or CT findings. We hope that the case we report here will increase awareness of cervical infection due to a foreign body and help avoid future
Figure 5 Postoperative magnetic resonance images. A: Sagittal T1-weighted image shows that the epidural abscess (arrow) was less than that before surgery; B: Sagittal T2-weighted image demonstrates that the abscess in the posterior pharyngeal wall (arrow) was obviously less than that before surgery.

Figure 6 X-ray of cervical spine (fifth week after operation). No fish bone was detected. The nasogastric tube was placed in the esophagus.

misdiagnosis by orthopedists.

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Li SY et al. Delayed cervical infection with fish bone


Neonatal biliary atresia combined with preduodenal portal vein: A case report

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A 1-mo-and-4-d-old child was admitted to the hospital in January because of yellowish skin. After surgical consultation, surgical intervention was recommended. The child underwent Hilar-jejunal anastomosis, duodenal rhomboid anastomosis, and abdominal drainage under general anesthesia. During the operation, the PV was located at the anterior edge of the duodenum.

CONCLUSION

Diagnoses: (1) Congenital biliary atresia; (2) PD-PV; and (3) Congenital cardiovascular malformations. Outcomes: Recommendation for liver transplantation. Lessons: The choice of treatment options for neonatal biliary atresia combined with PD-PV.
A female infant, G1P1, had a gestational age of 37 wk and 4 d. On the fourth day after birth, the baby developed yellowing of the facial skin, which progressively aggravated. The skin over the trunk region also turned yellowish, and it progressed further. Admission diagnoses were: (1) Neonatal hepatitis syndrome; (2) Abnormal liver function; and (3) Congenital cardiovascular malformations. The patient’s body temperature was normal, all vital signs were stable, and the stool was still light yellow and slightly whitish. The electroconvulsive therapy report from the outside hospital showed that the liver function was disrupted with biliary obstruction. After surgical consultation, surgical intervention was recommended.

**Case Presentation**

**Chief Complaints**

A female infant, G1P1, had a gestational age of 37 wk and 4 d. On the fourth day after birth, the baby developed yellowing of the facial skin, which progressively aggravated. The skin over the trunk region also turned yellowish, and it progressed further. Admission diagnoses were: (1) Neonatal hepatitis syndrome; (2) Abnormal liver function; and (3) Congenital cardiovascular malformations. The patient’s body temperature was normal, all vital signs were stable, and the stool was still light yellow and slightly whitish. The electroconvulsive therapy report from the outside hospital showed that the liver function was disrupted with biliary obstruction. After surgical consultation, surgical intervention was recommended.

**History of Present Illness**

On the fourth day after birth, the baby developed yellowing of the facial skin, which progressively aggravated. The skin over the trunk region also turned yellowish, and it progressed further. Admission diagnoses were: (1) Neonatal hepatitis syndrome; (2) Abnormal liver function; and (3) Congenital cardiovascular malformations. The patient’s body temperature was normal, all vital signs were stable, and the stool was still light yellow and slightly whitish. The electroconvulsive therapy report from the outside hospital showed that the liver function was disrupted with biliary obstruction. After surgical consultation, surgical intervention was recommended.

**History of Past Illness**

She was admitted to the Neonatology Department with the diagnosis of “newborn jaundice” in the outpatient clinic. The meconium passed by the child was resolved within 24 h after birth, and it turned yellow within 2-3 d. Bowel movements occurred 1-2 times a day, and the color of stool was pale yellow, without clay colored stool. Urine was normal.

**Personal and Family History**

A female infant, G1P1, had a gestational age of 37 wk and 4 d.
Physical examination
Upon admission, clinical examination showed body temperature: 37 °C, pulse: 140 beats/min, respiratory rate: 40 beats/min, weight: 3760 g, clearly conscious, good reaction, crying loudly, steady breathing, moderate yellowing of the skin on the face, trunk, and limbs, the sclera was yellowish, and the skull was not deformed. There were no special features in the face. The fontanelle measured about 2.0 cm × 2.0 cm, and it was flat. The nose did not move, the lips were not cyanosed, the neck was soft, the breath sounds of both lungs were thick, and no dry or wet rales were heard. The heart rhythm was uniform, the heart sound was medium, no murmur was heard, and the abdomen was soft. The liver was located 2 cm below the ribs, and it did not touch the spleen. Bowel sounds were normal, 3-4 sounds per minute. The umbilicus was dry, and the umbilical chakra was not red. The muscle tension of the limbs was normal, and the foraging and sucking reflexes could be elicited.

Laboratory examinations
Outpatient examination of liver function revealed: γ-glutamyl transpeptidase: 114.5 U/L, total protein: 58.5 g/L, albumin: 58.5 g/L, prealbumin: 104 mg/L, globulin: 15.6 g/L, albumin-globulin ratio: 2.75, high-sensitivity C-reactive protein: 0.32 mg/L, glutamic-pyruvic transaminase: 91.3 U/L, glutamic oxaloacetic transaminase: 166.4 U/L, indirect bilirubin: 100.02 μmol/L, direct bilirubin: 129.88 μmol/L, total bilirubin: 229.9 μmol/L; and a normal TORCH test.

Imaging examinations
Color Doppler ultrasound showed no obvious abnormal echo in the liver, gallbladder, pancreas, and kidneys. Heart Doppler ultrasound revealed interruption of the inferior vena cava and continuation of the odd vein, persistence of the left superior vena cava, and a patent foramen ovale.

MULTIDISCIPLINARY EXPERT CONSULTATION
After surgical consultation, surgical intervention was recommended.

FINAL DIAGNOSIS
(1) Congenital biliary atresia; (2) PD-PV; and (3) Congenital cardiovascular malformations.

TREATMENT
The child underwent laparoscopic exploration under general anesthesia. During the operation, the PV was located at the anterior edge of the duodenum (Figure 1). Intraoperative diagnosis was PD-PV. Upon exploring the gallbladder, it was found that the gallbladder was poorly developed and had the shape of a cord. Intraoperative cholangiography showed that the intrahepatic bile duct was visualized by percutaneous puncture catheter-based injection of the contrast agent, but the biliary tract system was not clearly visualized, the duodenum was not visualized, and there was no contrast agent in the abdominal cavity. The intestinal loops were filled with gas and were dilated (Figure 2). Then the child was switched to open surgery, and the hilar tissues were carefully dissected. The fibrous mass in the hilar tissue was freed, and the fibrous mass and part of the liver parenchyma were removed. A light yellow bile secretion was noted. The gallbladder and choledochal cyst wall were removed from the trocar of the umbilical cord, and the mesangium was repaired. Hilar-jejunal anastomosis was performed.

OUTCOME AND FOLLOW-UP
The child’s symptoms were gradually relieved, and then she was discharged. During follow-up, the child’s condition gradually improved, but deterioration of the child’s
Figure 1 The child underwent laparoscopic exploration under general anesthesia. During the operation, the portal vein was located at the anterior edge of the duodenum.

Figure 2 Intraoperative cholangiography showed that the intrahepatic bile duct was visualized by percutaneous puncture catheter-based injection of the contrast agent, but the biliary tract system was not clearly visualized, the duodenum was not visualized, and there was no contrast agent in the abdominal cavity.

condition could not be ruled out, which would require liver transplantation or other treatments. Finally, the child was lost to follow-up due to change in contact information of the child’s family.

DISCUSSION

The relationship between neonatal biliary atresia and PD-PV should be considered in depth. In this study, the baby developed yellowing of the facial skin, which progressively aggravated. The skin over the trunk region also turned yellowish, and it progressed further. The child was admitted to the neonatology department with the diagnosis of “newborn jaundice” in the outpatient clinic. Further investigation showed that the liver function was disrupted due to biliary obstruction. Intraoperative cholangiography showed that the intrahepatic bile duct was visualized by percutaneous puncture catheter-based injection of the contrast agent, but the biliary tract system was not clearly visualized, the duodenum was not visualized, and there was no contrast agent in the abdominal cavity. The intestinal loops were filled with gas and were dilated. On laparoscopic exploration, the PV was located at the anterior edge of the duodenum. Upon exploring the gallbladder, it was found that the gallbladder was poorly developed and had the shape of a cord. Based on the above findings, post-operative diagnoses of congenital biliary atresia and PD-PV were established. After surgical treatment combined with drug therapy and other comprehensive treatments,
the child’s symptoms were gradually relieved, and then she was discharged.

Biliary atresia of the bile duct in the first part of the duodenum before the PV can occur individually, as found in such cases, or it can occur in combination. It is categorized as deformation of the congenital anatomic structure. There are a limited number of published studies describing the correlation of biliary atresia and PD-PV with the onset of deformity. Given the paucity of reported cases, the current study provides timely insights with regard to planned treatment and outcomes for this combination syndrome.

Features of PD-PV

Since 1921, Knight first described PD-PV [6], and so far, less than 100 cases have been reported in the literature. Each report often presents the case of only 1 child, and most of the reports have presented cases of only 5 children, which indicates that the deformity is very rare. Its true incidence cannot be accurately calculated because in some cases PD-PV does not produce any clinical symptoms before it is detected.

PD-PV originates from the persistent primordial yolk vein or is related to abnormal rotation of the midgut. For example, abnormal intestinal rotation and duodenum and stomach reversal may result in PD-PV [7]. Three quarters of children with PD-PV have some concomitant malformations, such as cardiovascular malformations, gastrointestinal malformations, and biliary malformations [8] or are considered to be part of other syndromes, such as polysplenia or heterotaxy. Isolated PD-PV, including symptomatic or asymptomatic PD-PV, accounts for only a quarter of all cases [9].

PD-PV is considered to be an external cause of congenital duodenal obstruction. Researchers have been studying how a low-pressure blood vessel can cause thick-walled duodenal obstruction [7]. In most cases, duodenal obstruction is caused by other related deformities, and PD-PV is just an accompanying deformity. In the study by Vilakazi et al [10], in only 10 cases duodenal obstruction in children was found to be caused by PD-PV alone. PD-PV may cause complete or partial duodenal obstruction. Characteristically, vomiting can occur within a few hours after birth, and feeding cannot be tolerated. Partial duodenal obstruction presents with repeated episodes of vomiting and growth retardation. Snavely and Breakell [10] reported that PD-PV caused portal hypertension, variceal bleeding in the fundal venous plexus, and death of the patient. Autopsy revealed that the PV became narrowed due to abnormal position, which affected the blood flow of the PV and caused portal hypertension.

PD-PV diagnosis and treatment

Preoperative diagnosis of PD-PV is very rare. This disease entity may not be discovered until childhood or adulthood, or it may be discovered accidentally on abdominal computed tomography. A total of 5%-10% of children with biliary atresia are accidentally diagnosed with PD-PV during surgery. PD-PV combined with the anterior common bile duct of the duodenum has also been reported; however, cholecystectomy poses a great risk for children with PD-PV [11], or it is accidentally discovered during cholecystectomy in adults [12].

The prenatal diagnosis of congenital duodenal obstruction is based on obvious polyhydramnios and the double bubble sign displayed by B-ultrasound. The PD-PV is a cause of prenatally diagnosed duodenal obstruction, established by B-ultrasound, which has not been found in the literature presented in domestic and foreign reports [13].

Abdominal color Doppler ultrasound and computed tomography can be used in cases with a clear diagnosis of duodenal obstruction before surgery. If the vascular structure is found in the front of the pancreas, it has an important diagnostic value. PD-PV is a rare cause of duodenal obstruction. It is not necessary to diagnose PD-PV before surgery because all children with duodenal obstruction require laparotomy or laparoscopic exploratory surgery. However, it is very important to identify PD-PV during the operation because PD-PV occasionally does not cause obstruction, but it may only be discovered accidentally during the operation, which may result in intraoperative complications, especially in children with intestinal rotation or abnormal internal organs. These unconventional anatomical positions put the children at risk of iatrogenic injuries, including iatrogenic bleeding from abnormal veins or damage to the bile duct and dilated duodenum.

Duodenal obstruction has the potential to progress to a surgical emergency. However, children should not undergo surgery immediately. Instead, they should receive gastrointestinal decompression, oxygen inhalation, electrocardiogram monitoring, and fluid rehydration. Surgery should be performed after the child achieves hemodynamic stability and electrolyte balance. Due to high incidence of malformations related to this disease entity, which is similar to that in splenic abnormalities [14], it is necessary to
conduct a systematic review of children to detect malformations, including evaluation of heart malformations. Cases of children with biliary atresia are extremely rare. The only treatment for PD-PV-induced duodenal obstruction is surgical treatment, and the normal anatomical relationship should be restored as much as possible. The clear surgical method is duodenal rhomboid anastomosis in front of the PV or diversion surgery, such as gastroduodenal anastomosis in front of the PV. Thorough examination of the abdominal cavity should be performed to rule out other related malformations. Dissociation of the anterior wall of the duodenum needs to be carefully performed to avoid damage to the duodenum and PV. The duodenal papilla should be avoided when the proximal obstruction is cut open. For duodenal rhomboid anastomosis, the duodenal incision edge should not be very close to the PV to avoid stenosis of the PV. During the operation, the location of the obstruction must be accurately judged to determine the surgical approach. Due to complicated biliary atresia, the patient of the current study underwent “duodenal rhomboid anastomosis + duodenal jejunal Roux-en-Y anastomosis.”

The genetic origin of PD-PV is still unclear. Although it is very rarely found in clinical practice, it is a likely cause of fetal or infantile duodenal obstruction and may cause a potential risk to surgery; thus, it should receive the attention of clinicians.

Surgical treatment of biliary atresia
Kasai radical resection opened a new era of “uncorrectable” biliary atresia treatment. To date, Kasai radical resection is still the preferred surgical method for biliary atresia, and liver transplantation is a treatment method in case of failure of advanced Kasai radical resection[15,16]. Kasai radical surgery emphasizes early diagnosis and treatment; the age of surgery should be around 60 d, and the maximum age should not exceed 90 d[17].

The key to Kasai radical operation is to completely remove the hepatic hilar fibrous mass. The operation is best performed under a surgical magnifying glass, so that the side of the cut section reaches the liver parenchyma at the entry of the PV and the longitudinal level reaches the posterior wall of the PV. The depth of removal of the hilar fibrous mass is the key to this operation. Very superficial excision may not ensure reaching the appropriate small intrahepatic bile duct, and very deep excision may cause damage to the liver parenchyma and affect the function of the surgical anastomosis. Generally, only a thin layer of the membrane is preserved on the liver surface when the hilar fibrous mass is removed; secondly, electrocoagulation should be performed cautiously to stop bleeding from the incision, especially when the left and right liver ducts enter the liver parenchyma. Compression may also be performed, and it has partial hemostasis effect.

Various modified surgical approaches: After the classic portojejunostomy described by Kasai, although many modified procedures have been proposed to reduce the possibility of complicated cholangitis, the results are not ideal. The most commonly used modifications include external drainage and intussusception type anti-reflux valve placement. However, neither the “ventilation” nor the “valve” method has much effect on reducing the incidence of retrograde cholangitis. In the early 1990s, some scholars proposed that intussusception anti-reflux valve can reduce the occurrence of reflux cholangitis after biliary atresia. However, more recent studies have shown that targeting the regurgitant valve may be effective for anti-reflux but less effective at preventing cholangitis. A possible explanation for this dichotomy is that cystic dilatation of the intrahepatic bile duct accompanied by cholestasis has become a potential target for bacterial colonization. Therefore, although the regurgitant valve works, infection cannot be avoided.

Views on the application of laparoscopy: With the widespread application of laparoscopy, there are related reports on laparoscopy for radical operation of biliary atresia, but its clinical efficacy remains to be explored. Because biliary atresia is a rare disease, individual physicians find it difficult to accumulate surgical experience. For hilar operations with abundant blood supply, electrocoagulation may also affect the bile flow of the remaining microbiliary ducts in the hilar region, which will also affect the postoperative efficacy. Therefore, the author believes that the radical operation of laparoscopic biliary atresia should be cautiously performed. Laparoscopy for cholangiography is indeed a minimally invasive method. If the ability to perform radical surgery for biliary atresia is limited, then it is not recommended to only perform cholangiography and then arbitrarily conclude that the extrahepatic biliary system in the hilar area has completely disappeared. This is due to more than 90% of children with biliary atresia developing hilar fibrous masses within 3 mo when the hilum is
Drug treatment after biliary atresia surgery: Effective drug treatment is extremely important for improving the prognosis after portoenterostomy. Although surgery can prolong the lifespan of children, it cannot reverse liver damage and progressive cirrhosis. Ultimately, 75%-80% of children need liver transplantation for long-term survival[18,19]. In recent years, it has been recognized that the immune-mediated damage of the bile duct and liver may be related to the onset of biliary atresia and the progressive deterioration of liver function after surgery. It is possible to change the course of the disease through drug adjuvant therapy.

Postoperative hormone therapy: Corticosteroids, the main component of adjuvant therapy, can significantly improve the quality of life after surgery and increase the survival. Due to the inflammatory nature of cholangitis itself and the abnormal immune mechanism, it may be related to the onset of biliary atresia. Theoretically, the application of drugs, such as steroids, after hepatoenteric anastomosis should be very effective in reducing immune-mediated liver damage, improving bile drainage, and reducing the incidence of reflux cholangitis. Since Gad et al[20] reported that short-term shock therapy with glucocorticoids can increase bile flow, many treatment institutions have adopted short-term shock therapy for 1 to 2 wk after surgery. Dillon et al[21] proposed that compared with the non-hormonal group, oral high-dose steroids [prednisone 4 ms/(kg d), initial] in combination with ursodeoxycholic acid and antibiotic treatment at 6-22 wk after surgery can effectively enhance the bile clearance rate of children and improve the survival rate of autologous liver within 5 years. Meyers et al[22] introduced the application of 10, 8, 6, 5, 4, 3, and 2 ms/(kg d) prednisone via the intravenous route for 7 d, followed by oral prednisone 2 ms/(kg d). The method of continuous 8-12 wk application is also believed to significantly improve bile drainage and increase the survival time of children with autologous liver compared with the hormone-free group. Wang et al[23] summarized the application results of long-term use of high-dose steroids. Compared with short-term shock therapy, steroids can improve the short-term bile drainage in children with biliary atresia and reduce the incidence of cholangitis; however, the effect of prolonging the survival time of autologous liver has not been clearly demonstrated. Complications and safety during the use of hormones require further observation and evaluation. In any case, the application of hormones after biliary atresia is widely performed.

Long-term application of choleretic drugs after surgery: In addition to hormones, choleretic drugs also include dehydrocholic acid, glucagon, dinoprostone, and ursodeoxycholic acid. Among them, ursodeoxycholic acid has been studied in depth. It can significantly improve the deficiency of essential fatty acids and reduce the level of bilirubin. It is currently used as a routine drug and has provided good effects. No adverse reactions have been reported. It is clinically recommended to take ursodeoxycholic acid 10 mg/(kg·d) orally. Ursodeoxycholic acid is started after the operation and usually continued for 1 to 2 years. There are also reports of oral administration throughout life.

The application of prophylactic antibiotics after surgery: In the early 1980s, the second-generation cephalosporins (cephalosporin and cefuroxime) were combined with aminoglycosides (gentamicin and amikacin). After the 1990s, third-generation cephalosporins became dominant, and they were occasionally combined with aminoglycosides. The third-generation cephalosporins reach a sufficient level in the bile through the passive secretion pathway. Other advantages are that they can be administered at intervals of 12 to 24 h, which provides convenience for home treatment. Previous drug sensitivity tests have proved the effectiveness of cefoperazone and ceftriaxone. Unfortunately, in recent years, the sensitivity of cefoperazone in the treatment of cholangitis after Kasai operation has dropped from 88.9% to 75.0%[24, 25], which increases the need to identify new first-line antibiotics. It has been reported that trimethoprim/sulfamethoxazole and neomycin can reduce the incidence of cholangitis. According to Bu et al[26], these drugs can reduce the recurrence rate of cholangitis to 9.1% and 7.5%, respectively, and the first episode of cholangitis was delayed from 3 mo after surgery to 6 and 7 mo after surgery, thereby improving survival.

Liver transplantation and biliary atresia
With the development of liver transplantation, the prognosis of biliary atresia has greatly improved. According to current reports on liver transplantation at home and
abroad, biliary atresia is the most common indication. The average survival time of children with biliary atresia without surgery is 12 mo. After Kasai surgery, more than half of the children have repeated postoperative infections, and the survival rate is only 30% to 60%. Since Strong et al.[27] reported the success of the first liver transplantation for extrahepatic biliary atresia, more than 90% of children with successful liver transplantation have developed biliary atresia. Some scholars have proposed whether to perform liver transplantation directly to reduce hilar adhesions after Kasai operation, which causes difficulties during liver transplantation. It is still unclear whether the treatment of biliary atresia should be to directly perform liver transplantation or to perform liver transplantation after Kasai surgery; however, the current view is that treatment should be considered based on the child’s condition.

Kasai surgery and liver transplantation complement each other; children whose age is less than 90 d should undergo Kasai surgery first. If there is no bile flow or only temporary bile drainage after the operation, and the histological examination of the hilar region of the liver shows that the biliary tract has a small caliber and a small number of ducts, these children do not need to undergo the Kasai operation because repeated operations increase the difficulty of future liver transplantation. If the child is older than 90 d and there is no obvious chronic liver disease, then the hepatic hilar region can be dissected first to determine whether there are residual liver ducts. If there are open residual liver ducts, then the Kasai operation can be performed; otherwise liver transplantation should be performed. If the child has any obvious liver disease, such as liver cirrhosis and portal hypertension, then liver transplantation should be performed. Even if the bile drainage is satisfactory after the Kasai operation and the jaundice has gradually reduced, close follow-up should be performed over a long time. If liver disease occurs, liver transplantation should be performed as soon as possible.

CONCLUSION

In short, Kasai surgery is the first choice for treatment of biliary atresia, which may allow the child to achieve healing or buy precious time for liver transplantation. Postoperative comprehensive drug treatment plays an important role in improving the efficacy, and the success of liver transplantation significantly improves prognosis. However, it is very important to deepen our understanding of the etiology of biliary atresia, strive to improve the level of early diagnosis, and continuously improve the technique of portoenterostomy and perioperative management.

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Hemorrhagic transformation after acute ischemic stroke caused by polycythemia vera: Report of two case

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Abstract

BACKGROUND
Polycythemia vera (PV) is a chronic myeloproliferative disorder characterized by an increase in red blood cells in the peripheral blood. Previous work has reported the occurrence of thrombosis or hemorrhage arising in the cerebral vasculature secondary to PV. However, hemorrhagic transformation after PV-associated acute ischemic stroke has not been previously described.

CASE SUMMARY
We herein present two cases of PV where hemorrhagic transformation occurred after an acute ischemic stroke. Case 1 was a 57-year-old woman with a history of hypertension who was admitted for left-sided weakness. Case 2 was a 68-year-old man who was admitted for a 10-d sudden left arm weakness. Imaging examinations for the two patients revealed hemorrhagic transformation after acute ischemic stroke. Both patients had JAK-2-V617F mutation and received antiplatelet therapy. Both of them had a good prognosis during the follow-up.

CONCLUSION
This report suggested that hemorrhagic transformation may occur in acute ischemic stroke caused by PV. Antiplatelet drugs do not seem to influence the long-term outcomes in such patients. Future research should focus on establishing a standard antiplatelet treatment strategy for this condition.

Key Words: Polycythemia vera; Acute ischemic stroke; Hemorrhagic transformation; Antiplatelet treatment; Thrombosis; Case report

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Core Tip: Polycythemia vera (PV) is a rare, myeloproliferative disorder. Ischemic stroke is the most frequent neurologic manifestation of PV. However, hemorrhagic transformation after acute ischemic stroke caused by PV has not been previously reported. Here, we present two patients with PV who developed hemorrhagic transformation after sustaining an acute ischemic stroke. Antiplatelet drugs did not lead to poor long-term outcomes in our patients.

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INTRODUCTION
Polycythemia vera (PV) is a rare, myeloproliferative disorder characterized by the overproduction of erythrocytes, granulocytes, and megakaryocytes. It has been widely recognized that PV increases the incidence of thrombotic events, especially cerebral infarctions and transient ischemic attacks. Previous studies have revealed that ischemic stroke is the most frequent neurologic manifestation of PV[1]. Although not as common as thrombosis, hemorrhagic stroke has also been associated with PV[2,3]. To our knowledge, hemorrhagic transformation after acute ischemic stroke caused by PV has not been previously reported. Here, we present two patients with PV who developed hemorrhagic transformation after sustaining an acute ischemic stroke.

CASE PRESENTATION

Chief complaints
Case 1: A 57-year-old woman presented with a chief complaint of left-side weakness for 5 d (Supplementary Figure 1).
Case 2: A 68-year-old man was admitted to our hospital with left arm weakness for 10 d (Supplementary Figure 2).

History of present illness
Case 1: The patient had hypertension for 3 years.
Case 2: The patient was a smoker with an otherwise unremarkable medical history.

History of past illness
Case 1: The patient had hypertension for 3 years.
Case 2: The patient was a smoker with an otherwise unremarkable medical history.

Personal and family history
Case 1: The patient had hypertension for 3 years.
Case 2: The patient was a smoker with an otherwise unremarkable medical history.

Physical examination
Case 1: On admission, the patient’s blood pressure was 154/93 mmHg. Physical examination revealed obvious redness on her face and hands, as well as left hemiplegia with a muscle strength grade of 3/5.
Case 2: Neurological examination showed the patient to be healthy, although he experienced left hemiplegia of 0/5 as assessed by the manual muscle test.
**Laboratory examinations**

*Case 1:* Laboratory testing revealed a leukocyte level of $9.3 \times 10^9/L$, hemoglobin level of 19.8 g/dL, and hematocrit of 66.7%. Inflammation, coagulation, and autoimmunity markers were all negative. In addition, an ultrasound examination of her lower extremities detected left intermuscular venous thrombosis. Abdominal ultrasound revealed mild splenomegaly (spleen thickness: 43 mm). Bone marrow biopsy and positive JAK-2-V617F mutation tests provided strong evidence for PV.

*Case 2:* Routine blood testing highlighted that the patient possessed an erythrocyte count of $10.6 \times 10^12/L$, hematocrit of 71.7%, hemoglobin 22 g/dL, and platelet count of $794 \times 10^9/L$. Other blood sample tests revealed no obvious abnormalities. Abdominal ultrasound revealed splenomegaly (spleen thickness: 46 mm). A diagnosis of PV was suspected and a subsequent bone marrow biopsy and a positive JAK-2-V617F mutation confirmed this diagnosis.

**Imaging examinations**

*Case 1:* Brain computed tomography (CT) showed patchy high-density changes in right parietal low-density lesions (Figure 1A). Magnetic resonance imaging confirmed an acute cerebral infarct in the right parietal and occipital lobes with restricted diffusion (Figure 1B and C). CT-angiography imaging revealed only mild atherosclerosis (Figure 1D). A magnetic resonance venogram (MRV) was unremarkable (Figure 1E).

*Case 2:* On admission, brain CT revealed infarctions in the right parietal and temporal lobes (Figure 2A). Three days later, a brain CT re-examination revealed an infarct lesion in the right cerebral hemisphere with a right parietal hematoma (Figure 2B). Brain magnetic resonance angiography, MRV, cardiac ultrasonography, and 24-h dynamic electrocardiogram revealed no obvious abnormalities.

**FINAL DIAGNOSIS**

*Case 1:* The patient was diagnosed with hemorrhagic infarction in addition to PV.

*Case 2:* The presence of post-ischemic stroke parenchymal hematomas was concluded to be derived from the patient’s PV.

**TREATMENT**

*Case 1:* The patient received hydroxyurea and hydration treatment, as well as antiplatelet therapy (aspirin 100 mg daily). CT re-examination after 1 wk demonstrated the resolution of the hemorrhage within the infarction lesions (Figure 1F). Due to the high risk of thrombotic complications, anticoagulation treatment followed by antiplatelet therapy was initiated 1 mo after symptom onset.

*Case 2:* The patient was consequently given antiplatelet therapeutics, hydration, and cytoreductive therapy. However, 3 d later, the patient suffered a hemiplegia deterioration, accompanied by left-side weakness and drowsiness.

**OUTCOME AND FOLLOW-UP**

*Case 1:* At the 6-mo follow-up, the patient retained slight weakness and mild disability (modified Rankin Scale score, 1). She was stable in hematology and neurology outpatient follow-ups without any recurrence of vascular complications.

*Case 2:* Three months after disease onset, the patient improved to ambulatory care and was provided a brace (modified Rankin Scale score, 3). He was referred for hematology outpatient monitoring with chemotherapy with hydroxyurea follow-ups. To prevent secondary strokes, a regimen of low-dose aspirin (100 mg daily) was reinitiated 6 mo after symptom onset. Currently, he is recovering well with aspirin and hydroxyurea.
DISCUSSION

Stroke is a prevalent disorder in neurology clinics. Its common causes include atherosclerosis, cardiogenic embolism, and small vessel disease among others. By contrast, hematological diseases rarely underly a stroke, accounting for less than 1% of cases[4, 5]. PV, as a chronic hematological disorder, is typically associated with an increased
Our cases further suggest that in PV patients, hemorrhagic transformation can occur after an acute ischemic stroke, a clinical manifestation that has yet to be reported.

Ischemic stroke is considered to be the first presenting symptom in more than 15% of PV patients [4]. The peak incidence of PV occurs between 50-70 years of age, and these ages coincide with a high incidence of stroke [7]. However, the etiology behind increased thrombotic events in PV patients is not fully understood. The mechanisms are likely multifactorial. First, increased hematocrit and blood viscosity may decrease cerebral blood flow and form a prothrombotic state for patients with PV [1]. Second, JAK2 V617F mutations, which occur in 95% of PV cases [8], cause endothelial damage to systemic vessels, and confer a differentiation advantage towards megakaryocytes, thereby increasing intrinsic platelet reactivity [9,10]. Activated platelets will adhere and aggregate on ruptured plaques, resulting in thrombosis formation. Coincidingly, endothelial dysfunction in vessels facilitates leukocyte migration, which in turn triggers an inflammatory cascade in a similar way to atherosclerotic lesions [11]. Moreover, malignant cells can release cytokines and other mediators and provoke an inflammatory response in the vascular endothelial cells. Third, an increase in erythrocytes could obstruct small vessels and form an embolic infarct in the brain [12]. Consistent with this mechanism, microembolic signals on transcranial doppler sonography have been detected in patients with PV, indicative of cardiac embolism [3]. Finally, the hemodynamic infarct is common in PV. Previous work has shown that erythrocytosis decreases plasma volume and leads to a relative thrombocytosis, consequently accelerating thrombogenesis to form a hemodynamic infarct [13].

Hemorrhagic transformation is a frequent complication of acute ischemic stroke, especially after tissue-plasminogen activator intravenous thrombolysis or mechanical thrombectomy [14]. Moreover, massive cerebral infarction and cardioembolic stroke are associated with an increased risk of hemorrhagic transformation [15,16]. The mechanism behind hemorrhage in PV patients, an unusual presentation, has rarely been explored.

Consistent across all causes of ischemic stroke, and present in our first case, infarction is always accompanied by brain edema, which leads to compression of the peripheral vasculature. Increased permeability of the vascular wall caused by vascular compression enhances the risk of hemorrhagic transformation [17]. Furthermore, PV increases blood volume, and this, in turn, brings high pressure to the vessel wall, resulting in vessel overfilling and microaneurysm formation [18]. Once vessel rupture and microaneurysms occur, hemorrhage may follow. Moreover, spontaneous hemorrhages in PV patients may be also associated with platelet dysfunction caused by abnormal proliferation of bone marrow cells [19]. In our second case, we further speculate a role for antiplatelet therapy in causing hemorrhage. However, although neither of our cases developed cerebral venous thrombosis, we cannot exclude that impaired venous drainage, caused by PV, may have also contributed to hemorrhagic infarction [20].

There is a high risk of thrombotic events in PV patients [21]. Antiplatelet therapy can be useful for decreasing the risk of thrombosis and related morbidities. The European Collaboration on Low-Dose Aspirin in PV study confirmed that low-dose aspirin can safely prevent thrombotic complications in PV patients without contraindications [22]. A meta-analysis also suggested that the use of low-dose aspirin in patients with PV is associated with a reduced risk of all-cause mortality, and does not increase the risk of bleeding [23]. For both of our cases, aspirin was also the main preventive treatment for long-term adverse vascular events. For our patients, hemorrhagic transformation as a contraindication existed in the acute phase of stroke. After the resolution of the hemorrhage, reinitiating antiplatelet drug did not overtly cause long-term negative outcomes. Future research should focus on the treatment of this condition.

**CONCLUSION**

Our case report suggests that hemorrhagic transformation can occur following acute ischemic stroke in PV patients. Antiplatelet drugs do not lead to poor long-term outcomes in such patients.
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REFERENCES


Treatment of lower part of glenoid fractures through a novel axillary approach: A case report

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Author contributions: Jia X, Zhou FL, Zhu YH, Jin DJ, and Liu RP were clinicians involved in the diagnosis, management, treatment and follow-up of patient; Jia X and Zhou FL reviewed the literature and contributed to the drafting of the manuscript; Yang ZC and Liu RP assisted in reviewing the literature and drafting the manuscript; Jia X, Zhou FL and Liu RP analyzed and explained the imaging results; Liu WX helped us to draw a sketch to vividly describe the operation technique; Liu RP was responsible for design and revision of the relevant knowledge content of the manuscript; all authors approved the final version of the paper before submission.

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Abstract

BACKGROUND
Based on the location and size of the fracture block, open reduction and internal fixation can be employed or assisted for shoulder arthroscopy in the treatment of glenoid fractures. However, the treatment of lower part of glenoid fractures through a novel axillary approach has not been reported so far.

CASE SUMMARY
A 22-year-old right-handed man was transferred to our outpatient clinic because of right shoulder injury during a traffic accident. X-ray examination after admission suggested the fracture of the lower part of the right glenoid and an ipsilateral proximal humeral fracture. Three-dimensional (3D) computed tomography (CT) further suggested that the size of the fracture block of the lower part of the right glenoid was 3.4 mm × 16.2 mm. The patient was diagnosed as the fracture of the lower part of the glenoid, also known as bony Bankart lesion without shoulder dislocation. After general anesthesia, the patient was surgically treated with the open reduction internal fixation through a novel axillary approach. 3D CT and shoulder joint function were reexamined at 12 mo of follow-up, showing acceptable recovery.

CONCLUSION
This case report describes a novel axillary approach adopted in an open reduction with cannulated screw and wire anchor internal fixation. After a follow-up for more than 12 mo, 3D CT and shoulder joint function examinations display a good recovery.

Key Words: Glenoid fracture; Approach; Operative technique; Case report
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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Core Tip: Based on the location and size of the fracture block, open reduction and internal fixation can be employed or assisted for shoulder arthroscopy in the treatment of glenoid fractures. However, the treatment of lower part of glenoid fractures through a novel axillary approach has not been reported so far. This study reports a case with lower part of glenoid fracture and treated with open reduction with cannulated screw and wire anchor internal fixation through a novel axillary approach. After a follow-up for more than 12 mo, reexaminations of three-dimensional computed tomography and shoulder joint function display a good recovery.

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INTRODUCTION

Generally speaking, scapular fractures are often caused by high-energy trauma in traffic accidents[1]. Intra-articular fractures account for 1% of scapular fractures[2]. Glenoid fractures take up nearly 0.1% of total body fractures and 10% of scapular fractures[3]. The treatment of glenoid fracture depends on the size and displacement of the fracture fragments, including non-surgical treatment, open surgery, or open surgery with arthroscopy[4]. Schofer et al[5] suggested that the functional effects are significant after the conservative treatment of scapular fractures. However, Rollo et al[6] considered that non-surgical treatment of scapular fractures may cause pain, vascular problems, delayed union, malunion, persistent shoulder symptoms, or loss of arm function. Most of the Bankart lesions in the anterior and posterior glenoid fractures and superior labrum anterior and posterior lesions to the glenoid can be treated by surgery under arthroscopy[7-9]. However, the lower part of the glenoid fractures, especially large fracture masses, are difficult to be surgically treated with arthroscopic reduction and fixation, and open reduction internal fixation (ORIF) is recognized as a better choice for these specific cases[1,8]. It is generally known that the axillary has a relatively complex anatomical structure, and there are considerably important blood vessels and nerves passing through the axillary.

Accordingly, a novel axillary approach should be adopted during surgical treatment of the lower part of glenoid fractures, which can prevent the damage to the axillary vessels and nerves as much as possible, but clearly expose the fracture area of the subaxillary glenoid. Thus, a novel axillary approach from the muscle space was designed to make sure that the lower part of the glenoid fractures could be successfully reduced and fixed.

CASE PRESENTATION

Chief complaints
A 22-year-old right-handed man suffered from right shoulder pain for 24 h because of the traffic accident.

History of present illness
The patient had right shoulder pain with limited movement, and could not raise the right arm. No abnormal sensation in the right upper limb was examined.

History of past illness
The patient denied the history of right shoulder disease and operation.
Physical examination
Physical examinations showed right shoulder tenderness, limited movement of the right shoulder, no numbness, limited finger movement, and vascular injury.

Laboratory examinations
The results of preoperative laboratory examinations were normal.

Imaging examinations
X-ray examination after admission suggested the lower part of the right glenoid fracture with an ipsilateral proximal humeral fracture (Figure 1A). Three-dimensional (3D) computed tomography (CT) further suggested that the size of the fracture block was 3.4 mm × 16.2 mm (Figure 1B).

FINAL DIAGNOSIS
According to the history and preoperative imaging examination, the patient was finally diagnosed as the lower part of the right glenoid fracture with an ipsilateral proximal humeral fracture.

TREATMENT
On day 5 after the injury, the patient was surgically treated by ORIF through a novel axillary approach following general anesthesia. The patient was placed on a fluoroscopic operating table in a lateral position. A longitudinal incision was made in the armpit, followed by exposure of the anterior edge of the latissimus dorsi by separating subcutaneous tissues (Figure 2A and B). The axillary nerve under the latissimus dorsi was exposed and separated, which was traversed from the medial side of the armpit to the lateral side. Subsequently, the posterior brachial circumflex artery and vein, under the axillary nerve, were exposed. The blood vessels and nerves were protected by a tender traction. Next, the joint capsule of lower part of the glenoid was exposed between the gap of axillary nerve and circumflex blood vessel (Figure 2C and D). Moreover, the joint capsule was cut transversely to expose the fracture block, fracture end and articular surface of the glenoid. Anatomic reduction was achieved under a direct vision. After the fracture reduction, two 1.5 mm fine Kirschner wires were used for temporary fixation, and then the fracture block was fixed with one cannulated screw (3 mm in diameter, 18 mm in length), and then two 2.7 mm wire anchors were used to strengthen the fixation (Figure 2E). After removal of the glenohumeral joint under a direct vision, the fracture block was exposed and fixed stably. The gauze equipment was counted, and the wound was washed and sutured layer by layer.

Another anteromedial approach of the shoulder joint under the same body position was adopted for surgical treatment of the ipsilateral proximal humeral fracture. After open reduction, the proximal humeral locking plate was used for fixation.

OUTCOME AND FOLLOW-UP
The patient’s forearm was suspended for 3 wk postoperatively. Postoperative exercises of the elbow, wrist and hand were encouraged during the first 3 wk. A passive range of motion exercises were initiated at the third wk. At the sixth wk, patients were instructed to start active auxiliary exercises. During the follow-up period for more than 12 mo, imaging (including fracture of subaxillary glenoid and ipsilateral proximal humeral) (Figure 1) and functional examinations were conducted (Table 1).

DISCUSSION
Ideberg classification of scapular fractures is the most common classification of intra-articular glenoid fractures. The classification system is modified by Goss, involving 6 types of fractures[10]. Among them, type II fractures are those of the lower part of the glenoid, which induce the instability and dislocation of the shoulder joint[11]. If surgical treatment is required, reduction and wire anchor fixation for small fractures
Table 1 Demographic data and results of following

<table>
<thead>
<tr>
<th>Case number</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Mechanism of Injury</th>
<th>Ideberg fracture classification</th>
<th>Follow-up time (mo)</th>
<th>Postoperative constant score</th>
<th>Postoperative bone healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>22</td>
<td>Traffic accident</td>
<td>Type II</td>
<td>12</td>
<td>95</td>
<td>Bony union</td>
</tr>
</tbody>
</table>

Figure 1 Preoperative and postoperative radiography images of the patient. A: Preoperative X-ray; B: Preoperative three-dimensional (3D) reconstruction; C: X-ray image at 1 wk postoperatively; D: 3D reconstruction at 1 wk postoperatively; E: X-ray image at 12 mo postoperatively; F: 3D reconstruction at 12 mo postoperatively.

can be performed under the shoulder arthroscopy. However, arthroscopic reduction and fixation are difficult to be performed in cases with large fracture masses or those with the scapular neck involved. van Oostveen et al[12] believed that appropriate surgical methods according to different types of fractures can achieve satisfactory results.

In this study, a novel axillary approach in the lateral decubitus position was designed. It is generally known that the axillary has a relatively complex anatomical structure, and there are considerable important blood vessels and nerves passing through the axillary. Vascular and nerve damage can be easily caused because of the complicated anatomical structure. The axillary approach proposed in this study was a novel approach initiated from the anterior edge of the latissimus dorsi and passed through the space between the axillary nerve and the circumflex scapular vessel (Figure 2). This approach can avoid the main blood vessels and nerves in the armpit, which also directly enters to the subscapular fracture area. Moreover, the proposed approach had multiple advantages like an easy exposure of the operation area, a direct access to the surgical site, achievement of fracture reduction and fixation under a direct vision, and prevention of the axillary nerve and vessel damages.

In the present study, the Constant score of shoulder joint reached 95 in the patient with inferior rim fractures of the glenoid after surgical treatment, which was better than the average Constant score of 82 reported by Bartoniček et al[13].
Figure 2: Intraoperative photos and sketches. A: Surgical marker; B: A longitudinal incision was made in the armpit, followed by exposure of the anterior edge of the latissimus dorsi by separating subcutaneous tissues; C: The posterior brachial circumflex artery and vein, under the axillary nerve, were exposed. The blood vessels and nerves were protected by a tender traction; D: The fracture block was fixed with one cannulated screw and two wire anchors were used to strengthen the fixation; E: The sketches more vividly describes the whole operation process.

Shoulder arthroscopy has great advantages in the treatment of Bankart lesions[14, 15]. Generally speaking, surgery is preferred to displaced glenoid fossa fractures[16]. However, when the shoulder arthroscopy fails to reduce and fix scapular fractures with other parts of the scapula, ORIF is a good choice[17, 18]. Besides, ORIF is also suitable for fractures of the lower part of glenoid. Thus, the axillary approach was developed here. Besides the reduction and internal fixation of fresh fractures, the novel axillary approach was also proven to be a very good choice for patients with bone lesions, cysts, old fracture nonunion and subluxation of shoulder joint around the lower part of glenoid.

CONCLUSION

This case report describes a novel axillary approach adopted in the open reduction with cannulated screw and wire anchor internal fixation. The patient was surgically treated by ORIF through the novel axillary approach following general anesthesia. After a follow-up for more than 12 mo, 3D CT and shoulder joint function reexaminations showed a good recovery.

REFERENCES


Trigger finger at the wrist caused by an intramuscular lipoma within the carpal tunnel: A case report

Chao Huang, Hong-Juan Jin, De-Biao Song, Zhe Zhu, Heng Tian, Ze-Hui Li, Wen-Rui Qu, Rui Li

Abstract

BACKGROUND
Trigger finger at the wrist, which occurs with finger movement, is an uncommon presentation. Few reports describing cases of trigger finger at the wrist have been published. Thus, we present a case of an intramuscular lipoma arising from an anomalous flexor digitorum muscle belly in a 48-year-old female patient causing painful finger triggering at the wrist and carpal tunnel syndrome (CTS).

CASE SUMMARY
A 48-year-old woman with complaints of a catching sensation during wrist motion and a progressive tingling sensation on the palmar aspect of the right hand for approximately 2 years was referred to our hospital. Triggering of the index to middle finger was evident with a palpable and audible clunk over the carpal tunnel during passive motion. Tinel’s sign was positive over the carpal tunnel of the right wrist with a positive Phalen’s test. Nerve conduction studies of the median nerve demonstrated a right CTS. Ultrasound examination revealed a 2.5 cm × 2.0 cm subcutaneous hyperechoic mass with no obvious blood flow at the wrist of the right arm. Surgical excision of the tumor and muscle mass led to a resolution of the patient’s symptoms, and any triggering or discomfort disappeared. The patient has had no evidence of recurrence at more than 1 year of follow-up.

CONCLUSION
Triggering of the fingers at the wrist is rare. It must be noted that there are many possible causes and types of triggering or clicking around the wrist. Accurate diagnosis is mandatory to avoid inaccurate treatment of patients with trigger wrist. During the diagnosis and treatment of CTS, attention should be paid to the variation of tendon tissue in the carpal tunnel, to avoid only focusing on the release of transverse carpal ligament and ignoring the removal of anomalous muscle belly.

**Key Words:** Intramuscular lipoma; Trigger finger; Muscle belly; Flexor digitorum superficialis; Treatment; Case report

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**Core Tip:** Our manuscript presents a case of an intramuscular lipoma arising from an anomalous flexor digitorum muscle belly in a 48-year-old female patient causing painful finger triggering at the wrist and carpal tunnel syndrome. Moreover, we reviewed the literature and discuss its etiology. Our findings revealed that there are many possible causes and types of triggering or clicking around the wrist. The accurate examination and proper diagnosis are mandatory to avoid improper and time-wasting treatment for patients with trigger finger at the wrist. During the diagnosis and treatment of carpal tunnel syndrome, attention should be paid to the variation of tendon tissue in the carpal tunnel to avoid focusing only on the release of transverse carpal ligament and ignoring the removal of anomalous muscle belly.

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**INTRODUCTION**

Triggering of the fingers at the wrist is a relatively uncommon condition compared to trigger finger, which is the most common cause of pain and disability of the hands[1]. Triggering at the wrist occurs with finger or wrist motion[2]. Few reports describing trigger finger at the wrist have been published. The possible etiologies of the condition include an anomalous muscle belly in the carpal tunnel, tumor, or a rheumatoid nodule in the flexor tendons inside the carpal tunnel[3]. We present a case of trigger finger at the wrist caused by a combination of both tumor and anomalous muscle belly in the carpal tunnel. We report such a case of an intramuscular lipoma (IML) arising from anomalous flexor digitorum muscle belly in a 48-year-old female patient, causing painful finger triggering at the wrist and carpal tunnel syndrome (CTS). Moreover, to date, few reports describing cases of trigger finger at the wrist caused by IML arising from the anomalous flexor digitorum muscle (FDS) have been reported in the literature. Thus, we have reviewed the literature and discuss its etiology.

**CASE PRESENTATION**

**Chief complaints**
A 48-year-old woman complained of a catching sensation during wrist motion and a progressive tingling sensation on the palmar aspect of the right hand.

**History of present illness**
Patient’s symptoms started approximately 2 years ago with a catching sensation during wrist motion and a progressive tingling sensation on the palmar aspect of the right hand, which had been worsened the last 3 mo.
History of past illness
The patient was in good health and had no history of other diseases.

Personal and family history
The patient and her family had no history of other diseases.

Physical examination
There was a moderate palpable mass (3 cm × 2 cm) on the palmar side of her right wrist (Figure 1A). The mass was not tender and moved simultaneously up and down during flexor tendon movement. Paraesthesia, distributed over the palmar radial three and a half digits of the hand, developed after the onset of wrist triggering, suggesting CTS. The paraesthesia progressively worsened when performing manual tasks and when sleeping. During the physical examination, triggering of the index to middle finger was evident with a palpable and audible clunk over the carpal tunnel during passive motion. Tinel’s sign was positive over the carpal tunnel of the right wrist with a positive Phalen’s test. Active and passive ranges of motion as well as grip strength were normal, except for the right index finger, which became limited during flexion. Nerve conduction studies of the median nerve demonstrated a right CTS.

Imaging examinations
X-ray examinations revealed no abnormal findings. Ultrasound examination revealed a 2.5 cm × 2.0 cm subcutaneous hyperechoic mass with no obvious blood flow at the wrist of the right arm.

FINAL DIAGNOSIS
The clinical diagnosis was trigger finger at the wrist and CTS.

TREATMENT
Surgical exploration was performed through a longitudinal carpal tunnel incision (Figure 1B-D). After peeling back the skin and subcutaneous tissues, no subcutaneous edema was observed, and there was no obvious inflammation in the deep fascia. After removal of the deep fascia, the anomalous flexor digitorum muscle belly was shifted down abnormally, and a yellowish-white cable-like mass was observed at the distal end of the FDS of the index finger. The muscle fibers were bluntly peeled, and a 2.5 cm × 2.0 cm × 2.0 cm oval, yellow, soft mass with an intact capsule was visible. The mass arose from the anomalous muscle belly of the FDS, growing longitudinally and extending into the carpal tunnel. The mass was shifted synchronously with the tendon during passive flexion of the index finger. The mass was positioned outside the carpal tunnel during flexion and entered into the carpal tunnel at a depth of approximately 2.5 cm during overextension, extruding the flexor tendon and median nerve (Figure 2A and B). After careful separation, the mass outside the capsule was completely resected. Continuous exploration indicated the abnormal muscle belly shift of the FDS. During hyperextension, the mass extended into the carpal tunnel and slightly extruded the median nerve and the flexor tendon (Figure 2C and D). After the removal of the muscle bundles and muscle membranes that were abnormally shifted down, the entrapment on the wrist disappeared during passive movements. The median nerve was released to eliminate local compression. After fully controlling bleeding, the incision was rinsed and closed layer-by-layer. Postoperatively, the mass was dissected, and the section was composed of homogenous, yellow fine adipose tissues, with no obvious lesions, such as fibrosis or necrosis of the muscle bundles. Pathological findings indicated an IML due to the presentation of mature adipose tissue and fibrous tissue (Figure 3). The morphology was IML.

OUTCOME AND FOLLOW-UP
Postoperative 1-year follow-up showed no recurrence of the tumor, no abnormalities in movement and sensation of the index and middle fingers, and negative signs of Tinel and Phalen signs of the median nerve of the wrist.
**DISCUSSION**

Trigger finger at wrist is a rare condition and was first reported by Eibel\(^4\) in 1961. Most hand surgeons have no direct experience with trigger fingers at the wrist\(^1\). Suematsu \textit{et al}\(^3\) have classified the phenomenon of trigger finger into the following three categories: Class A trigger finger at the wrist is due to a tumor or a rheumatoid nodule occurring on the flexor tendon or tendon sheath, which enters and exits from the carpal tunnel; class B trigger finger at the wrist is due to an anomalous muscle belly (including an abnormal lumbrical muscle or abnormal muscle belly of the FDS); and class C trigger finger at the wrist is a combination of classes A and B\(^3\). Few cases of the above mentioned presentation caused by tumors, such as fibroma, rheumatoid nodule, and giant cell tumor, have been reported. However, IML has rarely been reported. In the present case, the trigger finger at the wrist was caused by the IML arising from the anomalous flexor digitorum muscle belly. Thus, our case was considered a class C trigger finger according to Suematsu’s classification\(^3\). In our case, intermittent median nerve compression was also associated with the trigger

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**Figure 1 Operating images of the entire surgical process.** A: Preoperatively, there was an intumescence at the distal end of the forearm (orange arrow); B and C: The mass was revealed layer-by-layer during the operation; D: The mass and surrounding fascia were completely removed, and the muscle belly of the flexor digitorum superficialis was abnormally shifted down (orange arrow).

**Figure 2 Entrapment symptoms appeared within the carpal tunnel during finger flexion and extension.** A: The tumor involved the flexor digitorum superficialis of the index finger in the carpal tunnel; B: In the passive flexion position of the index finger, the mass moved proximally with the flexor digitorum superficialis; C and D: In the extension position of the index finger, the mass moved with the flexor digitorum superficialis and extended into the carpal tunnel. In the overextension position, the mass further moved into the carpal tunnel, extruding the common flexor tendon sheath and the median nerve.
Lipomas are common benign tumors of different sizes that usually occur under the skin or in the large muscles of the thigh, shoulder, or upper arm\[5\]. Some lipomas that occur in the muscle are called IMLs, and the first case of IML in the trapezius muscle was reported in 1853\[6,7\]. Most of the IMLs occur in the trunk and proximal limbs, and tumors located in the wrist and fingers are rarely reported\[8,9\]. In 1988, Brand and Gelberman\[10\] reported the first case of lipoma in FDS causing triggering at the carpal tunnel and median nerve compression. An IML is a histologically benign, painless, and slow-growing mass. The clinical manifestations are mainly determined by the tumor location. When the mass is too large and invades the muscle, its movement may be restricted. When the mass compresses the nerve and vessel, corresponding paresthesia will appear and may affect the joint function\[11,12\]. In this case, the IML of the FDS shifted synchronously with the index finger and its distal end entered into the carpal tunnel. Therefore, the increased contents of the carpal tunnel extruded the median nerve, resulting in the CTS.

Imaging examination is the most important auxiliary method for IML diagnosis\[13\]. Warwick et al\[14\] believed that ultrasound examination is the first choice for the diagnosis of soft tissue tumors, by dynamically observing the relationship between the location and depth of the tumor and adjacent tissues\[14\]. Under ultrasound, IML mostly manifests as a clear mass with echo intensity equivalent to that of the subcutaneous fat but higher than that of the muscle and often without blood flow signals\[14\]. When it is difficult to assess the complete anatomical relationship between lipomas and adjacent structures by ultrasound, or when lipomas are suspected of malignant tumors, further magnetic resonance imaging (MRI) or computed tomography (CT) examinations are required. IML shows high signals on T1 and T2-weighted images of MRI, and low signal on fat-suppressed T2-weighted images. CT images show a low-density intramuscular mass with a negative Hounsfield value, and the attenuation is similar to that of adipose tissue. Several soft-tissue density bands of
Huang C et al. Trigger finger at the wrist caused by an IML

varying thicknesses that are occasionally interrupted and represent the muscle fibers therein [14]. Accompanied ossification can be better depicted on CT images [15].

In this case, the lipoma located specially should be distinguished from malignant tumors, such as highly differentiated liposarcoma, clear cell sarcoma, and fibrosarcoma in addition to intramuscular hemangiomas, ganglion cysts, and giant cell tumors of the tendon sheath. Intramuscular hemangiomas are characterized by abnormal proliferation of blood vessels in the muscle tissue; ultrasound can detect and enrich venous blood flow signals. Ganglion cysts that occur in the flexor tendon of the hand can also cause symptoms similar to CTS, and they can be identified by ultrasound images [16]. Histopathological examination of a giant cell tumor of the tendon sheath indicates that the tumor is rich in multinucleated giant cells and hemosiderin deposits. IMLs differ in tissue type and degree of differentiation and vary in sonographic appearance. The identification of IMLs mainly depends on the histopathological examination. Microscopically, there are atypical cells or mixture of vacuolated lipoblasts and fibroblast-like spindles, which are often in the intermuscular septa with increased number and thickness. Moreover, there are some vascular components of different sizes, and inflammatory cells and mucus-like areas are often observed around the intermuscular septa [17-19].

Treatment of IML depends on tumor location, size, and clinical symptoms related to the lesion. Observation without treatment is applicable for a small lipoma that does not cause functional restrictions [20]. For patients with obvious signs and discomforts, the tumor can be removed by surgery. Currently, the recurrence rate of IML is believed to be very low. However, the recurrence rate after treatment has been historically reported to be between 3% and 62.5% [21-23]. The follow-up period ranges from several months to decades, and the specific period is determined by the investigators [21-23]. Relapses are thought to be due to the incomplete clearance of lipomas during surgery, which is most likely due to the tumors being adjacent to important anatomical structures or fear of limited functions resulting from complete removal of the affected muscles [7]. Therefore, tumor cytoreduction is also an acceptable option for tumors not suitable for complete resection or in the case of complete resection that can cause severe functional impairment [24]. Generally, chemotherapy and radiation therapy are generally not recommended due to the benign nature of IMLs [7].

In this case, the IML originated from the anomalous muscle belly of FDS and grew longitudinally along the tendon and shifted with the index finger during flexion and extension. The tumor was located outside the carpal tunnel during flexion and extension and entered into the carpal tunnel at a depth of 2.5 cm during overextension. There was slight numbness on the radial side of the thumb, index finger, and middle finger, which is defined as typical CTS caused by median nerve entrapment. The tumor and surrounding tissues were completely removed intraoperatively and showed that the muscle belly of the FDS was abnormally shifted down. The distal end of the muscle belly of the FDS moved with the index finger and partially entered into the carpal tunnel. Christensen [25] had proposed three types of anomalous muscle belly of the FDS: (1) The flexor digiti “superficialis” derived from the carpal ligament and the fascia palmaris or the tendon itself; (2) The elongated muscle bellies continuing through the carpal tunnel before becoming tendinous; and (3) A digastic type in which the palmar muscle belly replaces the tendon. This case belongs to the second type among them. As previously reported, the muscle belly of the FDS that is excessively shifted down is also the cause of CTS [1,26]. Particularly, when the symptoms of CTS are significantly related to physical activities, the presence of muscles with abnormal structures needs to be considered. Generally, MRI contributes to improving the accuracy of preoperative diagnosis [26]. For CTS caused by the anomalous muscle belly, location, size, and symptoms of the muscle belly determine whether a surgical treatment is required. Javed and Woodruff [27] believed that when the mass is unable to touch, only the release of the transverse carpal ligament is sufficient to eliminate completely the symptoms [27]. Beyond that, the removal of the abnormal muscle belly is necessary if the abnormal muscle belly can be reached and extended distally. Resection of the abnormal muscle belly can reduce the risk of recurrence or results in only partial remission after surgery, avoiding the need for secondary surgery [27]. In addition, resection of the muscle is recommended if a normal flexor digitorum profundus tendon is present, which warrants a normal range of motion of the finger [26]. In the present case, the symptoms of CTS were mild and considered to originate from the IML. Apart from tumor resection, resection of the anomalous muscle belly of the FDS was concurrently performed to relieve these symptoms. The patient had no recurrence and CTS symptoms during follow-up.
CONCLUSION

Triggering of the fingers at the wrist is rare. It must be noted that there are many possible causes and types of triggering or clicking around the wrist. Accurate diagnosis is mandatory to avoid any inaccurate treatment of patients with trigger finger at the wrist. During the diagnosis and treatment of CTS, attention should be paid to the variation of tendon tissue in the carpal tunnel, to avoid focusing only on the release of transverse carpal ligament and ignoring the removal of anomalous muscle belly.

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Thrombolysis and embolectomy in treatment of acute stroke as a bridge to open-heart resection of giant cardiac myxoma: A case report

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Abstract

BACKGROUND
Cardiac embolism is a common cause of ischemic stroke in young adults. Neurological complications associated with atrial myxoma most frequently include cerebral infarct due to embolus. Early complete resection of giant cardiac myxoma is the key to its treatment and prevention of stroke recurrence.

CASE SUMMARY
A 42-year-old, previously healthy woman was admitted to the hospital with sudden-onset inability to speak and right-sided hemiplegia. While sweeping the floor 2 h prior to hospital admission, the patient developed sudden inability to express herself or understand what others were saying, accompanied by dyskinesia of the right limb, inability to walk or hold objects, and involuntary choreiform movements of the left upper limb. The patient was diagnosed with cerebral embolism and cardiac myxoma, complicated by left middle cerebral artery occlusion. The acute stroke was treated with intravenous thrombolytic therapy and arterial embolus retrieval as a bridging therapy to open resection of left atrial cardiac myxoma. The patient condition improved remarkably following initial thrombolysis and embolectomy and subsequently underwent emergency open resection of the atrial cardiac myxoma. She had no recurrence during 1-year follow-up.

CONCLUSION
Strong consideration should be given to urgent intravenous thrombolysis (rt-PA, alteplase) in young adult stroke patients at the time of hospital admission. The present case demonstrated a highly successful outcome that combined thrombolysis and arterial embolus retrieval as a bridge to early complete resection of a
INTRODUCTION

Ischemic stroke in young adults is defined as an acute ischemic cerebrovascular disease that occurs in patients aged 18-45 years[1]. Approximately 10%-14% of ischemic strokes occur in young adults[2]. Cardiac embolism is a common cause of ischemic stroke in young adults, accounting for approximately 20% to one-third of all strokes[3]. Cardiac valve and endocardial lesions are the most common, in addition to congenital heart disease, recent myocardial infarction, and cardiac tumors. Atrial myxoma represents the most common type of primary cardiac tumor in adults, accounting for as many as 83% of all primary tumors of the heart. Most cardiac myxomas (CMs) are located in the left atrium, attached to the interatrial septum. Neurological complications associated with atrial myxoma most frequently include cerebral infarct due to embolus.

CASE PRESENTATION

Chief complaints

A 42-year-old, previously healthy woman was admitted to the hospital with sudden-onset inability to speak and right-sided hemiplegia.

History of present illness

The patient suddenly was unable to express herself or understand what others were saying, accompanied by dyskinesia of the right limb, inability to walk or hold objects, and involuntary choreiform movement of the left upper limb, while sweeping the floor, 2 h prior to hospital admission. She denied nausea and vomiting, limb convulsions, incontinence, or loss of consciousness.

History of past illness

The patient had a free previous medical history.

Personal and family history

The patient had no history of trauma or preceding infection.

Physical examination

The patient’s admission vital signs included that temperature was 36.9 °C, heart rate was 72 beats per minute, respiratory rate was 18 breaths per minute, blood pressure
was 134/115 mmHg, and oxygen saturation in room air was 99%. The clinical neurological examination revealed mental clarity, depression, complete mixed aphasia, both eyes stared to the left, pupils that bilaterally were of equal size and shape, with a diameter of 3 mm, and normal light reflex. The nasolabial fold on the right side was shallow, and the tongue uncooperative. The drop test of the right limb was positive and there was no response to stimulation; the left upper arm demonstrated involuntary choreiform movement, and the left lower leg stimulated sensitive flexion. Both Chaddock’s sign and Babinski’s sign were positive on the right. The heart rhythm was regular, and heart sounds were hyperdynamic with a grade 3/6 systolic murmur at the apex, and rumble-like murmur.

**Laboratory examinations**

Blood analysis revealed: Neutrophils 79.5% (nL, 50%-70%), platelets 344 × 10^9/L (nL, 100-300 10^9/L); hemoglobin 103g/L (nL, 110-150 g/L); mean hemoglobin concentration 295 g/L (nL, 320-360 g/L). The mean erythrocyte volume was 67.7 fL (nL, 82-95 fL); CRP was 78.61 mg/L (nL, 0-10 mg/L); and leukocytes, erythrocytes, coagulation, D-dimer, renal function, electrolytes as well as urine analysis were normal. Fingertip blood glucose was 7.4 mmol/L. Chest X-ray and arterial blood gas were also normal. A 12-lead electrocardiogram was normal with sinus rhythm.

**Imaging examinations**

A noncontrast computed tomography (CT) scan of the brain showed no abnormality (Figure 1A). The NIHSS score was 18 points (level of consciousness question 2, level of consciousness instruction 2, gaze 2, facial paralysis 1, right upper limb 4, right lower leg 4, and aphasia 3). The patient fulfilled criteria for intravenous thrombolysis and she was successfully treated with intravenous thrombolysis using alteplase (0.9 mg/kg, 10% of the total dose was administered intravenously as a bolus, followed by an infusion of the remaining dose over 60 min) without signs of bleeding, and alteplase was initiated within 140 min of symptom onset. Cerebral angiography was conducted immediately and showed focal cerebral ischemia resulting from a distal middle cerebral artery occlusion (Figure 1B). A Solitaire FR stent and microcatheter were pulled back simultaneously during blood aspiration with a 50 cc syringe in the guiding catheter to minimize the risk of distal emboli. A red jelly-like thrombus was withdrawn out of the stent (Figure 1C) and sent for the rapid pathological examination which was suggestive of atrial myxoma (Figure 2A). A tentative diagnosis was made of cerebral arterial occlusion due to embolism from a cardiac tumor. Re-examination showed that the left middle cerebral and left anterior cerebral arteries were both patent. Successful 100% recanalization was achieved (Figure 2B). Subsequent echocardiography showed the following: A mild increase in left atrial dimension (38 mm) and an abnormal hypoechoic mass measuring 6.5 cm × 3.5 cm, with a regular shape and homogeneous internal echo, which moved with the cardiac cycle. The neoplasm remained in the mitral orifice during diastole and prolapsed into the left atrium during systole (Figure 2C).

**MULTIDISCIPLINARY EXPERT CONSULTATION**

The patient should undergo surgical treatment of the left atrial myxoma through a median sternotomy under cardiopulmonary bypass. Due to the large tumor size, the patient was at risk of cardiac arrest due to the re-shedding of mucous tissue or fragments. A preoperative conference included neurologic and cardiac anesthesiologists, a cardiac surgeon, and a neurosurgeon. There was no personal or family history. Specifically, there was no history of coronary heart disease, atrial fibrillation, or arrhythmia.

**FINAL DIAGNOSIS**

The patient’s final diagnosis was acute stroke, left middle cerebral artery occlusion, and CM.
Figure 1 Head computed tomography before operation, intraoperative angiography, and stent embolectomy. A: Head computed tomography showed no abnormalities; B: Cerebral angiography showed that the left middle cerebral artery was occluded (orange arrow); C: Thrombus removed with a stent (Solitaire FR 4.0 mm × 20 mm).

Figure 2 Arterial thrombosis pathology, angiography, and echocardiography. A: Histopathological image showing scattered mucinous tumor cells and streaked polygonal eosinophil stromal cells in a mucinous-like matrix (hematoxylin-eosin staining, magnification, 10 × 10); B: Cerebral angiography showing that the left middle cerebral artery was patent (orange arrow); C: Pre-operative transthoracic echocardiogram showing that the internal diameter of the left atrium and left ventricle were abnormal but an irregular, space-occupying mass was visible in the left atrium, with a pedicle in the atrial-septal space with marked motion.

**TREATMENT**

After discussion, the patient and her husband consented to surgical resection of the left atrial myxoma through a median sternotomy under cardio-pulmonary bypass. The procedure was completed without complications and pathological examination (Figure 3A) confirmed the diagnosis of myxoma (Figure 3B). Although straddling the mitral valve, the mass remained in the left atria throughout the cardiac cycle. On the second postoperative day, repeat neurological examinations showed that the patient had regained mental clarity and fluent speech, the right nasolabial sulcus was shallow, the muscle strength of the right limbs was 4/5, and there were no sensory abnormalities. Chaddock’s sign and Babinski’s signs had reverted to negative on the right. The NIHSS score at 24 h after stroke onset was 3 points (facial paralysis 1, right upper extremity 1, and right lower extremity 1). Blood analysis revealed: Hemoglobin 102 g/L (nL, 110-150 g/L) and normal neutrophils, platelets, leukocytes, erythrocytes, coagulation, D-dimer, renal function, and electrolytes. CRP restored to the normal range (7.25 mg/L; elevated CRP levels were more likely to be associated with stress from acute stroke). Brain magnetic resonance imaging at 4 d showed an area of hyperintensity in the left insular lobe, frontal lobe, parietal lobe, and occipital lobe, indicating acute cerebral infarction (Figure 4A), consistent with her weakness in the right upper extremity. Review of head CT at 14 d showed patchy area of low density within the lesion in the left basal ganglia region (Figure 4B). Computed tomographic angiography imaging showed excellent patency of the involved left middle cerebral artery (Figure 4C). The NIHSS score had dropped to 2, and the modified Rankin scale (MRS) score was 2 at discharge.
OUTCOME AND FOLLOW-UP

The NIHSS score was 1, and the MRS score was 0 at the 90-d follow-up. There was no recurrence of symptoms and the patient had recovered very well without any sequelae at the 1-year follow-up. During this period, warfarin was taken orally for anticoagulation, and INR indexes were monitored.

DISCUSSION

CM account for only 0.5% of acute cerebral infarctions[4], and atrial myxoma is the most common primary cardiac tumor. Neurological complications associated with atrial myxoma most frequently include cerebral infarct due to embolus[5]. The mechanism of stroke in CM is believed to be emboli that originate from two sources: Thrombus on the surface of tumor tissue, and actual detachment of tumor tissue[6]. These frequently lead to embolic cerebral infarct, most typically in young women, with a female predominance between the third and sixth decades of life[7]. The main distribution of the infarctions is in the internal carotid artery system, although they may involve multiple vascular systems. The incidence of stroke is also associated with the position of the myxoma, and small-size myxomas cannot be ignored for the risk of
stroke[8]. The young female patient had no commonly recognized high-risk factors (for example, hypertension and diabetes) predisposing to stroke, and without typical high-risk factors for cardiovascular disease and no concerning family history. The cardiac murmur detected on cardiac auscultation at the time of her hospital admission might have been a clue to cardiogenic embolism. The patient was promptly treated by thrombolysis and bridging embolectomy. Pathologically, the embolus had the form of clear mucus jelly, suggesting the presence of CM. The age and sex of the patient were consistent with those of previously reported series, with a female predominance between the third and sixth decades of life. Irrespective of the successful outcome of this patient, cerebral infarction caused by CM is a serious problem. For large vascular occlusion caused by CM, even with timely treatment utilizing rt-PA intravenous thrombolysis, success rates are still very low at approximately 10%, bleeding conversion rate is about 10.23%[5], and the curative effect is not satisfactory[9]. Mechanical arterial embolectomy can quickly open occluded blood vessels in up to 53%, but cerebral infarction due to CM has been shown to be recurrent[7]. To prevent recurrent embolic events and potentially sudden death, CM should be operated on as soon as diagnosed and safe to proceed. The longer the time interval between ischemic events and CM resection, the higher the risk of recurrent cerebral embolism[10]. Sethi[11] performed emergency peripheral vascular and cardiac surgery on a patient with acute massive cerebral infarction due to CM, and the patient performed well. Delayed surgical resection was associated with an increased risk of complications from the myxoma[4]. Shah et al.[12] reported 10-, 20-, and 30-year survival rates of 77.0%, 51.8%, and 33.6% in CM. The prognosis of CM after surgical resection is good, and the recurrence rate is about 1%-4% in scattered cases[13]. Although the recurrence rate is low, warfarin anticoagulation was used for 1 year to prevent recurrence in the case.

CONCLUSION

In this case, the occurrence of a large cerebral infarct was successfully avoided after intravenous thrombolytic bridging arterial thrombectomy, and the left atrial myxoma resection was performed on the day of admission so as to reduce the risk of recurrent ischemic stroke.

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**CASE REPORT**

**Breast adenoid cystic carcinoma arising in microglandular adenosis: A case report and review of literature**

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**Author contributions:** An JK contributed to conceptualization and supervision; An JK and Kim EK do the original draft preparation; An JK, Kim EK and Kwak HY do the data curation; An JK, Woo JJ and Kim EK do the formal analysis; all author validate, review and edit the manuscript.

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**Abstract**

**BACKGROUND**

Breast adenoid cystic carcinoma (AdCC) is a rare invasive carcinoma composed of epithelial and myoepithelial cells. Microglandular adenosis (MGA) is a rare benign proliferative lesion consisting of small, uniform, and round glands formed by a single layer of epithelial cells and basement membrane without a myoepithelial cell layer. MGA may progress to atypical MGA and carcinoma arising in MGA. Among various invasive carcinomas from MGA, AdCC has been rarely reported. Here, we report a case of AdCC arising in MGA.

**CASE SUMMARY**

A 59-year-old woman was diagnosed with a newly developed density on a routine mammogram. The density was similar to or slightly lower than that of the breast parenchyma. Sonography showed an irregular mass with a slightly higher echo than that of fat. Magnetic resonance imaging showed an irregular mass with a similar T1 signal intensity and a slightly higher T2 signal intensity compared to muscles or the breast parenchyma. The lesion showed heterogeneous internal enhancement with an initially slow and delayed persistent enhancing pattern. Microscopically, the tumor was composed of invasive AdCC, *in situ* AdCC, and MGA. AdCC is composed of basaloid and ductal epithelial cells forming cribriform or solid sheets, or haphazardly scattered small cribriform or tubular glands. MGA showed small glands with a single epithelial lining and retained lumen. S-100 staining was strongly positive in MGA area. The patient underwent breast-conserving surgery with sentinel lymph node biopsy.

**CONCLUSION**
Breast AdCC arising in MGA showed unique imaging findings that was different from usual invasive cancer.

**Key Words:** Breast neoplasms; Fibrocystic breast disease; Carcinoma; Adenoid cystic; Case report

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**Core Tip:** Many pathological or clinical studies have been reported for adenoid cystic carcinoma (AdCC) arising in microglandular adenosis (MGA), but few reports have been reported of radiological findings. In our case, it was characterized by iso- or slight hypo-density in the mammogram and slightly higher echo than that of fat in the ultrasound examination with higher T2 signal intensity and a persistent enhancing pattern in breast magnetic resonance imaging. Although AdCC shows a favorable prognosis and MGA has long been considered a benign entity, there is a risk of MGA becoming malignant and a complete resection should be performed.

**INTRODUCTION**

Adenoid cystic carcinoma (AdCC), a rare breast cancer, accounts for 0.1%-3.5% of all breast tumors. It is known to have a good prognosis[1-5]. AdCC is composed of two main neoplastic cells: (1) Altered myoepithelial cells grouped in nests or outlining characteristic cribriform space; and (2) Epithelial cells lining small ductule-like true lumina[6,7]. AdCC belongs to ‘rare and salivary gland-type tumors’ among epithelial tumors of the breast in World Health Organization (WHO) classification[2]. Recently, it has been reported that microRNA expression profile of breast AdCC differs from that of salivary gland AdCC[7]. It helps us understand different clinical behaviors of tumors depending on the original site.

Microglandular adenosis (MGA) is a rare benign proliferative lesion consisting of small, uniform, and round glands formed by a single layer of epithelial cells[8,9]. These glands are surrounded by basement membranes without myoepithelial cell layers. Absence of the myoepithelial layer is a characteristic feature that distinguishes MGA from ductal and lobular histology of the breast. Infiltrative proliferation of these glands and absence of the myoepithelial layer may mimic invasive breast carcinoma[8]. Although MGA is a benign entity, it may progress to atypical MGA and carcinoma arising in MGA[10-14]. Various invasive carcinomas arising in MGA have been reported. However, AdCC and its imaging findings have been rarely reported[12,15]. In this study, we report a case of AdCC arising in MGA.

**CASE PRESENTATION**

**Chief complaints**

A 59-year-old woman visited our hospital for a routine breast checkup. Since she first had a breast examination at our hospital in 2017, she has been undergoing regular checkups every year. Last year, her breast examination showed negative findings. However, a mammography (MG) performed this year revealed a new density.

**History of present illness**

She is currently on medication for high blood pressure and diabetes, and has no other breast symptoms.
History of past illness
She had no history of breast surgery.

Personal and family history
She had no family history of cancer, including breast cancer.

Physical examination
The breast lesion was not clearly palpable on physical examination.

Laboratory examinations
No specific laboratory examinations were performed for breast lesion in this patient.

Imaging examinations
In the MG, focal asymmetry was noted in the right upper outer peripheral breast (Figure 1). The density was similar to or slightly lower than that of the breast parenchyma. It was not accompanied by distortions or microcalcifications. In the ultrasound (US) examination, the lesion was shown as a 1.5 cm, irregularly shaped mass with an angular margin (Figure 2). The echo was slightly higher than that of fat. There was no increased vascularity in the color Doppler study. In breast magnetic resonance imaging (MRI), the lesion was shown as a 1.3 cm mass with an irregular shape and margin located in the right upper outer peripheral breast, about 6 cm from the right nipple. The mass showed a similar T1 signal intensity and a slightly higher T2 signal intensity compared to muscles or the breast parenchyma (Figure 3). The lesion exhibited reduced diffusivity with hypointensity in diffusion-weighted images and hypointensity in the apparent diffusion coefficient map compared to normal breast tissues. In the contrast enhancement study, the lesion showed heterogeneous internal enhancement with an initial slow and delayed persistent enhancing pattern. There was no axillary lymph node metastasis.

Pathological examination
The patient underwent breast-conserving surgery and sentinel lymph node biopsy. Grossly, an ill-defined whitish tumor of roughly 1.6 cm × 1.4 cm was observed. Microscopically, invasive cancer showed diffuse infiltrating nests of cribriform or solid sheets composed of two types of cells: basaloïd and ductal epithelial cells (Figure 4A and B). The cribriform space was filled with bluish or pinkish mucoid materials that were Periodic acid Schiff-positive (Figure 4C and D). Surrounding breast tissue also showed extensive intraductal proliferation of tumor cells forming small cribriform or tubules. Small round glands lined by benign-looking uniform cells were noted at the periphery of the intraductal carcinoma, suggesting in situ AdCC arising in the background of MGA (Figure 5). Benign small glands of MGA were p63 negative but S-100 positive. However, in situ AdCC was p63 positive but S-100 negative, similar to that of invasive element (Figure 6A). Immunohistochemical staining revealed myoepithelial differentiation with strong p63 positivity (Figure 6B) and epithelial differentiation with cytokeratin (CK) (Figure 6C), CD117, and epithelial membrane antigen (EMA). Triple markers of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor2 (HER2) were negative. The Ki-67 proliferation index was low (less than 17%). There was no lymphovascular or perineural invasion. There was no tumor metastasis in sentinel lymph nodes.

FINAL DIAGNOSIS
The lesion was confirmed as adenoid cystic carcinoma arising in microglandular adenosis.

TREATMENT
After the breast-conserving surgery and sentinel lymph node biopsy, adjuvant radiation therapy was performed at the site of excision.
Figure 1 Mammography showing a focal asymmetry. On cranio-caudal (A) and medio-lateral-oblique (B) view, the lesion was located in the right upper outer peripheral breast (arrows). The density was similar to or slightly lower than that of the breast parenchyma. There were no associated parenchymal distortions or microcalcifications.

Figure 2 Ultrasonography showing an irregular mass. A: On B-mode ultrasonography, the lesion showed an irregular shape and angular margin (arrow). The echogenicity was slightly higher than that of fat; B: In the color Doppler study, there was no internal or rim vascularity (arrow).

OUTCOME AND FOLLOW-UP
The patient had the first follow-up six months after surgery. There were no specific abnormalities other than postoperative changes.

DISCUSSION
Breast AdCC is classified into three subtypes: classic AdCC, solid-basaloid AdCC (SB-AdCC), and AdCC with high-grade transformation[2]. Classic AdCC shows a central cribriform area and a peripheral area with a tubular architecture. Both areas have the same cellular compositions of epithelial and myoepithelial cells. The glandular space is lined by epithelial-type cells that produce mucins. The pseudolumina is filled with stromal matrix, including basal membranes. Classic AdCC lacks nuclear atypia and necrosis. It shows a low mitotic count. An in situ component is rarely seen in classic AdCC. In addition to classic features of AdCC, SB-AdCC is characterized by solid nests composed of basaloid cells with marked nuclear atypia, high mitotic count, and necrosis[16]. Breast AdCC associated with high grade carcinoma is rare. It is classified into AdCC with high-grade transformation[2]. Classic AdCC shows favorable behavior. SB-AdCC and AdCC with high-grade transformation show worse prognosis than classic AdCC[2]. In immunohistochemistry, epithelial cells are positive for CK7, CK8, and EMA. In some cases, they are positive for CK5/6[17]. Myoepithelial cells show positivity for CK14, CK5/6, P63[18], and myoepithelial markers such as heavy-
Figure 3 Breast magnetic resonance imaging showing an irregular mass in right breast. In breast magnetic resonance imaging, the lesion showed similar T1 signal intensity (A) and slightly higher T2 signal intensity (B) compared to muscles or the breast parenchyma. The lesion showed reduced diffusivity with hyperintensity in diffusion-weighted images (C). In the contrast enhancement study, the lesion showed heterogeneous internal enhancement (D) with an initial slow and delayed persistent enhancing pattern (E and F).

chain myosin, calponin, S100, and CD10. CD117 is usually strongly positive in the luminal component of AdCC. The tubular component of classic AdCC, unlike MGA, is composed of two cell types: epithelial cells and myoepithelial cells. Tubules contain mucins and basement membrane materials.

MGA has the following histologic findings: A single layer of cuboidal epithelium, clear to eosinophilic cytoplasm, rare mitotic nuclei figures, and well-preserved gland lumen and basement membranes[8,13,14,19]. Atypical MGA has features of architectural complexity, cellular expansion in the lumina, prominent nucleoli, and vesicular nuclei. In situ carcinoma from MGA shows frequent mitotic figures, obvious cytologic atypia, and obliteration of the gland lumen. Invasive carcinoma arising in MGA usually forms a microscopic solid tumor mass with infiltrative growth, desmoplastic reaction, severe cytologic atypia, and increased mitosis[13-15]. MGA, atypical MGA, and carcinoma from MGA have common immunohistochemical profiles of ER, PR, HER2, and CK5/6 negativity but CK8/18, S-100, and epithelial growth factor receptor positivity[11,13,15]. Khalifeh et al[11] have reported that Ki 67 and P53 expression could be reliable markers to distinguish MGA from atypical MGA or carcinoma from MGA because their positivity tends to increase as the lesion progresses to malignancy.

Acs et al[15] have reported 17 cases of AdCC coexisting with MGA. They suggested that AdCC might develop in a background of MGA or from MGA. They described morphological spectra of lesions with MGA, atypical MGA (also called AdCC in situ), and invasive AdCC. Altered myoepithelial cells appear to be the major neoplastic element in both AdCC and atypical MGA. Cells were stained similarly to what was seen in the myoepithelium of the breast with three markers: S-100 protein, SMA, and vimentin. MGA, atypical MGA, and AdCC show similar growth patterns with expansile or infiltrative patterns. They have a very limited metastatic capacity, showing a favorable prognosis. Rico et al[12] have reported that among carcinomas arising in MGA, not otherwise specified ductal carcinoma, metaplastic carcinoma, and salivary gland type carcinoma account for 63.4%, 35.2%, and 27.4%, respectively. Among salivary gland type carcinomas, AdCC was the most common carcinoma arising in MGA.
In our case, the tumor was composed of invasive AdCC, in situ AdCC, and MGA. Invasive AdCC showed cribriform or solid sheets composed of two cell types in the desmoplastic stroma, which was a differentiating point with in situ AdCC. Loss of basement membrane is also a characteristic of invasive cancer that could be distinguished from in situ cancer. Laminin or collagen IV staining could be helpful for the differentiation. In situ or atypical AdCC showed haphazardly scattered small cribriform or tubular tumor glands in fat tissue in the same pattern as MGA. Just next to the in situ components, small tubular glands with single epithelial lining and retained lumen were present, suggesting remaining MGA. In this area, S-100 staining was strongly positive, but p63 negative, compared to S-100 negative and p63 positive of in situ or invasive AdCC.

In the past, we have reported that ductal carcinoma in situ (DCIS) arising in MGA [20]. However, not many reports on imaging findings of carcinoma arising in MGA...
An JK et al. Breast AdCC arising in microglandular adenosis

Figure 6 Immunohistochemical staining. A: In situ adenoid cystic carcinoma showed S-100 negativity, whereas microglandular adenosis was strongly positive for S-100 staining; B: Immunohistochemical staining for p63 showed diffuse myoepithelial differentiation of the tumor cells; C: Immunohistochemical staining for cytokeratin showed epithelial cell differentiation of the tumor cells. Magnification: 200 ×.

have been published since then. Choi and Bae[10] have reported multifocal invasive carcinoma associated with DCIS and invasive ductal carcinoma associated with encapsulated papillary carcinoma, both arising from MGA. The former showed a small nodular density in the MG and a suspicious, small hypoechoic lesion on US. The latter showed a lobulated, heterogeneous hypoechoic mass on US. Oh et al.[21] have reported one case of invasive carcinoma arising in MGA. Mammogram showed an irregular isodense mass with a spiculated margin and irregular hypoechoic mass in US examination. Breast MRI showed an irregular mass with heterogeneous enhancement with a delayed washout kinetic curve. Adjacent segmental non-mass enhancement was confirmed as MGA and atypical MGA.

Imaging findings of AdCC of the breast are very diverse. In the MG, AdCC shows irregularly shaped, circumscribed, ill-defined, or microlobulated margins with iso- or hyper-density. It also appears as an architectural distortion or asymmetry[22-26]. In the US examination, it shows an irregular shape, circumscribed or ill-defined margins, and iso-, hypo- or complex echogenicity[22,23,25,27,28]. In MR images, it shows circumscribed round mass with intermediate T2 SI and persistent enhancing curve[23], increased T2 SI with variable kinetic curves[22], spicules and early phase enhancement[28], and mixed cystic and solid mass with irregular shape and margin, and rapid and heterogeneous enhancement[25]. However, imaging findings of AdCC arising in MGA have not been described yet. To the best of our knowledge, this is the first report of imaging findings of AdCC arising in MGA.

In our case, in the MG, the lesion had no common invasive cancer features such as high density, distortion, spiculation, or suspicious microcalcifications, except for developing density. Therefore, it would be missed unless comparison with previous mammographic images was made. The density was similar to that of the breast parenchyma or slightly less. On US, sonographic echo of the lesion was slightly higher than that of fat. As the contrast between the hyperechoic breast tissue and the lesion was unclear, it was difficult to clearly distinguish the margin of the lesion in B-mode ultrasound, even with a harmonic image. Therefore, our sonographic diagnosis was a low-suspicion lesion with the possibility of a benign lesion, not breast cancer. In breast MRI, a slightly increased T2 signal intensity and a persistent enhancing pattern were seen, similar to other reports on MRI findings of AdCC. MGA might also show imaging findings similar to breast malignancy[29]. Thus, it is currently unclear which characteristics of MGA can affect imaging findings of AdCC arising in MGA. Further case collections and analysis are needed in the future to characterize this rare lesion.

For the treatment of primary AdCC of the breast, Treitl et al.[1] have reported that radiation therapy or sentinel node excision besides a primary surgical therapy might not be warranted due to the tumor’s indolent course. Kulkarni et al.[30] have reported that AdCC has characteristics of lower grade, hormone receptor negativity, and node negativity compared to an invasive ductal carcinoma. Therefore, AdCC was treated with less axillary surgery, fewer mastectomy, and less chemotherapy and hormone therapy. However, there is no treatment policy for AdCC arising in MGA due to the rarity of this type of malignancy. Although many published studies have suggested a relatively favorable prognosis for carcinomas arising in MGA, MGA may no longer be considered simply a benign proliferative lesion as it can progress to aggressive breast cancer. Resetkova et al.[31] have emphasized the importance of complete excision of the mass and reported a recurrent case of high-grade in situ carcinoma within the residual MGA after primary surgery for this invasive tumor arising in atypical MGA. Therefore, appropriate treatment should be performed according to the patient’s clinical status considering the general treatment strategy for invasive cancer with complete excision of MGA.
CONCLUSION

AdCC is a rare breast malignancy with a favorable prognosis. Although MGA has long been considered a benign entity, it has the risk of progression to malignancy. Therefore, in the case of AdCC arising in MGA, an appropriate treatment should be performed according to the clinical stage of the patient. In particular, complete resection should be performed so that no MGA remains. Imaging findings of AdCC occurring in MGA were characterized by iso- or slight hypo-density in the MG and slightly higher echo than that of fat in the US examination with higher T2 signal intensity and a persistent enhancing pattern in breast MRI.

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Diagnosis and management of ophthalmic zoster sine herpete accompanied by cervical spine disc protrusion: A case report

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Core Tip: If the development of shingles does not occur in patients with complex
INTRODUCTION

The causes of atypical facial pain and headache are variable, and one of them is herpes zoster (HZ) [1]. Zoster sine herpete (ZSH) is an atypical clinical manifestation of HZ. ZSH has been defined as pain in a dermatomal distribution without a rash and is more difficult to diagnose than typical HZ because there is no vesicular eruption. Misdiagnosis of ZSH can lead to prolonged severe neuropathic pain, nerve palsy, myelitis, pneumonitis, otitis externa, ophthalmic complications, and fatal complications, such as encephalitis or stroke [2].

Ophthalmic ZSH was first described by Ross in 1949. When ZSH involves the ophthalmic division of the trigeminal nerve, it causes symptoms such as trigeminal neuralgia and headache [3, 4]. As ZSH is uncommon, it is usually not suspected, especially when accompanied by other problems, until other common causes for the symptoms are ruled out. Herein, we report a case of ZSH that occurred in a patient with sudden hearing loss and cervical spine abnormalities. The patient was diagnosed based on serologic examination findings and clinical manifestations and treated successfully with antiviral management and stellate ganglion blocks.

CASE PRESENTATION

Chief complaints

A 75-year-old woman complained of sharp and shooting pain in the right frontal region for one month.

History of present illness

The patient had received a cervical epidural block twice at an orthopedic clinic because of sudden shoulder pain in the C4/5 dermatome and atypical headache. However, she still had sharp and shooting pain in the right frontal region. The pain was so severe that she could not sleep at night and touch her hair. Eighteen days after the symptoms occurred, she collapsed due to dizziness. One month after initial onset of symptoms, the patient was admitted to the otorhinolaryngology department of our hospital and received steroid pulse therapy for sudden left hearing loss. In addition, the patient was referred to a pain clinic. When the pain physician asked the patient about her symptoms, she said that the right forehead hurt the most. No typical rash was observed in the patient’s ear or the area of pain. There was no history of a rash or trauma (Figure 1).

History of past illness

The patient had no previous diagnosis.

Personal and family history

The patient had no significant family history.

Physical examination

No neurological abnormalities were observed. The patient’s symptoms were not provoked by neck movement or pressure over tender points in the neck and did not worsen with the Spurling’s test.
Laboratory examinations
The result for varicella-zoster virus (VZV)-IgM (titer 2.7) was positive in a test conducted to determine the cause of sudden hearing loss. The test was performed 23 days after the onset of pain. When she was referred to the pain clinic one month after the occurrence of symptoms, VZV-IgG and polymerase chain reaction (PCR) tests were performed to precisely determine the patient’s condition. Serum VZV-IgG (titer, 4.26) finding was positive. However, DNA in the serum was not detected by PCR testing.

Imaging examinations
Brain computed tomography and magnetic resonance imaging (MRI) were performed to diagnose central origin lesions, but no abnormalities were observed. MRI of the cervical spine was performed under the suspicion of cervicogenic headache and cervical radiculopathy, and C3/4 central disc protrusion, C4/5 disc protrusion, right neural foramina stenosis at C4/5, focal compression of the spinal cord at C4/5, and C5/6 disc protrusion were observed (Figure 2).

FINAL DIAGNOSIS
The final diagnosis of the case was ophthalmic ZSH.

TREATMENT
First, a stellate ganglion block was planned for rapid control of severe pain. Stellate ganglion blocks were administered four times, once every two days. At the same time, antiviral management (valacyclovir 1 g, three times per day for 7 d) was performed.

OUTCOME AND FOLLOW-UP
After the first stellate ganglion block using 6 mL of 0.375% ropivacaine was administered, the patient reported that she could wash her hair. Stellate ganglion block was performed three more times, after which the numeral rating scale score reduced from 10 to 0. The pain was effectively controlled. The patient was discharged without pain.

DISCUSSION
In this case, the patient experienced continuous pain in a specific area innervated by the ophthalmic branch of the trigeminal nerve. She also experienced pain in the shoulder and neck because of an abnormal cervical spine. She had previously received...
a cervical epidural block two times, and her neck and shoulder pain were alleviated, but the headache worsened within one month. Concurrently, the patient collapsed due to sudden hearing loss in the left ear and was hospitalized. The pattern of pain corresponded to neuropathic pain, and both VZV-IgG and VZV-IgM were observed in the serum. We initiated antiviral management and administered ultrasound-guided stellate ganglion block under the suspicion of ZSH, and her headache was completely resolved in a week.

The most important aspect in diagnosing HZ is vesicle history[1]. The diagnosis of ZSH is difficult because there are no vesicles in the area associated with pain. Owing to its rarity, it is generally not considered as the cause. In this case, the patient had an abnormal cervical spine (C3/4, C4/5, C5/6) with C4/5 right neural foramina stenosis. She experienced not only a headache but also shoulder and neck pain. She had restricted range of motion in the neck. Usually a cervicogenic headache worsens due to provocation maneuvers and is diminished following diagnostic cervical epidural blockade, which were not observed in our case [5]. Therefore, cervicogenic headache could be excluded. Headache can be caused by a tumor or cranial nerve problem, but there was no abnormality on brain MRI and neurologic examination conducted by a neurologist. As the area associated with the pain was innervated by the ophthalmic branch of the trigeminal nerve, trigeminal neuralgia was considered. However, trigeminal neuralgia is characterized by touch-evoked paroxysmal attacks, unlike the pain in this patient.

Diagnosis is usually based on clinical manifestations; however, serological examinations can be used for diagnosis. When a patient has a primary infection with VZV, VZV-IgM will be positive, but VZV-IgG will not be detected[6]. Both VZV-IgM and VZV-IgG are detected in case of reactivation of VZV[6]. VZV-IgM can be detected in a narrow time window during the early VZV reactivation period[7]. VZV DNA findings are usually negative when a VZV-specific antibody response occurs[7]. The most valuable tests are the detection of VZV DNA or VZV-IgG in cerebrospinal fluid (CSF) [8]. However, immunoglobulin tests and PCR test using CSF were not performed because the patient refused CSF tapping. Some studies have reported that serum VZV-IgG has no diagnostic value because such antibodies can be detected in nearly all adults throughout life[8]. In this case, acute zoster pain was suspected because positive laboratory findings of VZV-IgM was observed 24 d after the onset of symptoms. Since VZV-IgG and PCR tests were not performed at the same time, it is difficult to diagnose based on serology alone. The possibility that the virus had been lost due to the activation of the immune response was considered. In conclusion, a diagnosis with only serological examination was not possible in this case. Diagnosis would have been easier if VZV DNA detection in the CSF or saliva was performed.

The patient was female and elderly. Therefore, delayed antiviral therapy could cause serious complications. Antiviral therapy and stellate ganglion blocks were administered based on serological findings and clinical symptoms, which were indicative of ZSH. Consequently, severe neuropathic pain on her right face disapp-
eared within a week.

**CONCLUSION**

ZSH of the trigeminal nerve should be considered as a cause of severe headache associated with the area this nerve innervates. Early diagnosis and treatment of ZSH can help not only reduce pain but also prevent fatal complications.

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Hemorrhagic pericardial effusion following treatment with infliximab: A case report and literature review

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Abstract

BACKGROUND
Infliximab (IFX) is an anti-tumor necrosis factor alpha (TNF-α) agent that is widely used for the management of a variety of autoimmune and inflammatory diseases, including Crohn’s disease (CD). As a result of its increasing administration, new complications have emerged. Hemorrhagic pericardial effusion, secondary to IFX therapy, is a rare but life-threatening complication.

CASE SUMMARY
A 27-year-old man was diagnosed with CD (Montreal A2L3B1) 6 years prior. After failing to respond to mesalazine and methylprednisolone, he took the first dose of IFX 300 mg based on his weight (60 kg, dose 5 mg/kg) on December 3, 2018. He responded well to this therapy. However, on January 21, 2019, 1 wk after the third injection, he suddenly developed dyspnea, fever, and worsening weakness and was admitted to our hospital. On admission, computed tomography scan of the chest revealed a large pericardial effusion and a small right-side pleural effusion. An echocardiogram showed a large pericardial effusion and normal left ventricular function. Then successful ultrasound-guided pericardiocentesis was performed and 600 mL hemorrhagic fluid was drained. There was no evidence of infection and the concentrations of TNF-α, IFX, and anti-IFX antibody were 7.09 pg/mL (reference range < 8.1 pg/mL), < 0.4 μg/mL (> 1.0 μg/mL), and 373 ng/mL (< 30 ng/mL), respectively. As the IFX instruction manual for injection does mention pericardial effusion as a rare adverse reaction (≥ 1/10000, < 1/1000), so we discontinued the IFX. Monitoring of the patient’s echocardiogram for 2 mo without IFX therapy showed no recurrence of hemorrhagic pericardial effusion. Follow-up visits and examinations every 3 to 6 mo until April 2021 showed no recurrence of CD or pericardial effusion.

CONCLUSION
This is a case of hemorrhagic pericardial effusion following treatment with IFX. It
INTRODUCTION

Anti-tumor necrosis factor alpha (TNF-α) agents including infliximab (IFX), adalimumab, golimumab, and certolizumab pegol are widely used in the management of a variety of autoimmune and inflammatory diseases. Crohn’s disease (CD) is characterized by chronic inflammation that mainly targets the gastrointestinal tract. Due to increased administration of anti-TNFα agents, new complications have been reported such as infections (tuberculosis, viral, bacterial and fungal infections), systemic lupus erythematosus-like reactions, arterial and venous thromboembolism, pericarditis, and pneumonitis[1-4].

Here, we present a rare case of a 27-year-old male patient with hemorrhagic pericardial effusion following treatment with IFX. This complication disappeared following discontinuation of IFX. We also review the literature. We searched the literature using the keywords “pericarditis OR pericardial effusion OR pleuropericarditis OR cardiac tamponade AND infliximab” and found that pericarditis or pericardial effusion, is a rare but serious complication of IFX, especially cardiac tamponade. To enhance our understanding of this complication, we analyzed cases of IFX-associated pericardial complications reported in the literature.

CASE PRESENTATION

Chief complaints
A 27-year-old man had intermittent abdominal pain and mucosanguineous feces for 6 years. He was admitted to our hospital with complaints of dyspnea, fever, and worsening weakness.

History of present illness
The patient was diagnosed with CD (Montreal A2L3B1) 6 years previously. He had suffered from mucosanguineous feces, abdominal pain, and an anal fistula for 6 mo. Colonoscopy, biopsy, and multi-slice computed tomography (CT) enterography were performed. Negative blood tests were observed and no opportunistic infections were found. He was prescribed mesalazine 3 g/d for 1 year without complications but
primary symptoms were only partially relieved. One year later, his symptoms of abdominal pain and loose stool were aggravated, and gastroscopy showed involvement of the upper gastrointestinal tract. He was treated with oral methylprednisolone 48 mg/d for 10 d. The dose was reduced by 4 mg every 2 wk without any improvement in symptoms. He continued to take mesalazine 2 g/d. In December 2018, reexamination with colonoscopy and biopsy showed stenosis of the sigmoid colon accompanied by numerous new ulcers. He was examined at another hospital and from then to the present, no extraintestinal manifestations occurred. The patient was advised by the doctor to undergo IFX therapy and he stopped taking mesalazine after excluding tuberculosis and other viral or bacterial infections. On December 3, 2018, he took the first dose of IFX 300 mg based on his weight (60 kg, dose 5 mg/kg). After 2 and 6 wk, he received the second and third IFX injection and a maintenance dose was planned every 8 wk thereafter. He responded well to this therapy, his symptoms disappeared and he had formed stools, and colonoscopy was planned after four doses of IFX. However, on January 21, 2019, 1 wk after the third injection, he suddenly developed dyspnea, fever, and worsening weakness and was admitted to our hospital.

**History of past illness**
The patient had no previous medical history, and no history of chest trauma or cardiac procedure.

**Personal and family history**
The patient had no family history

**Physical examination**
He was febrile, tachycardiac (120 bpm), and normotensive. Our clinical considerations were heart disease or pulmonary embolism.

**Laboratory examinations**
An electrocardiogram on admission was negative for acute changes and his troponin I and creatine kinase-MB levels were normal. There were no abnormalities in his white cell count or platelet count, and the coagulation index was normal. Viral titers including Epstein-Barr virus, cytomegalovirus, coxsackie B virus, human immunodeficiency virus and bacterial serologies were negative. A T-spot test was also negative. Blood, stool, and urine cultures were all negative. Laboratory examinations were remarkable for an elevation in C-reactive protein (CRP) to 65.24 mg/L (reference < 5.00 mg/L) and an elevated erythrocyte sedimentation rate of 48 mm/h. The procalcitonin level was normal.

**Imaging examinations**
CT scan of the chest revealed a large pericardial effusion and a small right-side pleural effusion (Figure 1), and excluded the diagnosis of pulmonary embolus. An echocardiogram showed a large pericardial effusion and normal left ventricular function (Figure 2). Then successful ultrasound-guided pericardiocentesis was performed and 600 mL hemorrhagic fluid was drained.

**FINAL DIAGNOSIS**
The final diagnosis of the presented case was hemorrhagic pericardial effusion secondary to IFX therapy. Although we have not seen similar symptoms in previously treated patients, the IFX instruction manual for injection does mention pericardial effusion as a rare adverse reaction (≥ 1/10000, < 1/1000), and similar cases have been previously reported. Due to the absence of documented infection or other identifiable causes of hemorrhagic pericardial effusion, the specific time frame of IFX infusion, and no recurrence in the absence of IFX therapy, a diagnosis of hemorrhagic pericardial effusion secondary to IFX therapy was made.

**TREATMENT**
The patient discontinued IFX and received supportive treatment for 3 d.
Li H et al. Hemorrhagic pericardial effusion following infliximab therapy

Figure 1 Chest computed tomography shows pericardial effusion and a small right-side pleural effusion.

Figure 2 Echocardiography shows pericardial effusion and normal left ventricular function.

OUTCOME AND FOLLOW-UP
Along with a decrease in pericardial effusion, the patient’s fever and shortness of breath also gradually resolved. The patient was discharged on the 7th d with a plan to stop IFX therapy in the future. The patient was followed every 3 to 6 mo till April 2021. The total follow-up time is 26 mo. At present, his symptoms have disappeared, the fecal test and occult blood are negative, and CRP is less than 10 mg/L. Colonoscopy showed scars and a few pseudopolyps, and echocardiography showed no pericardial effusion.

DISCUSSION
Inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) are common primary diseases treated with IFX[5-8]. Pericardial effusion following IFX treatment is a rare complication. Seventeen reported cases of pericardial complications during IFX therapy, including our patient, are summarized in Table 1. Of nine reported cases with IBD, hemorrhagic pericardial effusion occurred in two patients[9], including our patient. All reported cases of cardiac tamponade due to IFX occurred in IBD patients [1-3,9]. Elderly patients with RA seem to suffer from more severe complications. It seems that these patients tend to have a high titer of anti-IFX antibodies and a strong type III immunologic reaction, and failure of IFX therapy for extra-articular manifestations may be responsible. The duration of IFX treatment varies from 1 wk to 6 years, with an average of 72.9 wk. For clinical presentation, fatigue, dyspnea, and chest pain are common in these cases. Besides, heart failure, fever, and swelling are also potential warning signs.
<table>
<thead>
<tr>
<th>Cases</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Primary disease</th>
<th>Pericardial complications</th>
<th>Clinical presentation</th>
<th>Duration of IFX Treatment</th>
<th>Follow-up treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>Female</td>
<td>RA</td>
<td>Transudate, constrictive</td>
<td>Right heart failure: leg edema and anorexia</td>
<td>40 d</td>
<td>Infliximab discontinuation, pericardiocentesis</td>
<td>Pericardial effusion not increased</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>Female</td>
<td>RA</td>
<td>Hemorrhagic</td>
<td>Shortness of breath, right heart failure</td>
<td>14 mo</td>
<td>Pericardiocentesis</td>
<td>Recurrent disease, pericardiectomy</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>Female</td>
<td>RA</td>
<td>Infective pericarditis</td>
<td>Cardiac failure, fatigue, dyspnea</td>
<td>6 yr</td>
<td>Stop etanercept, pericardiocentesis and pericardial drain, antibiotics</td>
<td>White cell count normalized, CRP fallen</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>Female</td>
<td>RA</td>
<td>-</td>
<td>Dyspnea</td>
<td>4 yr</td>
<td>Steroid</td>
<td>Readmitted with recurrent symptoms, pericardiocentesis</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>Female</td>
<td>RA</td>
<td>-</td>
<td>Cardiovascular collapse</td>
<td>4 mo</td>
<td>Pericardiocentesis, steroid</td>
<td>Clinical symptoms and pericardial effusion improved</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>Male</td>
<td>RA</td>
<td>Hemorrhagic, DILE</td>
<td>Fever, cough, polyarthralgia, chest pain</td>
<td>22 wk</td>
<td>Infliximab discontinuation, steroid</td>
<td>Clinical symptoms and pericardial effusion improved</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>Male</td>
<td>RA</td>
<td>Purulent</td>
<td>Collapse</td>
<td>3 wk</td>
<td>Pericardiocentesis, antibiotics, infliximab discontinuation</td>
<td>Fenestration for residual pericardial effusion</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>Male</td>
<td>RA</td>
<td>-</td>
<td>Chest pain, chest discomfort</td>
<td>15 mo</td>
<td>Antibiotics, steroid</td>
<td>Recurrent disease, pericardiectomy</td>
</tr>
<tr>
<td>9</td>
<td>51</td>
<td>Female</td>
<td>UC</td>
<td>DILE</td>
<td>Chest pain, shortness of breath, fatigue</td>
<td>1 wk</td>
<td>Infliximab discontinuation, steroid</td>
<td>Clinical symptoms improved</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>Female</td>
<td>UC</td>
<td>Cardiac tamponade</td>
<td>Chest pain, dyspnea</td>
<td>1 mo</td>
<td>Infliximab discontinuation, pericardiocentesis, diuresis</td>
<td>No recurrence or persistent cardiac dysfunction</td>
</tr>
<tr>
<td>11</td>
<td>59</td>
<td>Male</td>
<td>UC</td>
<td>Non-infectious</td>
<td>Left-sided chest pain</td>
<td>1 mo</td>
<td>Infliximab discontinuation, NSAIDS, adalimumab</td>
<td>No recurrence of pericarditis</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>Male</td>
<td>UC</td>
<td>Hemorrhagic, cardiac tamponade</td>
<td>Shortness of breath, diffuse joint swelling and aches, general malaise</td>
<td>1 wk (infliximab was reintroduced)</td>
<td>Infliximab discontinuation, antibiotics</td>
<td>Progressive shortness of breath and recumbent chest pain, pericardiocentesis, steroid and pericardial drain were performed, pericardial effusion decreased</td>
</tr>
<tr>
<td>13</td>
<td>41</td>
<td>Male</td>
<td>UC</td>
<td>DILE, cardiac tamponade</td>
<td>Pleuritic chest pain, dyspnea</td>
<td>19 mo</td>
<td>Infliximab discontinuation, steroid</td>
<td>No residual pericardial effusion</td>
</tr>
<tr>
<td>14</td>
<td>30</td>
<td>Female</td>
<td>CD</td>
<td>Fibrinous, cardiac tamponade</td>
<td>Pleuritic chest pain, dyspnea</td>
<td>12 mo</td>
<td>Infliximab discontinuation, pericardial window, mediastinal chest tube, steroid</td>
<td>No recurrence of symptoms of pericarditis</td>
</tr>
<tr>
<td>15</td>
<td>57</td>
<td>Male</td>
<td>CD</td>
<td>Purulent, cardiac tamponade</td>
<td>Chest pain, fever, general malaise</td>
<td>8 yr</td>
<td>Infliximab discontinuation, pericardial window, antibiotics</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>16</td>
<td>39</td>
<td>Male</td>
<td>CD</td>
<td>DILE</td>
<td>Pleuritic chest pain, nausea, weakness</td>
<td>8 mo</td>
<td>Steroid</td>
<td>Severe arthralgia when used infliximab one more time; no recurrence of lupus-like symptoms after infliximab discontinuation</td>
</tr>
<tr>
<td>17</td>
<td>27</td>
<td>Male</td>
<td>CD</td>
<td>Hemorrhagic</td>
<td>Dyspnea, fever and worsening weakness</td>
<td>7 wk</td>
<td>Infliximab discontinuation, pericardiocentesis</td>
<td>Clinical symptoms and pericardial effusion improved</td>
</tr>
</tbody>
</table>
Three cases had infections with RA or CD[2,10]. Given that IFX has an immunosuppressive effect, this may play a role in an increased risk of infection. Drug-induced lupus erythematosus (DILE) occurred in 4 reported cases of RA, ulcerative colitis, or CD[3,4,11,12]. However, in 5 cases, pericardial fluid was not drained to identify its properties[13-15]. Patients between 50 and 60 years of age had the highest incidence of complications, and those with RA had the greatest number of complication types.

IFX is a monoclonal anti-TNFα antibody, which is widely used in IBD and other immune disorders. Patients with pericardial effusion during anti-TNFα therapy are rare, and mostly have RA and DILE[1,3,16,17]. In our patient, he had neither RA nor DILE. In this case, the association between the onset of symptoms after initiating IFX therapy and resolution of symptoms after discontinuing IFX was evident, and no other medication was administered at the same time. In addition, there was no evidence of infection. All these factors suggest that IFX infusion was the most likely etiology of hemorrhagic pericardial effusion in this patient. In 17 reported cases, most underwent performed IFX discontinuation and pericardiocentesis, including ours, and all of their clinical symptoms and pericardial effusion improved. On the other hand, one reported case did not stop IFX, and only steroid was given to control the DILE condition; severe arthralgia occurred when IFX was used one more time. Therefore, IFX discontinuation and pericardiocentesis would be effective treatments. Meanwhile, steroid, adalimumab and antibiotics for infection could also be appropriate options.

The exact mechanism of IFX-induced hemorrhagic pericardial effusion has not been clearly identified. IFX is a mouse/human chimera and monoclonal IgG1 antibody, 35% mouse-derived and 65% human-derived, and can join the variable regions of mouse antibodies to the constant regions of human IgG1. As a result of this partly murine composition and strong antigenicity, IFX might trigger an immunogenic reaction and antibody production. A high titer of anti-IFX antibodies and a strong type III immunologic reaction may be a possible cause of pericardial effusion. On the other hand, high titer of anti-IFX antibodies may decrease the drug concentration and effect, due to rapid clearance by newly produced antibodies. Therefore, we speculate that the high titers of anti-IFX antibodies in this patient, led to an autoimmune reaction to anti-TNFα agents, and the process mimicked infection. As anti-TNFα antibodies could not be used as a treatment option, further control and management of CD was challenging. With pseudopolyps and scars, he is now in the remission stage, and an intense surveillance and endoscopic examination has been scheduled.

With the increasing use of anti-TNFα agents for CD, many novel complications are being reported. Beside of biological agents, other categories being considered for the treatment CD include thalidomide, immunosuppressants, steroids, and enteral nutrition. Due to the heterogenetic mouse antigen, IFX is not always the best choice for patients, and other types of anti-TNFα agents with homologous proteins or biologicals with different targets could be considered.
CONCLUSION

Physicians should increase their awareness of this rare but life-threatening complication of IFX. Early recognition helps prevent the occurrence of hemorrhagic pericardial effusion and minimize the impact on the natural evolution of the disease.

REFERENCES


Wernicke's encephalopathy in a rectal cancer patient with atypical radiological features: A case report

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Author contributions: Nie T and He JL analyzed the data and drafted the manuscript; Nie T designed the study and revised the manuscript; all authors have read and approved the final manuscript.

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Abstract

BACKGROUND
Wernicke's encephalopathy is a disease caused by thiamine deficiency. The lesions usually involve the periphery of the aqueduct, midbrain, tectum, third ventricle, papillary body, and thalamus. It is very rare to affect the vermis and cerebellar hemispheres.

CASE SUMMARY
We report a 77-year-old female patient admitted to the emergency department of our hospital for 2 d of unconsciousness. Brain magnetic resonance imaging showed increased diffusion weighted imaging signals in the bilateral thalamus, periventricular regions of the third ventricle, corpora quadrigemina, vermis, and cerebellar hemispheres. Wernicke's encephalopathy was considered. She was given thiamine therapy and became conscious after the treatment.

CONCLUSION
Wernicke's encephalopathy may have various imaging manifestations. Clinicians should keep in mind that Wernicke’s encephalopathy may occur in patients who experience prolonged periods of malnutrition.

Key Words: Wernicke's encephalopathy; Atypical radiological features; Vermis; Cerebellar hemispheres; Case report

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Core Tip: Wernicke's encephalopathy is a disease caused by thiamine deficiency. Wernicke's encephalopathy may have various imaging manifestations. Typically, the lesions are distributed symmetrically in the thalamus, mamillary bodies, corpora quadrigemina, and periaqueductal areas. Lesions can also be found atypically in the
INTRODUCTION

Wernicke's encephalopathy is a disease caused by thiamine (vitamin B1) deficiency. It was first believed that Wernicke's encephalopathy was caused by the malabsorption of vitamin B1 after chronic alcohol abuse. Alcohol abuse is related to the complications of liver cirrhosis, such as the gastrointestinal tract having a low absorption rate at the mucosal level and the consequent malnourishment. In addition to alcohol abuse, severe vomiting, fasting, gastrointestinal surgery, chronic diarrhea, systematic disease, hemodialysis, hyperthyroidism, anorexia nervosa, and genetic factors may cause insufficient intake of vitamin B1 or vitamin B1 use disorder. Wernicke's encephalopathy may have various imaging manifestations. We report a rare case of Wernicke’s encephalopathy affecting the cerebellum.

CASE PRESENTATION

Chief complaints

A 77-year-old female patient was admitted to the emergency department of our hospital for 2 d of unconsciousness.

History of present illness

Approximately 1 mo prior to this visit, the patient presented with recurrent vomiting and bloody stools. Diarrhea, breathing problems, dizziness, and limb weakness were denied by the patient’s family in the course of the disease.

History of past illness

The patient had hypertension for 8 years. The blood pressure ranged from 120-140/70-100 mmHg after taking amlopidine.

Personal and family history

The patient had a disease-free personal and family history.

Physical examination

On admission, the vital signs were normal. Physical examination showed that the patient was confused. The neurological examination revealed that the diameter of both pupils was 0.3 cm, and the pupillary light reflex was sensitive. She could move her extremities unconsciously, and bilateral pathological signs were negative.

Laboratory examinations

Biochemical tests, thyroid function, autoantibodies, and vasculitis antibodies were normal. The results of blood electrolyte and arterial blood gas analyses were unremarkable. Blood tests showed decreased hemoglobin (93 g/L) and increased D-dimer (1380 µg/L). One tumor index, carcinoembryonic antigen, was increased mildly (10.02 g/mL). Fecal occult blood test result was positive.

Imaging examinations

Abdominal contrast-enhanced computed tomography (CT) revealed thickened walls of the lower part of the rectum and distal bowel obstruction. Brain CT findings were
cerebellum, cranial nerve nucleus, red nucleus, caudate nucleus, cerebral cortex, and other atypical areas. We report a female patient with atypical lesions involving the vermis and cerebellar hemispheres. She was given thiamine therapy and became conscious after the treatment.

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unremarkable. Chest CT revealed a pleural effusion on the left. Brain magnetic resonance imaging (MRI) showed extensive abnormal signal lesions not only in the periaqueductal region but also in the cerebellum. Specifically, lesions were located in the bilateral thalamus, the periventricular regions of the third ventricle, the corpora quadrigemina, the vermis, and the cerebellar hemispheres (Figure 1), with increased signal intensity on T1-weighted imaging, T2-weighted imaging, and diffusion weighted imaging (DWI).

**FINAL DIAGNOSIS**

At first, the radiologists indicated that the periaqueductal lesions suggested Wernicke's encephalopathy and that the cerebellar lesions suggested acute infarction. After combining the clinical manifestations and a literature review, all these abnormal signal intensity lesions were considered Wernicke's encephalopathy lesions. First, the lesions in the cerebellum involved both the vermis and the bilateral cerebellar hemispheres, which were basically symmetrical and did not match the distribution of blood vessels. Second, a few papers indeed reported the involvement of the cerebellar hemispheres in Wernicke's encephalopathy.

**TREATMENT**

The above examinations also showed gastrointestinal bleeding. The patient was highly suspected of having rectal cancer. She was given gastrointestinal decompression and intravenous nutrition. She was immediately given 200 mg vitamin B1 thrice a day intravenously.

**OUTCOME AND FOLLOW-UP**

Four hours after the injection, the patient became sober. She complained of dizziness and weakness. Physical examination showed nystagmus and bilateral limb ataxia. On the 7th day after administering vitamin B1, the patient underwent colonoscopy, which indicated a rectal tumor. Biopsy pathology confirmed a moderately differentiated adenocarcinoma. Finally, she refused surgical assessment and was discharged on the 14th day after hospitalization with a modified Rankin scale score of 1.

**DISCUSSION**

Wernicke's encephalopathy is an encephalopathy caused by vitamin B1 (thiamine) deficiency first discovered by Carl Wernicke in 1881. It is more commonly observed as a metabolic encephalopathy caused by chronic alcoholism, long-term heavy alcohol abuse, and thiamine deficiency. Alcoholism accounts for about 50% of causes of Wernicke's encephalopathy[3]. The causes of thiamine deficiency include vomiting in pregnancy, malnutrition, anorexia nervosa, liver disease, total gastrectomy, jejunectomy, gastric cancer, malignant tumors, pernicious anemia, chronic diarrhea, long-term renal dialysis, parenteral nutrition deficiency, etc. Animal experiments have shown that chronic alcoholism can lead to malnutrition, mainly thiamine deficiency, which can then aggravate the chronic alcoholism[4,5]. It has been reported that the proportion of patients with nonethanol poisoning is 39% to 50%[1]. Hyperemesis during pregnancy, acute pancreatitis, and temporary fasting are more common after total parenteral nutrition. Supplementing vitamin B1 as early as possible is the key to the treatment of this disease. Patients diagnosed and treated in time can fully recover.

The classic triad of mental impairment, ataxia, and ocular symptoms occurs in only 8% of patients[6], while some only show one or two of the triad. In addition to these typical clinical manifestations, Wernicke's encephalopathy may also be characterized by many atypical symptoms or signs, leading to clinical misdiagnosis. According to various reports, these atypical manifestations include stupor, hypotension, tachycardia, hyperthermia, seizures, hearing disorders, fever, and spastic paralysis[7]. In our case, recurrent vomiting and subsequent ileus decreased the absorption of nutrients. Finally, the patient appeared unconscious due to a long-term lack of
Nie T et al. Wernicke’s encephalopathy with atypical radiological features

Figure 1 Diffusion-weighted imaging. A-E: Axial diffusion-weighted imaging showing bilateral and symmetric high signals at the level of the periventricular regions of the third ventricle, medial portion of bilateral thalamus, corpora quadrigemina (A and B), vermis, (C) and cerebellar hemispheres (D and E); F: Sagittal T2-weighted imaging lesions.

Patients with Wernicke’s encephalopathy can have pathological lesions in multiple locations, such as the mammillary bodies, brain stem, periventricular regions of the third ventricle, thalamus, hypothalamus, vermis, and vestibule nuclei. Studies suggest that CT is not reliable in the diagnosis of Wernicke’s encephalopathy\[^2\]. In the acute stage of Wernicke’s encephalopathy, head CT is negative. MRI is the preferred routine imaging method for diagnosis. It has been reported that its sensitivity is 53%, specificity is 93%, and positive predictive value is 89%\[^8,9\]. MRI is currently considered to be the most valuable method for diagnosis. On MRI, the lesions are consistent with the pathological features of the disease, showing long T1 signals, long T2 signals, high fluid-attenuated inversion recovery signals, and high DWI signals in the acute phase. The most sensitive diagnostic modality for Wernicke’s encephalopathy is DWI. Sometimes the signal changes in the other phases are not obvious. Typically, the lesions are distributed symmetrically in the thalamus, mammillary bodies, corpora quadrigemina, and periaqueductal areas. Lesions can also be found atypically in the cerebellum, cranial nerve nucleus, red nucleus, caudate nucleus, cerebral cortex, and other atypical areas. Atypical findings are found more frequently in nonalcoholic patients\[^10\]. Cerebellum involvement on imaging is rare, but autopsy studies have demonstrated that the anterior-superior vermis or anterior hemisphere is affected in more than half of patients with Wernicke’s encephalopathy. The involvement of atypical sites is usually seen in association with the involvement of typical sites and is thought to indicate progression of the disease\[^1\]. Lesions may persist or disappear after treatment.

In our case, there were lesions in the vermis and cerebellar hemispheres in addition to typical imaging changes around the aqueduct. It is extremely rare in the published papers\[^11\]. Wernicke’s encephalopathy is an emergent event in the neurology department. Nonalcoholic Wernicke’s encephalopathy is easily misdiagnosed. Once a diagnosis is suspected, it is advised that vitamin B1 should be administered immediately. The guidelines recommend administration of 200 mg vitamin B1 three times daily, preferably intravenously instead of intramuscularly\[^6\]. It is generally considered that adverse reactions to vitamin B1 are very rare. The effect of vitamin B1 may also partly or completely reverse the damage to nervous tissue\[^12\]. However,
delayed diagnosis and treatment can lead to progression of the disease. Ultimately, the patient may develop Korsakov's syndrome and even die. The treatment course of vitamin B1 use is not clear. Our patient’s symptoms improved dramatically after supplementation with vitamin B1, potentially confirming her condition as Wernicke’s encephalopathy.

**CONCLUSION**

Our case illustrates that Wernicke's encephalopathy may have various imaging manifestations. It can cause not only structural lesions around the aqueduct but also large-area limited signals on DWI in the cerebellum. It is difficult to diagnose early, especially in patients with atypical syndromes and imaging changes. Careful recording of medical features and analysis of imaging changes are necessary. Clinicians should keep in mind that patients who have difficulty eating due to recurrent vomiting are at high risk of Wernicke’s encephalopathy due to malnutrition.

**REFERENCES**


Total hip revision with custom-made spacer and prosthesis: A case report

Yang-Bo Liu, Hao Pan, Li Chen, Hao-Nan Ye, Cong-Cong Wu, Peng Wu, Lei Chen

Abstract

BACKGROUND
Both periprosthetic joint infections (PJIs) and severe femoral segmental defects are catastrophic complications of total hip arthroplasty (THA), and both present a significant challenge in revisional surgery. There are limited data available to guide clinical decision making when both occur concurrently.

CASE SUMMARY
A 61-year-old woman presented with a 6-mo history of a sinus tract at the site of her original THA incision. Radiological imaging revealed a total hip joint implant with an ipsilateral segmental femoral defect. Based on histological, radiological, laboratory, and clinical features, a diagnosis of concurrent chronic PJI and segmental femoral defect (Type IIIB, Paprosky classification) was made. After multidisciplinary team discussion, three-dimensional (3D)-printed, custom-made antibiotic spacers were created that could be used to mold antibiotic-loaded cement spacer. These were placed following PJI debridement in the first stage of revision surgery. After the PJI was eliminated, a 3D-printed, custom-made, femoral prosthesis was created to repair the considerable femoral defect. After 20-mo follow-up, the patient had excellent functional outcomes with a near-normal range of hip movement. So far, neither evidence of recurrent infection nor loosening of the prosthesis has been observed.

CONCLUSION
We describe a case of “two-stage, custom-made” total hip revision to treat PJI with a concurrent segmental femoral defect. Use of a personalized, 3D-printed...
spacer and proximal femoral prosthesis led to satisfactory hip function and no early postoperative complications. Use of a customized implant provides surgeons with an alternative option for patients where no suitable spacer or implant is available. However, the long-term function, longevity, and cost-effectiveness of the use of custom-made prostheses have yet to be fully explored.

**Key Words:** Total hip arthroplasty; Joint revision; Prosthesis-related infections; Bone loss; Bone cement; Antibiotics; Case report

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**Core Tip:** This paper reports a pioneering technique where a 3D-printed, custom-made antibiotic spacer and femoral prosthesis were used in revisional surgery for a challenging case of periprosthetic joint infection with a concurrent femoral segmental defect after total hip arthroplasty. A review of other relevant cases from the literature is presented, and the potential challenges and solutions of novel, personalized reconstructive methods are discussed.

**INTRODUCTION**

The safety and effectiveness of total hip arthroplasty (THA) have led to this being one of the most commonly performed operations worldwide, with more than 1 million hips replaced each year according to Organisation for Economic Co-operation and Development (OECD) data[1]. With the rise in the volume of primary THA performed, the total volume of revisional surgery (including complex re-revision) is projected to grow by 137% in the United States by 2030[2]. Infection and significant bone defects after THA are devastating and costly complications that are challenging to resolve. Here we present a rare case of two-stage revisional surgery for THA, in which both a 3D-printed, customized spacer and proximal femur prosthesis (PFP) were used to manage periprosthetic joint infection (PJI) with a concurrent segmental femoral defect.

**CASE PRESENTATION**

**Chief complaints**

A 61-year-old woman presented to our orthopaedic service with a 6-mo history of a non-healing ulcer and tract over the site of her original THA incision.

**History of present illness**

The patient reported low-grade fevers, particularly in the afternoons, and she had received several previous courses of antibiotics for deep infection at the wound site.

**History of past illness**

In September 2012, the patient had a severe car accident and was diagnosed with a left distal radius and ulna fracture (23r-E/4.2 and 23 μmol/L/3.1; ICD-10: S52.50 and S52.60), left acetabular fracture (62B3.1; ICD-10: S32.40), left femoral intertrochanteric and ipsilateral head fracture (31A2.3 & 31C1.3; ICD-10: S72.14 & S72.05), right-sided transverse process fracture at L1(ICD-10: S32.01), and multiple left-sided rib fractures (5-7th, 9th, 11th, ICD-10: S22.42). Internal fixation of the left proximal femoral fracture and ipsilateral femoral head fracture was performed, but later failed and she underwent total hip arthroplasty (THA) appropriately 6 mo after her initial injury. Four years after her primary THA, the patient had required a further open reduction of the replaced left hip due to another accident.
Personal and family history
No other relevant family history was reported

Physical examination
On examination, the patient had swelling over the left hip region, with mild pain on pressing the swollen area. The healed THA wound site was moist with pale secretions, and a deep leading sinus tract was identified.

Laboratory examinations
The patient’s haematological profile revealed a raised erythrocyte sedimentation rate (ESR, 74 mm/h; normal: 0-20 mm/h), and biochemistry demonstrated a raised level of C-reactive protein (CRP, 48.3 mg/L; normal: 0-8 mg/L). All other blood results were within normal limits. A swab test along the sinus tract grew an Enterococcus species on culture, which was consistent with the previous sinus tract examination.

Imaging examinations
Plain radiography of the left hip in the anteroposterior plane demonstrated a post-THA hip with a severe proximal femoral defect (Figure 1).

FINAL DIAGNOSIS
The result of histological examination of a biopsy sample and bacterial cultures from the non-healing sinus tract over the incision site scar led to a diagnosis of PJI (ICD-10: T84.52), corroborated by the serum biochemistry results[3]. The femoral defect was classified using the Paprosky system as Type IIIB, and the acetabular defect as Type IIC.

TREATMENT
Two-stage total hip revisional surgery was conducted using a 3D-printed, customized antibiotic-loaded cement spacer (ALCS) during the first stage and a personalized proximal femur prosthesis (PFP) for the second stage. Postoperatively, intravenous vancomycin was administered twice daily at a dose of 15 mg/kg for the first 7 postoperative days, followed by oral moxifloxacin (400 mg every 24 h) for a further 2 wk as recommended by the DISA (Infectious Diseases Society of America) guidelines [4].

OUTCOME AND FOLLOW-UP
Postoperative inflammatory markers, including ESR and CRP, were monitored weekly for 8 wk, revealing the return to the normal range within 4 wk. The patient was kept non-weight bearing for 6 wk from the day of surgery, and then was allowed to partially weight bear for the following 6 wk before full weight bearing at 12 wk after surgery onwards. At her last follow-up (20 mo after surgery), she was asymptomatic and had significant functional improvement of her left hip with a Harris Hip Score of 91. Radiographs demonstrated no signs of implant loosening (Figure 2), and her serum markers were within normal limits.

DISCUSSION
This report describes a challenging case of chronic PJI with a concomitant segmental femoral defect, which were managed by a two-stage revisional procedure using custom-made, 3-D printed ALCS and PFP, respectively. There were several key learning points throughout the treatment pathway that will be beneficial for surgeons faced with this challenge in the future.

Custom-made antibiotic-loaded cement spacer
Prefabricated antibiotic-loaded interval spacers are available in various configurations. However, certain cases with complex anatomy and pathoaetiology warrant custom-
made spacers. In the previous literature, both standard and customized spacers have similar infection clearance rates, and each has their own merits based on the clinical circumstances\[5,6\]. In this case, the treating surgeon attempted to manually transform an “off-the-shelf” spacer to fix the anatomy\[7\], but the reformed spacers were inadequate. Therefore, customized spacer molds were designed using computed tomography (CT) and three-dimension (3D) model data (Figure 3A and B). The molds were divided into two blocks, which could be accurately aligned using complementary locating bars and holes. Several discharge channels were included to allow space for excess cement to be removed (Figure 3C and D). The custom-made ALCS (Figure 4A and B) replaced the infected prosthesis to create a near anatomical left hip joint (Figure 5A). The patient was so satisfied with the first-stage revision that she consistently refused her scheduled 2nd-stage until a second fall occurred 6 mo after the first-stage surgery (Figure 5B).

A binding bundle of Kirschner wires surrounded by several single wires was settled to strengthen the positioning of the ALCS. This remained functional in the patient's body for nearly 6 mo (2 to 3 times longer than expected).
In our experience, the advantages of custom-made spacers included retention of limb length and lateral offset, both of which made it easier to perform further revisional surgery[8]. Moreover, custom-made spacers also allow the treating surgeon to control the type and dosage of antibiotics[9].

**Antimicrobial therapy**

After reviewing sensitivities of the bacterial culture, 2 g of vancomycin were combined with each pouch of PALACOS MV+G cement, which delivered a safe and effective dosage of gentamicin[10]. Because ALCS can deliver high local concentrations of antibiotics, this can enter systemic circulation and result in toxicity or other adverse reactions such as acute renal failure, hepatic failure, and bone marrow depression[11, 12]. Due to the high local concentration of vancomycin in the custom-made ALCS, the concentration of intravenous vancomycin administered postoperatively was down-titrated to ensure safe levels of delivery. The patient’s serum vancomycin concentration after surgery has been maintained above twice the minimal inhibitory concentration as recommended by Whiteside et al[13].

**Custom-made, 3D-printed prosthesis**

Reports to date of the operative management of severe proximal femoral osteopenia (classified as Paprosky types IIIb and IV) have included impaction grafting[14], allograft prosthesis composite (APC)[15,16], and prosthetic implants (i.e., modular mega-prostheses)[17]. Each of these methods has unique advantages and limitations [17-19]. Standard modular prostheses are an available option for proximal femoral reconstruction in many cases and have been developed to be broadly applicable across
several patient groups and fracture morphologies. Where standard prosthetic implantation is feasible, the estimated 5-year survival rate is encouraging at approximately 90.7%\cite{20}. However, for some cases, custom-made prosthesis is needed to facilitate reconstruction (Table 1)\cite{21-26}.

To reconstruct this large, atypical segmental femoral bone deficiency, a custom-made PFP was designed and manufactured by a qualified medical implant provider (Beijing Chunlizhengda Medical Instruments Corporation, Beijing, China) (Figure 6A). To adjust the lower limb length to fit the uneven proximal cortical bone, three accessory ring blocks of different height (5 mm, 10 mm, and 15 mm) were made available. The 10 mm block was chosen intraoperatively to neutralize any shortening of the femur. The postoperative radiographs showed excellent resolution of the proximal femoral defect with the custom-made prosthesis. The patient regained a

Figure 5 Radiographs of the pelvis taken the day after the first-stage revision (anteroposterior plane) (A) and the left hip taken 6 mo after the first-stage revision (B). The spacer stem was bent (anteroposterior plane).

Figure 6 The custom-made prosthesis with porous design, and full lower limb radiographs taken the day after the second-stage revision. A: The custom-made prosthesis with porous design; B: Anteroposterior plane; C: Lateral plane.
Table 1 Literature review of custom-made femoral implants related total hip arthroplasty (with or without infection)

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of patients</th>
<th>Patient age (yr)</th>
<th>Follow-up (yr)</th>
<th>PJI</th>
<th>Type of femoral defect</th>
<th>Clinical outcome</th>
<th>Complications</th>
<th>Custom method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al</td>
<td>1 in 9</td>
<td>60</td>
<td>3.3</td>
<td>Chronic (for 50 yr)</td>
<td>Girdlestone resection</td>
<td>No recurrence of infection; walk unaided</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hsieh et al</td>
<td>9 in 24</td>
<td>59 (average)</td>
<td>4.2 (average)</td>
<td>All chronic</td>
<td>Type-III: 6 case</td>
<td>Type-I: 3 case</td>
<td>No recurrence of infection</td>
<td>2 fractures &amp; 1 dislocation</td>
</tr>
<tr>
<td>Westerman et al</td>
<td>1</td>
<td>14</td>
<td>0.8</td>
<td>No infection</td>
<td>III-B²</td>
<td>Symptom free</td>
<td>-</td>
<td>CT reconstruction</td>
</tr>
<tr>
<td>Wang et al</td>
<td>1</td>
<td>73</td>
<td>2</td>
<td>No infection</td>
<td>III-B²</td>
<td>Symptom free</td>
<td>-</td>
<td>3D printed titanium sleeve-prosthetic with allografts</td>
</tr>
<tr>
<td>Kamath et al</td>
<td>1</td>
<td>68</td>
<td>1.5</td>
<td>Chronic for both knee and hip</td>
<td>IV²</td>
<td>Hip disarticulation</td>
<td>TKA incision breakdown for infection</td>
<td>Mating of a PROSTALAC spacer with an intramedullary nail</td>
</tr>
<tr>
<td>Angelini et al</td>
<td>1 in 41</td>
<td>66</td>
<td>1.5</td>
<td>L3-mo after the first surgery</td>
<td>III-B²</td>
<td>Healed</td>
<td>Deep infection</td>
<td>3D-printed prosthetic implant</td>
</tr>
</tbody>
</table>

¹Classified according to the system proposed by the American Academy of Orthopaedic Surgeons.
²Classified according to Paprosky classification. PJI: Periprosthetic joint infection.

near-anatomical hip joint with significant symptomatic improvement after years of discomfort and loss of function (Figure 6B and C).

CONCLUSION

In this case report, we have demonstrated the safety, feasibility, and effectiveness of two-stage revisional surgery for chronic PFI with a concurrent segmental femoral defect using a 3D-printed customized ALCS (first-stage) and a custom-made PFP (second-stage). We propose that the advantages of the custom-made ALCS are retention leg length and lateral offset, facilitating second stage revision, a robust fixation, and a low risk of dislocation or breakage. The apparent advantage of the custom-made PFP is near-perfect anatomical reconstruction of the affected hip with maximal preservation of bone tissue. Although manufacturing custom-made spacers and femoral prostheses is expensive and time-consuming, it presents a useful alternative when there is no suitable standard implant.

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