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ABOUT COVER

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REVIEW

Current status of surgical treatment of colorectal liver metastases

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Abstract

Liver metastasis (LM) is one of the major causes of death in patients with colorectal cancer (CRC). Approximately 60% of CRC patients develop LM during the course of their illness. About 85% of these patients have unresectable disease at the time of presentation. Surgical resection is currently the only curative treatment for patients with colorectal LM (CRLM). In recent years, with the help of modern multimodality therapy including systemic chemotherapy, radiation therapy, and surgery, the outcomes of CRLM treatment have significantly improved. This article summarizes the current status of surgical treatment of CRLM including evaluation of resectability, treatment for resectable LM, conversion therapy and liver transplantation for unresectable cases, liver resection for recurrent CRLM and elderly patients, and surgery for concomitant hepatic and extra-hepatic metastatic disease (EHMD). We believe that with the help of modern multimodality therapy, an aggressive oncosurgical approach should be implemented as it has the possibility of achieving a cure, even when EHMD is present in patients with CRLM.

Key words: Colorectal cancer; Neoadjuvant therapy; Liver metastasis; Liver; Surgery; Liver transplantation; Hepatectomy; Laparoscopy

Core tip: Surgical resection has become the standard curative treatment for patients with resectable colorectal liver metastases (CRLM). In recent years, with the help of modern multimodality therapy, the outcomes

of surgical treatment have significantly improved. The current study summarizes the current status of surgical treatment of CRLM, including evaluation of resectability, treatment for resectable liver metastases, conversion therapy and liver transplantation for unresectable cases, liver resection for recurrent CRLM and elderly patients, and surgery for concomitant hepatic and extra-hepatic metastatic disease.

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INTRODUCTION

Colorectal cancer (CRC) is a major health burden with a worldwide estimate of 1.4 million new cases annually, resulting in approximately 694000 deaths[1]. The liver is the most common metastatic target organ for CRC. It has been estimated that as many as 25% of patients with CRC have synchronous liver metastases (LM), and about 60% of patients are found with metachronous LM on follow-up examinations[2,3]. LM is one of the major causes of death in patients with CRC[4].

Surgery for colorectal LM (CRLM) is increasingly being used as a part of multimodality treatment as it considerably improves the overall survival (OS)[5]. Unfortunately, only about 20% of CRLM patients have resectable cancer[6]. With the advent of highly effective chemotherapy and medical management, and advances in the surgical techniques of liver resection (LR), the pool of resectable patients with CRLM has expanded; metastatic lesions that were previously deemed terminal or nonsurgical are now being considered for surgical resection. According to recent reports, the 5-year survival of CRLM patients receiving surgery and neoadjuvant therapy has increased to up to 50%[7]. However, more than 70% of patients with CRLM after LR develop recurrence in the remnant liver[7,8]. Therefore, surgical resection for resectable CRLM is still a controversial and evolving topic within the realm of surgical oncology. This article aims to summarize the current status of surgical treatment of CRLM.

EVALUATION OF RESECTABILITY OF LM

Definition of resectability of CRLM

Resectable CRLM has no definite definition, and the criteria for "resectable" disease have evolved with the development of newer surgical techniques and technology. The traditional resectable criteria of CRLM first proposed by Ekberg *et al*[9] in 1986 included fewer than four intrahepatic metastatic lesions, no extrahepatic metastatic disease (EHMD), and being able to achieve a resection margin (RM) of at least 1 cm. With the recent development of surgical techniques, including liver three-dimensional reconstruction imaging technology, portal vein embolization (PVE), and associated liver partition and portal venous ligation (PVL) for staged hepatectomy (ALPPS), indications of LR for metastatic lesions have gradually widened, although they still vary among different centers. In 2014, van Dam *et al*[10] have expanded the historical CRLM resection criteria to include patients with four or more LM that could be present in both the lobes, patients with centrally located tumors, and those with resectable extrahepatic disease. Patients with the extended indications have shown more major complications (33.1% *vs* 19.5%) as well as a shorter OS (41.4 mo *vs* 68.8 mo) and median disease-free survival (DFS) (10.2 mo *vs* 22.0 mo) compared with the traditional indication group. The 10-year DFS rates (cure rates) were 15.8% in the extended indication group and 35.5% in the traditional indication group because fewer patients with extended indications underwent R0 resection compared with patients with limited indications (77.5% *vs* 92.9%)[10]. In 2015, a study conducted by Viganò *et al*[11] showed that hepatectomy was also safe in selected patients with eight or more LM, although these patients had a shorter 5-year OS (20.1% *vs* 44.2%) and recurrence-free survival (13.6% *vs* 28.7%) compared with patients with fewer than eight LM. It was gratifying to see that patients with eight or more LM, who had no risk factors including extrahepatic disease, no response to chemotherapy, and primary rectal cancer, had a similar 5-year OS to patients with fewer than eight LM (44% *vs* 44.2%)[11]. In 2017, Allard *et al*[12] evaluated the long-term outcomes after liver surgery for patients with 10 or more LM. The results showed that the 5-year OS of these patients was 30%. Patients who underwent a macroscopically complete (R0/R1) resection had 3- and 5-year OS rates of 61% and 39%, respectively, compared to 29% and 5% for patients with R2/no resection ($P < 0.0001$)[12]. Therefore, the number and even the size of LM lesions are no longer contraindications of resection, as long as all visible lesions can be resected with a tumor-free margin and sufficient remnant liver. The current criteria for resectability of CRLM are as follows: any tumor number, any tumor distribution in the liver, stable or resectable EHMD (excluding portal lymphadenopathy), functional liver remnant > 20% of the total liver volume, venous involvement amenable to venous resection or reconstruction, and a tumor-free margin[5]. We have summarized the current recommended criteria in comparison to traditional resectability criteria for CRLM in Table 1.

However, the criteria of resectability may vary even amongst the most experienced hepatic surgeons due to their different surgical experiences and techniques. We suggest that the determination of CRLM resectability should be based on oncological principles and technical

Table 1 Resectability criteria for colorectal liver metastases

Item	Traditional criteria	Current criteria
EHMD	No EHMD	Stable or resectable EHMD (excluding portal lymphadenopathy)
LM number	Fewer than 4 lesions	No limit
LM distribution	Unilateral	No limit
Vascular invasion	No involvement	Amenable to venous resection or reconstruction
Resection margin width	More than 1 cm	Beyond 1 mm with a tumor-free margin
% of FLR of total liver volume	> 20%	> 20% for normal liver and slight chemotherapy-associated liver dysfunction; > 30%–40% for severe chemotherapy-associated liver disease

EHMD: Extra-hepatic metastatic disease; LM: Liver metastases; FLR: Future liver remnant.

feasibility as outlined in the Hepato-Pancreato-Biliary Expert Consensus Statement 2012[13]. If the patients have favorable factors such as maximal tumor size < 40mm, age < 60 years, preoperative imaging using magnetic resonance imaging (MRI) and adjuvant chemotherapy, and the surgeons are confident to obtain a negative margin resection (R0) and sufficient remnant liver, the indication can be extended. If the patients have adverse prognostic factors associated with a very poor survival, such as no response to chemotherapy or unstable or unresectable extrahepatic disease, surgery may not be beneficial and the indications should be limited.

Imaging modalities

Sensitivity in detection of intrahepatic and extrahepatic metastases: The imaging methods useful for evaluating LM include trans-abdominal ultrasound (US), contrast-enhanced computed tomography (CT), contrast-enhanced MRI, and positron emission tomography (PET). Although US is a primitive preoperative imaging modality, US along with contrast-enhanced US (CEUS) has been widely used for detecting LM in clinical practice[14]. Nevertheless, CEUS has the advantages of real-time observation and shows a high specificity for characterizing focal liver lesions, comparable to CT and MRI[15].

A meta-analysis has shown that the sensitivities of CT, MRI, and PET/CT for the diagnosis of CRLM are 82.1%, 93.1%, and 74.1%, respectively; while the specificities are 73.5%, 87.3%, and 93.9%, respectively[16]. A review of the literature indicates that MRI, especially gadoxetate disodium (Gd)-enhanced MRI, is more sensitive than CT for detecting a liver lesion of less than 1 cm, particularly 5 mm[17]. From a cost-effectiveness point of view, contrast-enhanced MRI can be cost-effective, provided that it replaces contrast-enhanced CT and has an improved diagnostic accuracy[18]. However, neoadjuvant chemotherapy significantly decreases the sensitivity of CT and MRI[16]. Gd-enhanced and diffusion-weighted MRI in combination with contrast-enhanced ^{18}F-fluorodeoxyglucose PET/CT will allow confident detection of LM, which disappear on post-neoadjuvant chemotherapy contrast-enhanced CT[19]. In clinical practice, despite having limited sensitivity, CT appears to be adequate for determining the resectability of CRLM for the majority of patients.

The sensitivity and specificity of PET/CT for the detection of LM are similar to those of CT[20]. Most recent studies recommend PET/CT for the detection of occult distant metastases[21,22]. It can detect 25% of extrahepatic lesions and avoid worthless surgery in approximately 20% of patients[23]. Therefore, PET/CT can significantly contribute to the staging of patients with CRLM[23,24]. PET/CT staging is associated with a significantly improved actual long-term survival, thus providing valuable prognostic information that can guide surgical and oncological treatments[24]. However, in a randomized controlled trial, the use of PET/CT did not significantly affect the surgical management, compared with CT alone[25]. These findings raise concerns about the role of PET/CT in this setting. In spite of conflicting results, PET-CT may be useful for the detection of extrahepatic disease, particularly in patients with recurrent disease or a high tumor load (multinodular and/or large metastases) or for whom difficult hepatic resections are planned[26].

Preoperative anatomical localization: CT, MRI, and PET/CT are the mainstay methods used to assess the resectability of liver lesions. Of them, CT is the most common modality for the initial diagnosis of CRLM and is usually adequate for treatment planning. Staging of a patient with CRC includes a CT scan of the chest, abdomen, and pelvis to evaluate for metastatic disease, as the majority of metastases are clinically silent. The currently established standard for planning liver surgery is contrast-enhanced CT, which as a rule enables appropriate resection planning, *e.g.,* a precise identification and localization of primary and secondary liver tumors as well as the anatomical relationship to extrahepatic and/or intrahepatic vascular and biliary structures.

Intraoperative detection: Intraoperative US (IOUS) with and without contrast enhancement is recommended as a screening modality for detecting additional LM not seen on routine preoperative imaging. The use of IOUS and contrast-enhanced IOUS (CE-IOUS) improves decision-making by providing the most sensitive form of liver staging. The results of a study conducted by Arita *et al*[27] showed that during surgery, 25 additional

nodules were newly identified using IOUS, among which 21 patients had histologically proven CRLM. Twenty-two additional nodules were newly identified using CE-IOUS, among which 17 nodules in 16 patients were histologically diagnosed as CRLM. The planned surgical procedure was modified based on the IOUS and CE-IOUS findings in 12 and 14 patients, respectively[27]. Laparoscopic US combined with laparoscopic real-time near-infrared fluorescence imaging can enhance the sensitivity of detection[28]. This may be particularly important in the era of laparoscopic resections, in which surgeons lose the opportunity to palpate the liver.

Evaluation of the future liver remnant

Post-hepatectomy liver failure (PHLF) is a significant cause of morbidity and mortality. Independent predictors of PHLF can be categorized into three main categories: Patient-related, liver-related, and surgery-related factors[29]. The most crucial patient-related factors affecting the outcome of LR are the volume and function of the FLR. Therefore, preoperative evaluation of the FLR volume and estimation of the functional capacity of the liver should be performed before major LR in patients with a normal liver. Moreover, this evaluation should be conducted even when performing minor LRs in patients with diseased livers.

Several studies have reported on the impact of FLR volumetric analysis on the outcomes of LR[30,31]. Generally speaking, the FLR size should be at least 20% for patients with normal livers and those who have received chemotherapy for no more than 12 wk[32]; however, considering that there is significant chemotherapy-associated steatohepatitis or sinusoidal obstruction in those receiving preoperative chemotherapy for more than a 12-wk duration or more than eight cycles, this cut-off value should be increased to 30%–40% in order to avoid postoperative liver failure[32,33]. The reason for this increase is that the risks of major complications, liver failure, and mortality increase to 47%, 20%, and 13%, respectively, if the FLR is < 20% of the total volume[34]. Preoperative evaluation of the FLR by virtual segmental volumetry using three-dimensional CT has been found to be superior to that estimated using standard equations[30,31,35].

Liver function can be assessed by biochemical tests, the indocyanine green (ICG) clearance test, and ^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS). The ICG clearance test is primarily used to assess the hepatic function in patients with primary liver cancer and drug-induced liver injury with good accuracy[36-38]. However, its accuracy to predict the extent of chemotherapy-associated liver injury is not good. A study by Wakiya *et al*[38] has found that the preoperative ICG retention rate at 15 min (ICGR15) did not strongly correlate with the pathological sinusoidal injury and steatohepatitis scores in CRLM patients. The sensitivity and specificity of the ICG test for detecting pathological liver injury were 47% and 75%, respectively[33]. In order to perform a safe radical LR, it is necessary to estimate the hepatic functional reserve of the chemotherapy-associated liver based on a combination of several clinical indicators and not only rely on the ICG test. ^{99m}Tc-mebrofenin HBS is an effective method for determining liver function and can also provide information about the function of the segmental liver tissue; in addition, it has a good correlation with the ICGR15[39]. Moreover, it is a validated tool to assess the total and remnant liver function[40]. However, this method is not practical in clinical practice and has not been widely used.

In general, assessment of the FLR function should be conducted by combining the Child-Pugh score, FLR volume, and ICGR15 test results.

TREATMENT OF RESECTABLE CRLM

Timing of treatment in patients with synchronous CRLM

Optimal surgical management of patients with synchronous CRLM is still controversial. There are three main types of surgical strategies for synchronous CRLM patients[41]. The first type involves removal of the primary colorectal tumor, followed by chemotherapy and about 3–6 mo later with resection of LM as the final step (classic or bowel-first). The second type is synchronous resection of the primary tumor and LM in the same surgical procedure (combined). The third approach, commonly termed as the reverse or liver-first approach, involves LM resection as the first step, followed by chemo(radio)therapy, and removal of the primary tumor as the last step. The classical approach and the liver-first approach are both two-stage surgical procedures. In 2018, data from 1830 patients who lived in the United Kingdom showed that the percentages of patients who underwent the classical approach, the simultaneous approach, and the liver-first approach were 71.1%, 14.8%, and 14.2%, respectively[42].

The main advantages of the classical approach are avoidance of bowel-related complications (large bowel obstruction, bleeding, perforation, *etc.*) from the primary tumor and prevention of disease progression from the primary lesion. On the other hand, the main advantages of the liver-first approach are that it is possible to treat the metastatic disease before the resectable CRLM become unresectable and, as the liver is not exposed to chemoradiation, less FLR is required and fewer liver-related postoperative complications are caused. Hence, at most centers, the patients treated by the liver-first approach have more and larger LM compared to patients planned for the classical approach, and the primary tumor has no obvious obstruction, bleeding, or asymptomatic evidence[43,44]. A study of 623 patients with synchronous CRLM, of which 377 were treated by the classical approach and 246 by the liver-first approach, revealed that patients chosen for the classical approach more often had T4 primary tumors (23% *vs* 14%) and node-positive disease (70% *vs* 61%). The liver-first approach group had a higher

liver tumor burden score (4.1 *vs* 3.6). Yet, no difference was seen in the 5-year OS between the two groups (54% *vs* 49%)[45].

However, these staged surgical treatments have some shortcomings. First, patients need a second surgery, thereby increasing the length of hospital stay and health care costs[46]. Second, the median time from the first to the second operation varies between 4.7–7 mo for patients treated using the classical approach and 2–9 mo for patients treated using the liver-first approach[45,47]. Another problem is that 16.3%–35% of liver-first and bowel-first patients fail to proceed to the second operation due to postoperative complications or disease progression[43,47]. The advocates of staged surgical treatment suggest that the progression of LM or the primary tumor after the first operation is characteristic of aggressive tumor biology; therefore, allowing a period of time to see if there is progression avoids performing extensive resections in those who will not benefit[48,49].

With improvements in LR techniques, the proportion of patients undergoing either a liver-first approach or a simultaneous approach has increased in recent years, from 26.8% in 2010 to 35.6% in 2015[42]. Several studies have demonstrated that simultaneous resection can be safely performed in appropriately selected patients[50-52]. A study of 1430 patients with synchronous CRLM has revealed that the combined procedure is equally safe compared to the staged procedure in patients undergoing complex operations, and it should be considered as the first strategy due to its advantages of reduced readmission within 30 d, faster recovery, shorter hospital stay, decreased hospital cost, and same rates of major events or anastomotic leak[51]. A study conducted by Silberhumer's team also validated that there was no significant difference in the OS and DFS between the simultaneously resected and staged-resected patients, with 1-year survival rates of 90.5% and 92.6%, respectively, and 5-year survival rates of 38.5% and 38.9%, respectively[50]. However, Nanji *et al*[53] have argued that a selection bias resulted in better outcomes favoring the simultaneous approach because patients who underwent the simultaneous approach had fewer and smaller liver lesions and received less invasive resections. A meta-analysis and review recommended the following criteria to select patients for a simultaneous resection: Age < 70 years, LR of no more than three segments, colonic resection (especially a right-sided colectomy), and exclusion of coexisting severe conditions[54]. In short, simultaneous resection can be the recommended surgical approach in appropriately selected patients as it offers benefits to both the patients and the healthcare system.

Neoadjuvant chemotherapy (neoCTx) can control systemic disease, eliminate micro-metastatic disease, and even downsize metastatic liver lesions and the primary tumor. A study of 62 patients who underwent neoCTx, despite having resectable disease, found that 5 patients had progressive disease, 22 had stable disease, and 35 had partial response according to the RECIST criteria[55]. Among the patients with partial response, 29 had histopathologic downstaging[55]. Although its use remains controversial, several groups have found a positive survival benefit in synchronous CRLM patients with neoCTx[55]. A propensity score matching analysis of 149 patients showed that the 3-year DFS rate was significantly higher in patients with neoCTx than in those without (34.2% *vs* 16.8%, respectively)[56]. Furthermore, patients with partial response to neoCTx had better survival rates than those with stable or progressive disease[55]. Analysis of a single-institution prospective database including 1211 patients showed that the actual 10-year survival rate after resection of CRLM was 24%, with a 20% cure rate[57]. The authors suggested that preoperative strategies such as neoCTx would improve the actual 10-year survival and cure rates of patients with both a high clinical risk score and extrahepatic disease[57]. However, a two-center study over a 22-year period showed that neither the OS nor recurrence rates were improved using neoCTx in patients with solitary CRLM who underwent curative LR[58]. NeoCTx seems to be more beneficial for resectable patients with risk factors associated with an unfavorable prognosis.

Neoadjuvant bevacizumab-based chemotherapy has been found to be associated with a better OS in patients who underwent LR of synchronous CRLM, especially in patients treated by the classical approach[59]. However, the new EPOC randomized controlled trial for resectable CRLM showed that the progression-free survival was significantly shorter in the chemotherapy plus cetuximab group than in the chemotherapy alone group (14.1 mo *vs* 20.5 mo)[60]. Therefore, it is still unclear whether targeted therapy with cetuximab or bevacizumab should be offered with chemotherapy in the preoperative setting for resectable patients.

In summary, there are no significant differences in the outcomes between these three approaches in patients with synchronous CRLM[42]. The current evidence is insufficient to decide upon the optimal strategy for a given patient with synchronous CRLM. The timing of the resection and the type of surgical approach should be based on the patient characteristics and the protocols followed by individual centers. Individualized treatment should be offered by a multidisciplinary team after discussing the risks and benefits of each approach with the patient. We prefer concurrent surgery for eligible patients. Otherwise, we choose the classical approach or the liver-first approach based on the severity of the primary tumor and LM. In patients treated with neoCTx, there are chances of chemotherapy-related liver injury after receiving chemotherapeutic drugs. Hence, LR should be scheduled at 4–6 wk after the last day of conventional chemotherapy or 7–8 wk after the last day of bevacizumab-based chemotherapy[55,59].

RM

There are several factors affecting the prognosis after curative hepatectomy for CRLM, which include RM, size, number and location of LM, synchronous LM, stage of the primary colorectal tumor, peritoneal dissemination and so on[61,62]. Among these factors, only the RM is under the surgeon's direct control and can be modified to achieve optimal outcomes. To date, there is no consensus on the universal definition of a "positive" RM for CRLM. A positive RM is one of the risk factors for intrahepatic recurrence after curative resection of LM and is independently associated with the OS[63]. The results of a study on 2368 CRLM patients showed that all margin widths, including submillimeter margins, correlated with a prolonged OS, compared with an R1 resection, and that a tumor-free RM width > 1 cm had the longest median OS[63]. In the case of multiple LM, the R1 margin status was also associated with a worse OS among patients with a positive margin associated with the largest CRLM lesion[64]. A recent meta-analysis demonstrated that an R0 resection with a margin width > 1 cm was associated with both an improved DFS and OS, compared with an R0 resection with narrower margins, and that the RM (> 1 mm *vs* < 1 mm) was significantly associated with an improved OS at all time points[65]. These findings suggest that a LR with a negative RM should be performed whenever possible. Traditionally, a RM of at least 10 mm is considered the gold standard[66]. However, the controversy over the prognostic role of hepatic RM width continues.

Numerous studies have found that patients with subcentimeter or submillimeter margin widths do not have worse survival rates, suggesting the wider use of parenchymal-sparing hepatectomy (PSH) for CRLM in order to preserve the FLR[67-70]. In PSH, the aim is to obtain an oncologic resection with minimal tumor-free margins so as to preserve as much of the liver parenchyma as possible. Advocates of PSH argue that even a 1-mm tumor-free margin is sufficient in patients with CRLM[68]. Another systematic review reveals that the safety profile and oncologic outcomes of PSH are similar to those of anatomic LR for CRLM[70]. Hence, PSH may be considered an appropriate surgical approach in patients with CRLM.

Some researchers believe that it is tumor biology, not the surgical approach, that determines the prognosis[63,71]. The prolonged OS observed with submillimeter margins is not because the submillimeter R0 margin allows patients to survive longer; instead, submillimeter margin clearance is more likely to be achieved only when patients have good tumor biology[63]. The R0 resection rate and survival rate were higher among patients with CRLM having a fibrous capsule around the liver lesions than in those without it[72]. The KRAS mutation status also impacts the effect of the margin status on survival. A tumor-free margin provided a survival benefit to only patients with wild-type KRAS tumors, and the margin width was not found to be a prognostic factor in those with a KRAS mutant gene, in whom the OS with an R0 margin was similar to that in those with microscopically positive margins[67,71].

With the progress in modern chemotherapy, the prognostic influence of the RM status on survival has been studied but continues to remain controversial. A study of 466 CRLM patients showed that neoCTx did not influence the 5-year OS and DFS rates of the R0 group, but it had a positive influence on the R1 group[73]. Additionally, the OS and DFS rates were similar between R1 and R0 resections in patients treated with neoCTx[73]. Another research study also reported that the 5-year OS was not significantly associated with the margin status in bevacizumab-treated patients (46.8% *vs* 33% after R0 *vs* R1 resection, $P = 0.081$), in whom the 5-year survival rate was slightly worse (presumably reflecting more advanced disease) than among patients treated with cytotoxic agents alone[74]. Moreover, a prospective study of 334 patients with solitary CRLM showed that neoCTx did not influence survival, in either the entire patient group or in the subgroups with a positive or negative RM, but the patients treated with neoCTx and having a positive RM had a poorer survival than those with a negative RM[75]. The clear benefit for chemotherapy has been demonstrated in the adjuvant setting by several studies in which postoperative chemotherapy was found to be protective from recurrence regardless of the RM status[69,73,75,76]. Patients with a postoperative performance status > 2, who did not receive adjuvant chemotherapy, had a decreased progression-free survival and OS after LR for CRLM[77].

In summary, a wide RM (> 1 cm) should be attempted whenever possible. LR should not be precluded if narrower margins are anticipated in patients with multiple lesions or when resection borders are limited due to major vascular-biliary structures, since a submillimeter tumor-free margin may also improve survival.

Application of ablative techniques

Ablative techniques were initially used in patients with unresectable CRLM. In 2015, an international panel of ablation experts proposed that percutaneous ablation is suitable for patients with technically inoperable but limited liver disease and for those with limited liver reserve or co-morbidities that render them inoperable[78]. However, due to their safety, tolerability, repeatability, and less invasiveness, these techniques have been used to treat resectable CRLM patients[79]. A study of 53 resectable CRLM patients treated by LR or radiofrequency ablation (RFA) showed that the 1-, 3-, and 5-year cumulative survival rates in the RFA group were not significantly different compared to those of the LR group (85.7% *vs* 87.5%, 38.1% *vs* 53.1%, and 14.2% *vs* 31.3%, respectively), but the 1-, 3- and 5-year recurrence-free survival rates in the RFA group were significantly less than those in the LR group (76.1% *vs* 90.6%, 23.8% *vs* 56.3%, and 4.8% *vs* 28.1%,

respectively)[80]. A meta-analysis also pointed out that compared to patients treated by LR, the recurrence rate with RFA was higher than that of surgery[81]. Although the median survival time with microwave ablation and RFA in the treatment of CRLM was similar, the local recurrence rate with RFA was significantly higher than that of microwave ablation[82,83]. A study by Mulier *et al*[84] further disclosed that the local recurrence rate of open RFA was equivalent to that of LR for tumors < 3 cm; but for larger tumors, the local recurrence rate was higher.

Ablation techniques are also often used in combination with hepatectomy, and the approach is usually named as combined intra-operative ablation and resection (CARe). The use of CARe is especially suitable for patients with multiple LM. With CARe, the small lesions are ablated and the large lesions are resected, with the aim of preserving as much liver parenchyma as possible. The prognosis of patients treated with CARe has been found to be comparable to that of patients treated by LR alone[85,86]. In addition, retaining as much liver volume as possible helps to perform a salvage hepatectomy, if required, which increases the survival rate after recurrence of LM[87]. Additionally, ablation is also a suitable alternative to hepatic resection for isolated hepatic recurrence after surgery for CRLM, and it is associated with a better OS compared with systemic chemotherapy alone; therefore, ablation should be considered for patients with resectable liver recurrence who are unfit or unwilling to accept LR[88].

Aliyev *et al*[89] found that in comparison with the LR group, RFA patients have a higher American Society of Anesthesiologists (ASA) score (3.0 *vs* 2.6, respectively, $P = 0.002$), a more frequent incidence of cardiopulmonary comorbidities (60% *vs* 38%, respectively, $P = 0.045$), and tumors located deeper in the liver parenchyma (39% *vs* 12%). Although ablation seemed to be associated with a shorter progression-free survival, post-procedure morbidity was significantly lower with ablation. A meta-analysis pointed out that patients treated with RFA had a shorter hospital stay and fewer complications, compared to those treated by LR[81]. The incidence of complications with microwave ablation and RFA in the treatment of CRLM was similar[82,83].

In brief, ablation is only suitable for selected patients with LM of less than 3 cm, tumors located deep in the liver parenchyma, patients with a high ASA score, or cardiopulmonary comorbidities. Furthermore, the heat-sink effect should be taken into consideration while treating LM located near vessels as the size of the ablation zone is affected by the flow rate and the distance from the vessels[90].

Minimally invasive LR

Laparoscopic LR (LLR), characterized by "less invasiveness," is becoming increasingly popular for the treatment of primary and metastatic liver malignancies. The Oslo-Comet randomized controlled trial compared laparoscopic and open LR for CRLM and revealed that LLR was associated with a significantly lower post-operative complication rate (19% *vs* 31%, $P = 0.021$), a shorter hospital stay (56 h *vs* 96 h, $P < 0.001$), and a higher cost-efficiency; whereas there were no differences in the blood loss, operative time, resection margins, or 90-d mortality[91]. A recent meta-analysis demonstrated that a limited number (two or fewer) of metastases located in the left lateral segments are more suitable for LLR[92]. Moreover, the initial LLR for CRLM was associated with less inflammation, surgical stress, and postoperative adhesion, allowing a higher chance of repeated hepatectomies if recurrence occurred[93]. Concerning the technical difficulties and narrow operative field exposure, LLR for a major hepatectomy was adopted less frequently, but it was only attempted by a few specialized centers with a high volume of patients[94].

The da Vinci surgical system, also known as robot-assisted LR, is believed to overcome the disadvantages of a laparoscopy[95]. Robot-assisted LR is performed through a series of flexible mechanical arms, allowing more degrees of freedom, which can effectively avoid the "fulcrum effect" caused by rigid laparoscopic instruments. What's more, the robotic approach makes the surgical procedure more precise by providing three-dimensional vision and avoiding hand tremors. Therefore, robot-assisted LR can be used in narrow spaces or curved transections, and it is particularly suitable for the handling of metastases located in the posterior-superior segments[96]. Standard laparoscopy or robot-assisted LR for minor LRs can be performed with favorable perioperative and long-term outcomes. Nevertheless, the robotic approach offers more benefits for a major hepatectomy and challenging cases[97].

TREATMENT OF UNRESECTABLE CRLM

Some patients are initially considered to have unresectable CRLM due to the size, number, and location of the LM and other poor prognostic factors. However, it should be noted that the definition of unresectable CRLM is not widely recognized at this moment. In 2013, Takahashi and colleagues proposed the definition of unresectability as follows: multiple bilobar LM that require resection of more than 70% of the nontumorous liver for removal of all tumors leading to an inadequate FLR, tumors invading all three hepatic veins, tumors invading both the left and right branches of the hepatic artery or portal vein, and extrahepatic metastasis other than resectable pulmonary metastasis[98]. As previously mentioned, CRLM occupying bilateral liver lobes or an inadequate tumor-free FLR is a challenge. The metastatic disease is often considered unresectable if it is not possible to radically excise all of the lesions while preserving at least two contiguous segments with an adequate FLR volume, blood flow, and biliary

drainage[99]. Tumor shrinkage and FLR hypertrophy are the two most widely used approaches for converting unresectable CRLM to resectable disease.

With the availability of effective chemotherapy regimens and the development of innovative surgical techniques, an increasing number of patients whose disease is initially considered unresectable may find that their disease has become resectable following treatment. This process is known as conversion therapy. There are several methods to convert unresectable disease to a resectable state.

PVE or PVL

Preoperative PVE is the most widely used method for inducing atrophy of the liver segments to be resected and hypertrophy of the FLR, which can convert unresectable cancer into resectable cancer[100-103]. PVE is mainly used in patients when the preoperative FLR is < 25% of the total liver volume[103]. It takes about 4–6 wk following PVE for liver hypertrophy to occur. Recently, Xiao *et al*[100] have presented a new strategy for terminal branch portal vein embolization after six cycles of neoadjuvant therapy, which increases the FLR and causes remarkable tumor shrinkage, thus making LR feasible in 2 wk. However, there is an ongoing controversy surrounding PVE regarding the short-term safety of PVE and its long-term oncological benefit. A systematic review including 539 patients treated by PVE showed that 30% of these patients did not undergo LR, mostly due to tumor progression (84%); the median OS time in patients with PVE and non-PVE was 38.9 mo and 45.6 mo, respectively; the median DFS time was 15.7 (PVE) and 21.4 (non-PVE) mo, respectively[104]. Hence, some researchers believe that PVE should be carefully used because the usage of PVE in bilobar CRLM patients can accelerate the progression of disease in the remnant liver[105,106]. In contrast, other recent studies discovered that tumor progression after PVE has not been shown to affect the OS, and PVE followed by hepatectomy has been shown to be a safe and feasible strategy for unresectable CRLM[102,103,107]. A propensity score matched study of major LR with or without preoperative PVE showed that the PVE group and non-PVE group achieved similar 5-year OS (16% *vs* 9%, $P = 0.776$) and 3-year progression-free survival rates (14% *vs* 14%, $P = 0.866$), but it was remarkable that the PVE group had more extensive disease in terms of the number and diameter of LM and more often had synchronous disease[103].

PVL is another method to increase the FLR volume. A systematic review and meta-analysis showed that no significant differences were found in the rates of FLR hypertrophy [43.2% (PVE) *vs* 38.5% (PVL), $P = 0.39$] or in post-intervention mortality and morbidity[108]. However, the numbers of cancelled hepatic resections due to inadequate hypertrophy were significantly lower after PVL. But at the same time, PVL is more invasive than PVE because this method needs to be performed by laparoscopy or laparotomy[108].

For patients with bilobar CRLM requiring a major hepatectomy, the two-stage hepatectomy with PVE/PVL is the only curative option. In stage 1, the small metastatic lesions in FLR are resected in combination with synchronous PVL or percutaneous PVE after the operation to stimulate the growth of the FLR. Once the FLR becomes adequate, in the second stage, extensive LR is performed. This two-stage hepatectomy reduces the risk of liver failure and increases the chances of remission. Levi Sandri *et al*[109] reported their 10-year experience of two-stage hepatectomy in 46 patients with CRLM, among which 38 patients underwent PVL and the other patients underwent PVE. They observed that the long-term OS was 52 mo from the time of the first liver surgery[109]. A recent study has compared two-stage hepatectomy with one-stage major hepatectomy plus contralateral LR or ablation, and the results are encouraging. The two-stage hepatectomy group had fewer postoperative major complications (14% *vs* 26%, $P = 0.03$) and less hepatic failure (6% *vs* 20%, $P = 0.001$). Moreover, the two-stage hepatectomy group achieved a higher 5-year OS rate (35% *vs* 24%, $P = 0.016$)[48]. Although the two-stage hepatectomy approach is well established, it has been reported that almost one-third of patients fail to receive the second surgery due to tumor progression after the first surgery or an insufficient FLR[110].

Hence, how to deal with tumors in the FLR is extremely important. First, the appropriate selection of patients who are unlikely to experience tumor progression is vital, and this requires further study of tumor biology and the tumor microenvironment[104,109]. Second, multidisciplinary treatment such as neoadjuvant chemotherapy and transarterial chemoembolization should be tried to slow down the tumor progression[101]. Third, several methods including partial resection and ablation can be used to remove or destroy the tumors[48].

In conclusion, we recommend PVE as the preferred strategy to increase the FLR volume because it is a minimally invasive procedure for patients who do not need a staged LR. But in patients undergoing a two-stage hepatectomy, PVL is an ideal option because it can be performed intraoperatively and can avoid the additional cost of postoperative PVE with comparable outcomes as PVE.

ALPPS

In order to overcome the long waiting period for FLR regeneration after PVE/PVL, a new concept of LR called ALPPS, which allows rapid liver growth, was first described in 2012[111]. This procedure mainly includes two stages. In stage 1, the right portal vein is ligated with the simultaneous splitting of the liver parenchyma, usually along the falciform ligament or Cantlie's line, and resection of metastasis from the FLR. Stage 2 includes

specimen removal after several days, once the target FLR is achieved. The median time interval between the two stages of ALPPS is typically 8–11 d, which is significantly shorter than that of other methods[111-113].

A multicenter randomized controlled trial showed that the resection rate was higher in the ALPPS arm compared with the two-stage hepatectomy arm (92% *vs* 57%), with no differences in complications (Clavien-Dindo ⩾ 3a) (43% *vs* 43%), 90-d mortality (8.3% *vs* 6.1%), or R0 resection rate (77% *vs* 57%)[112]. However, a multicenter matched case–control study showed that the feasibility of ALPPS for CRLM was not significantly better than that of a two-stage hepatectomy, whereas the perioperative complications were obviously increased in the ALLPS group[113]. Another matched case–control study demonstrated that early oncologic outcomes of patients with advanced LM receiving ALPPS were not superior to the matched patients receiving systemic treatment with palliative intent[114]. A very recent meta-analysis also revealed that there was no difference in the final postoperative FLR between ALPPS and two-stage hepatectomy in patients with unresectable CRLM, but the morbidity and mortality rates were higher with ALPPS[115].

Recent studies have confirmed that ALPPS can be used as an alternative rescue procedure after unsuccessful PVE or two-stage hepatectomy; it has been shown to be safe and effective in those patients who failed to achieve FLR > 30%[112,116,117]. Rescue ALPPS can allow previously unresectable disease to become amenable to surgery. In addition, a KRAS mutation has been found to be an independent predictor of poor survival after ALPPS[118]. Therefore, although ALPPS may be a suitable approach for these patients, appropriate patient selection and proper preoperative counselling about the risks and benefits of the procedure are essential in order to achieve good outcomes. Liberal use of imaging studies and discussion with radiologists can help to obtain crucial preoperative and perioperative information, which may change the surgical plan and contribute to better oncologic outcomes[119].

Conversion chemotherapy

Chemotherapeutic and targeted biological agents can be used in unresectable cases to achieve tumor shrinkage so as to allow potentially curative resection. FOLFOX (oxaliplatin, fluorouracil, and leucovorin) and FOLFIRI (irinotecan, leucovorin, and fluorouracil) are the two standard chemotherapy regimens for unresectable CRLM. According to recent data, approximately 24%–52% of unresectable CRLM patients could be treated by conversion hepatectomy after receiving first-line systemic chemotherapy or hepatic artery infusion[120-122]. After conversion hepatectomy, these patients could achieve survival rates similar to those of patients who underwent an LR initially, with a predicted 5-year survival rate with conversion hepatectomy of 63%–76%[120-122].

The combination of FOLFOX or FOLFIRI with other drugs and targeted therapy for unresectable disease has been tested in clinical trials. Among these combined regimens, anti-epidermal growth factor receptor (EGFR) antibodies such as cetuximab and panitumumab as well as anti-vascular endothelial growth factor receptor (VGFR) monoclonal antibodies such as bevacizumab are the main components that have been proven to increase the response rate and tumor shrinkage[123-125]. The mutant-type (mt) KRAS status predisposes a patient with CRLM to a worse recurrence-free survival and OS, possibly as a result of aggressive tumor biology[126]. The KRAS mutation status remains an important predictor of response to these therapies. In patients with wild-type (wt) KRAS unresectable CRLM, the use of an anti-EGFR or anti-VGFR monoclonal antibody combined with standard chemotherapy regimens (FOLFOX or FOLFIRI) is not only preferred for the conversion to potentially curative resection, but it also improves the response rate, progression-free survival, and OS[123-125,127]. The results of a phase Ⅱ trial comparing the efficacy of panitumumab plus FOLFOX4 or FOLFIRI for unresectable wt-KRAS CRLM revealed that both the combined regimens achieved a high rate of early tumor shrinkage and offered a greater chance of curative resection[125]. In addition, the EREBUS cohort study performed to assess the effectiveness of cetuximab in wt-KRAS patients in real practice showed that the rate of CRLM resection was 27.2%, the 24-mo probability of CRLM resection was 33.6%, the median progression-free survival was 9.2 mo for the total cohort and 13.0 mo for resected patients, and the median OS was 23.0 mo for the total cohort and was not reached after 36 mo for those who were resected[123]. Moreover, bevacizumab is effective in both wt-KRAS and mt-KRAS patients[124,127-129]. A randomized clinical trial showed that among patients with untreated wt-KRAS metastatic colorectal cancer, there was no significant difference in the OS between the addition of cetuximab or bevacizumab to chemotherapy as the initial biological treatment[127]. Furthermore, a study by Hatano *et al*[129] involving patients who received mFOLFOX6 with either bevacizumab or cetuximab based on their KRAS status disclosed that the overall response rate was 64.7% (wt/mt, 77.3%/41.7%, P = 0.04) and the overall conversion hepatectomy rate was 67.6% (wt/mt, 77.2%/50.0%, P = 0.09).

Recently, an interesting discovery reported by several researchers was that the primary tumor location is associated with the oncological outcomes: a primary tumor located on the right side had a worse prognosis than a tumor located on the left side[130,131]. Therefore, cetuximab and panitumumab are only recommended for left-sided primary tumors with wt-KRAS CRLM. After resection of the downsized LM, routine adjuvant chemotherapy should be given to reduce the chances of tumor recurrence. The most preferred regimen for postoperative adjuvant chemotherapy is mFOLFOX6 for

3 mo after metastasectomy[132].

In addition, there are some predictors of long-term survival in patients receiving conversion chemotherapy followed by LR for CRLM. First, early-tumor shrinkage and the partial response rate by RECIST criteria are the most powerful predictors of a long survival. Moreover, early-tumor shrinkage > 30% after 8 wk of chemotherapy is significantly associated with the OS. The greater the depth of response, the longer the median duration of response and the higher the OS[133,134]. Second, a left-sided primary tumor resection prolonged the median OS; however, for colon cancer patients with right-sided tumors, resection showed no benefit[130,131]. Third, the patients with a carcinoembryonic antigen half-life after the third chemotherapeutic course of less than 20 d had a significantly better progression-free survival and OS[135]. Fourth, a favorable pathological tumor response was independently associated with the DFS[55]. These prognostic factors are helpful in selecting ideal candidates for this strategy and also can guide the clinical management of patients. We propose that the use of anti-EGFR or anti-VGFR monoclonal antibody combined with standard chemotherapy regimens (FOLFOX or FOLFIRI) should be the first choice for unresectable CRLM patients based on the KRAS mutant status.

Liver transplantation for unresectable CRLM

Liver transplantation can be regarded as the "ultimate" LR and is now gaining increasing interest for unresectable CRLM[6]. Liver transplantation for LM in the early 1990s achieved very poor perioperative outcomes and was abandoned[136]. However, in the past two decades, with dramatic improvements in surgical techniques and neoadjuvant therapy, which includes irinotecan, oxaliplatin, cetuximab, and bevacizumab, the prognosis of appropriately selected patients who underwent liver transplantation has improved, with 5-year OS rates reportedly reaching more than 50%, which is comparable with chemotherapy and other treatments for unresectable disease[137-139]. Toso *et al*[138] published an encouraging result of 12 patients with unresectable CRLM who underwent liver transplantation. The OS rates were 83%, 62%, and 50% at 1, 3, and 5 years, respectively. Most importantly, five patients had no recurrence and were still alive during the follow-up period, thus showing that long-term DFS can also be achieved through liver transplantation[138]. However, liver transplantation continues to remain a controversial treatment for unresectable CRLM.

The most important limiting factor for further use of liver transplantation is the shortage of grafts available. Quite a few patients have died due to tumor progression while waiting for a proper donor liver. Recurrence and death are still common after liver transplantation. In addition, ethical issues also remain to be resolved. Accounting for these reasons, distributing deceased donor grafts to patients with CRLM does not seem appropriate (at this point) as it will most likely impact the lives of other patients on the waiting list. Therefore, defining the patient population that would benefit the most from liver transplantation is crucial. Selection strategies should be based on prognostic factors found to be favorable for survival: diameter of the largest CLM < 55 mm, time interval of > 2 years between colorectal and transplant operations, pre-liver transplantation carcinoembryonic antigen level < 80 ng/mL, and responsive or stable disease under chemotherapy[140]. Further studies are needed to refine the risk stratification and optimize patient selection. Fortunately, several trials are ongoing to further address the potential of liver transplantation for unresectable CRLM[137,141].

REPEAT LR FOR RECURRENT INTRAHEPATIC CRLM

After the initial LR, the recurrence rate of CRLM has been estimated to be as high as 56.7%, with the most common site being the remnant liver[142]. There are several alternatives such as repeat hepatectomy, ablation, stereotactic body radiation therapy, transcatheter arterial chemoembolization, and systemic chemotherapy for the treatment of intrahepatic recurrent CRLM. Among these therapies, a repeat LR has been found to be feasible, effective, and potentially curative in some selected patients. The postoperative morbidity rate following the initial hepatectomy is not significantly different from that after a repeated hepatectomy, although repeated LR is associated with more perioperative risks due to dense adhesions, altered liver anatomy, and reduced liver remnant after the initial operation[143,144]. Moreover, postoperative complications after aggressive repeated hepatectomy for CRLM adversely affects the oncological outcomes[143].

Several studies have evaluated the long-term outcomes of repeated LR. A recent meta-analysis showed that compared with the initial LR, repeated LR has comparable postoperative outcomes and a similar long-term survival[145]. The 5-year survival rate was > 40% after repeated LR despite the DFS being lower than that of the initial hepatectomy[143,146,147]. Furthermore, redo-hepatectomy for single recurrent CRLM is as effective as primary surgical treatment for single CRLM. However, redo-hepatectomy for multiple recurrent CRLM is less effective than that for single recurrent CRLM[144]. Multiple CRLM, large tumor size, extrahepatic metastases, and short tumor-free interval predict significantly poor outcomes[144,148]. Therefore, only selected patients are suitable for repeated surgery.

We believe that the following criteria suggested by Luo *et al*[149], according to a systemic review and meta-analysis, can be used to select patients for repeated LR, which is associated with a significantly longer survival compared with other treatment therapies such as RFA, transarterial chemoembolization,

radiation, and chemotherapy: (1) DFS after initial LR > 1 year; (2) solitary CRLM; (3) unilobar CRLM; (4) maximal size of CRLM at the second LR < 5 cm; (5) absence of extrahepatic disease during the second hepatic resection; and (6) R0 resection at the second hepatectomy[149].

LR IN ELDERLY PATIENTS WITH CRLM

Patients aged over 65 years are often considered elderly[150,151]. Several papers have assessed the impact of age on morbidity and mortality following hepatectomy for CRLM. Although postoperative morbidity and mortality are significantly higher in those with an advanced age, LR for CRLM seems justified in selected elderly patients[151-153]. In a study on elderly patients, a major hepatectomy was found to be safe and feasible in the selected octogenarian patients, with no significant differences in the perioperative outcomes, DFS, or OS[154]. Mäkelä *et al*[155] have reported that even in the oldest patients (age > 80 years), favorable long-term survival can be achieved by surgical resection. As there is a higher possibility of noncancer-related deaths in elderly patients during the follow-up period, a slightly lower long-term survival is acceptable. Therefore, an elderly age should not be considered a contraindication to hepatic resection of CRLM. The main concern is the higher rate of postoperative complications caused by co-morbidities such as cardiopulmonary and cerebrovascular diseases[156]. These pre-existing disorders are frequently related to an increased difficulty in giving anesthesia and conducting an operation, with the risk of postoperative death. Hence, the strict assessment of the preoperative general condition and the careful selection of elderly patients are the keys to achieve satisfactory short- and long-term outcomes. Recent research has advocated the use of cardiopulmonary exercise testing for preoperative evaluation and enhanced recovery after surgery as a part of postoperative management in elderly patients[157]. The authors showed that in appropriately selected patients, the postoperative outcomes were comparable to the younger counterparts[157].

Considering the potential advantage of a minimally invasive approach for elderly patients such as less trauma and faster recovery, laparoscopic and robot-assisted LR have been attempted. Martínez-Cecilia *et al*[150] expanded the use of LLR for elderly patients, and their results suggested that LLR offers equivalent oncological outcomes, with a reduction in both minor and major postoperative morbidities in those aged > 70 years. Even compared with laparoscopic RFA, LLR for elderly people was safe and tolerable, with similar perioperative outcomes[158]. It seems that LLR for CRLM in elderly patients is a promising treatment option. Therefore, further randomized controlled trials are required to determine the real benefits and risks associated with LLR.

ROLE OF LR IN THE PRESENCE OF EXTRA-HEPATIC METASTATIC DISEASE

In CRC patients, 23%–38% of them have or will develop EHMD[159,160]. In the early 1990s, EHMD was considered as one of the contraindications of CRLM resection because of its low 5-year survival rate[161]. A population-based study of 15133 CRC patients showed that patients with isolated lung metastases had better cancer-specific survival and OS as compared to patients with metastases to the liver, bone, and brain[162]. Therefore, limited EHMD such as pulmonary EHMD is now no longer a contraindication of LR and patients can receive a R0 resection as long as the FLR is sufficient so that the patient can tolerate the major surgery of both the liver and EHMD[57,163,164]. The cure rate reached 19% in patients who received potentially curative resection of both the liver and EHMD[164]; this rate is comparable to CRLM patients without EHMD who received hepatectomy[57]. The median OS of patients undergoing resection for CRLM in the setting of EHMD was 34.4 mo, with estimated 3-, 5-, and 10-year survival rates of 49%, 28%, and 10%, respectively, with the combined use of effective chemotherapy and surgery[163]. Therefore, complete resection of concomitant hepatic and EHMD significantly prolongs survival.

Some studies have hypothesized that the location of the EHMD affects the prognosis[162,163,165,166]. Patients with minimal liver disease and EHMD of the lungs had the best outcomes, while those with peritoneal and lymph node metastases were associated with the worst prognosis. In a population-based study, the results showed that the OS time for CRC patients with isolated liver, lung, bone, and brain metastases was 16, 20, 7, and 5 mo, respectively[162]. The 3- and 5-year OS rates were 58% and 26% for pulmonary EHMD, 37% and 17% for peritoneal EHMD, and 35% and 15% for lymph nodal metastases; the combined relative risk of death after 5 years was 1.49 for lung EHMD, 1.59 for peritoneal EHMD, and 1.70 for lymph nodal EHMD[165]. The results of a retrospective study further showed that the survival time of patients with perihepatic lymph node metastases was significantly shorter than that for those patients without it (recurrence-free survival: 5.3 mo *vs* 13.8 mo; OS: 20.5 mo *vs* 71.3mo). The median OS was significantly longer in patients with para-aortic compared to hepatoduodenal ligament lymph node metastases (58.2 mo *vs* 15.5 mo). Patients with three or more perihepatic lymph node metastases had a significantly worse median OS than those with one or two (16.3 mo *vs* 25.4 mo)[166]. These findings suggest that there are marked differences in survival depending on which lymph nodes are involved.

The survival rates of patients who underwent resection were much higher than those of patients who only received chemotherapy[142,167]. However, unresectability of EHMD is a contraindication for curative LR, as it is extremely likely to result in a poor prognosis[163].

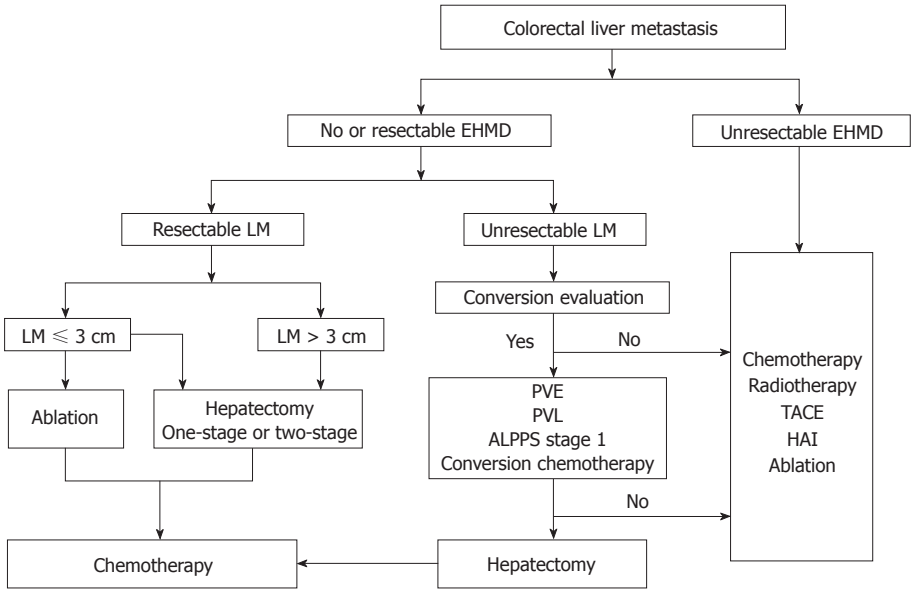

Figure 1 Management flow chart for colorectal liver metastases. EHMD: Extra-hepatic metastatic disease; LM: Liver metastases; PVE: Portal vein embolization; PVL: Portal venous ligation; ALPPS: Associated liver partition and PVL for staged hepatectomy; TACE: Transarterial chemoembolization; HAI: Hepatic artery infusion.

Thus, the resectability of EHMD should be evaluated before the surgical treatment of CRLM. Chua *et al*[168] considered that neoadjuvant chemotherapy could be used as a tool to assess the biological characteristics of a tumor. If a tumor has a positive response to chemotherapy, the patients may be selected for surgery of the liver and EHMD[168]. The scoring system also may be helpful to measure whether the EHMD should be resected. A predictive model was constructed by Adam *et al*[169] to select the appropriate candidates, and the five prognostic factors found were as follows: absence of isolated lung metastases, carcinoembryonic antigen level ⩾ 10 ng/mL, CRLM ⩾ 6 at the time of diagnosis, EHMD concomitant with CRLM recurrence, and the location of the primary tumor in the right colon[169]. The 5-year OS was 64% in the patients without all of these factors, whereas the presence of 4–5 factors reduced the 5-year OS to nil. They also built a risk scoring system in which three factors, LM size, EHMD site, and number of LM, were assigned 1 point each[169]. They found that the patients whose risk score was 3 had the worst outcomes, similar to those who received chemotherapy alone. The patients whose risk score was nil had the best outcome, similar to patients with resectable LM without EHMD. Even those at low risk can achieve a relatively long survival.

In summary, these recent studies provide some evidence that CRLM with concurrent EHMD can be resected to yield promising medium- and long-term survival; thus, it should no longer be considered an absolute contraindication to curative surgery in selected CRLM patients.

CONCLUSION

Treatment of patients with CRLM is still a major clinical challenge. Curative resection is the best treatment option to prolong the survival, but further work is needed to better identify patients who are likely to benefit the most from surgery. With the help of modern multimodality therapy such as effective systemic chemotherapy, an aggressive oncosurgical approach should be implemented as it has the possibility of achieving a cure even when EHMD is present in patients with CRLM. In some strictly selected patients, liver transplantation may be a potential treatment option. We propose a simple flow chart to help in planning out the treatment of patients with CRLM (Figure 1).

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MINIREVIEWS

The assessment of endosonographers in training

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Abstract

Endosonography (EUS) has an estimated long learning curve including the acquisition of both technical and cognitive skills. Trainees in EUS must learn to master intraprocedural steps such as echoendoscope handling and ultrasonographic imaging with the interpretation of normal anatomy and any pathology. In addition, there is a need to understand the periprocedural parts of the EUS-examination such as the indications and contraindications for EUS and potential adverse events that could occur post-EUS. However, the learning process and progress vary widely among endosonographers in training. Consequently, the performance of a certain number of supervised procedures during training does not automatically guarantee adequate competence in EUS. Instead, the assessment of EUS-competence should preferably be performed by the use of an assessment tool developed specifically for the evaluation of endosonographers in training. Such a tool, covering all the different steps of the EUS-procedure, would better depict the individual learning curve and better reflect the true competence of each trainee. This mini-review will address the issue of clinical education in EUS with respect to the evaluation of endosonographers in training. The aim of the article is to provide an informative overview of the topic. The relevant literature of the field will be reviewed and discussed. The current knowledge on how to assess the skills and competence of endosonographers in training is presented in detail.

Key words: Endosonography; Fine-needle aspiration; Education; Assessment; Educational; Learning curve; Clinical competence; Quality indicators

Core tip: Endosonography (EUS) has an estimated long learning curve including the acquisition of both technical and cognitive skills. However, the learning process and progress varies widely among trainees in EUS. Therefore, the performance of a certain number of EUS-procedures during training does not automatically guarantee adequate competence. Instead, assessment tools developed for the evaluation of endosonographers in training should better reflect the true competence of each individual trainee. This mini-review addresses the issue of clinical education in EUS and describes the current knowledge on how to assess the skills and competence of endosonographers in training in detail.

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INTRODUCTION

Endosonography (EUS) has become an important diagnostic and therapeutic tool for medical gastroenterologists, surgeons, and oncologists worldwide. The learning of EUS is a rewarding but demanding task with an estimated long learning curve[1]. The long learning curve is partly explained by the fact that EUS has several different clinical indications[2,3]. Moreover, many of the lesions examined by EUS include a wide range of possible diagnostic entities[4,5]. Consequently, the competent endosonographer needs to master not only multiple maneuvers with the echoendoscope and its accessories, but also endosonographic interpretation of the normal anatomy and any pathologic lesions (Figure 1). In the end, both cognitive and technical skills are essential to perform a safe EUS-examination of high quality.

In advanced endoscopy, the learning process and progress vary widely among trainees[1,6]. Therefore, the performance of a certain number of procedures during training does not automatically guarantee adequate competence in EUS. It is likely that an assessment tool that covers the different steps of the EUS-procedure and that is developed for the evaluation of endosonographers in training would be more appropriate than the count of procedures for assessing competence. Such tools would likely better depict the learning curve of EUS and reflect the true competence of each individual trainee[6].

This minireview addresses the issue of clinical education in EUS with respect to the evaluation of endosonographers training basic, diagnostic EUS with or without fine needle aspiration (EUS-FNA). The aim of this mini-review is to provide an informative up to date overview of the topic. The relevant literature of the field is reviewed and discussed. The current knowledge on how to assess the skills and competence of endosonographers in training is presented in detail.

TRAINING IN EUS - FOR WHOM, WHERE, AND HOW?

It is recommended that the EUS-trainee should have completed a minimum of two years of training or practice in routine endoscopy before initiating training in EUS[7]. However, the experience in advanced, therapeutic endoscopy might not be a prerequisite for successful, basic EUS-training[8]. Likewise, previous competence in transabdominal ultrasound is probably not vital for learning EUS[9].

There is limited data on the number of centers providing supervised training in EUS[10]. Although it is frequently reported[10], learning EUS by self-teaching without supervision is discouraged[7,9,11]. A large number of learning procedures are expected. Therefore, training in EUS should only be performed in centers that can provide a reasonably high volume of procedures along with experienced and motivated instructors[11]. This type of focused training is highlighted by a study published in 2005, which found that trainees in an advanced endoscopy fellowship in an academic center performed a larger number of supervised procedures compared with endosonographers trained in other types of practice[10]. Furthermore, it is important that the endosonographic findings of the trainee are co-evaluated by the supervisor in the early phase of training[11].

Ex vivo models used for training in EUS

Animal models can probably work as a facilitating tool for beginners or for trainees with little experience in EUS[12-14]. A live porcine model was evaluated by Bhutani *et al*[14] in a survey among 38 trainees with little experience in EUS, with these trainees participating in either of two EUS courses organized by the American Society of Gastrointestinal Endoscopy (ASGE) in 1997 and 2000. Over 90% of the respondents found the model helpful in enhancing their EUS skills but there was no measurement of the effect on the learning curve of EUS. Similar models have also been evaluated and have been found to be useful for the purpose of learning EUS-FNA[15,16].

In vivo supervised training in EUS

Even though *ex vivo*-models could be helpful tools in early EUS-training, they may not be available in all centers and cannot replace supervised training in true patients[7,11]. Regarding the equipment, the linear array echoendoscope can probably be introduced to trainees at the on-set of training. A period of initial training with a radial echoendoscope was shown to not

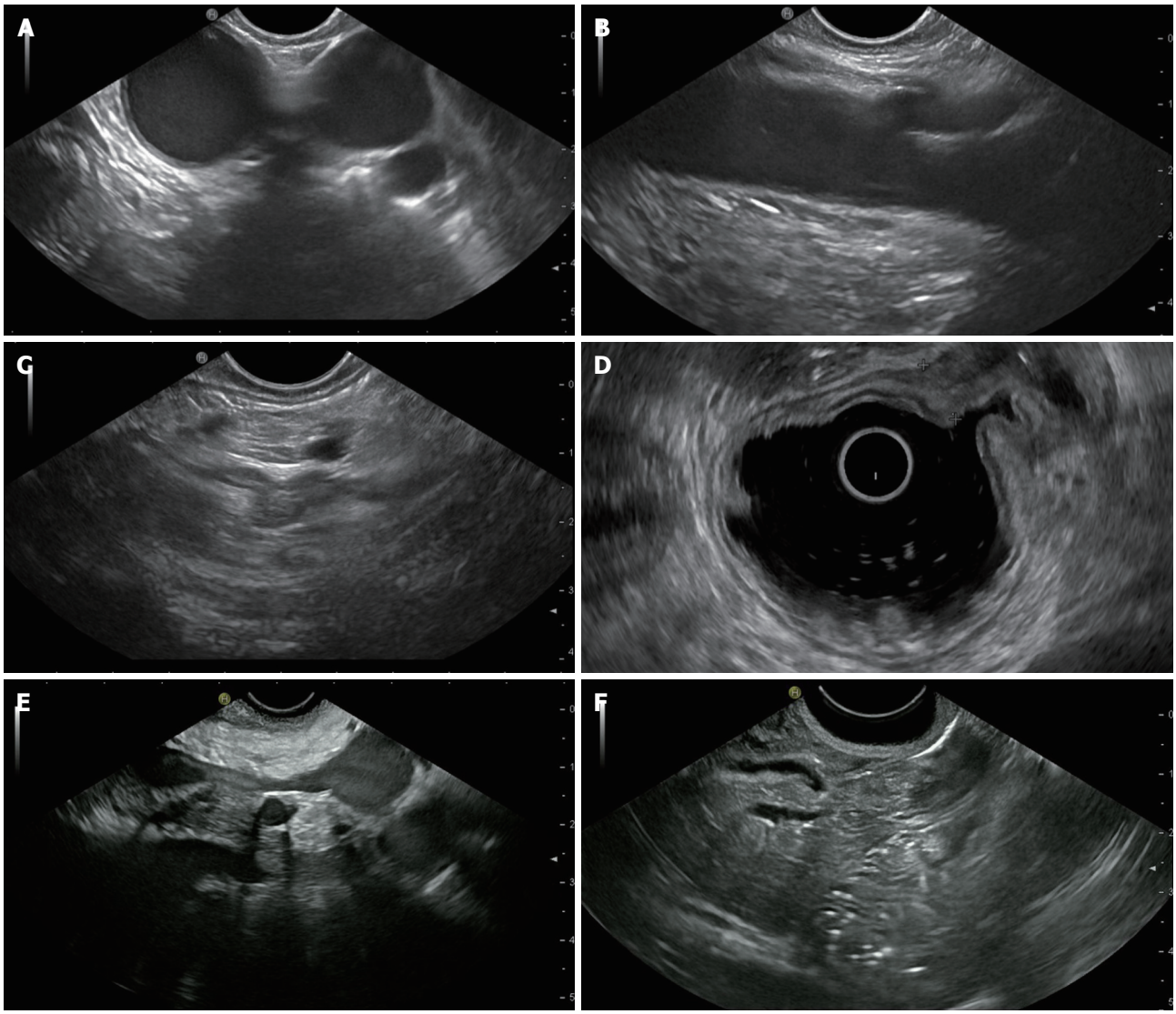

Figure 1 The endosonographic image of six characteristic views produced by a curvilinear array echoendoscope (Pentax EG3870UTK, Tokyo, Japan) and an ultrasound processor (Hitachi HI VISION Ascendus, Tokyo, Japan). Images by the authors. A: The aortopulmonary window (esophageal view); B: The abdominal aorta with the exit of the celiac trunc (gastric view); C: The left adrenal (gastric view); D: The stomach wall and its five layers (radial echoendoscope). Thickened wall (MALT-lymphoma) in the upper right part of the image; E: The pancreatic body including the splenic vein below (gastric view); F: The pancreatic head with the common bile duct and the pancreatic duct (duodenal view).

improve the performance of subsequent scanning with the linear array echoendoscope according to one study published in 2015[17]. The recommended design of training programs in EUS can be further studied by the guidelines issued by the ASGE[11,18].

The decision as to when to introduce the trainee to EUS-FNA has been a matter of debate. Some authors advocate long, previous experience with basic EUS with a thorough knowledge of the normal and abnormal anatomy before the introduction of EUS-FNA[19]. Others consider early trainee-performed EUS-FNA both appropriate and patient safe[20,21]. In a study by Coté *et al*[20] a supervisor-directed, trainee-performed EUS-FNA executed from the on-set of training, resulted in no recorded complications in a total of 305 patients. In addition, the performance characteristics of EUS-FNA including the diagnostic accuracy were found to be comparable (trainee *vs* supervisor). In another study by Mertz *et al*[21], the first 50 EUS-FNA:s of pancreatic masses performed by a non-experienced endosonographer were found to be safe with no adverse events detected. However, in this study, the diagnostic sensitivity for cancer was significantly higher after the first 30 EUS-FNA procedures. Therefore, it might be that the introduction of EUS-FNA could be considered by supervisors to already be performed at the on-set of training, at least from a patient safety point of view.

Continued learning after completed training

An important issue merits some attention: "How to ascertain that the obtained competence in EUS will be maintained after the completion of training in EUS?".

One way of ascertaining the maintenance of competence is to follow the recommendations issued by the ASGE[7], which encourage the trained endosonographer to log the annual number of EUS-procedures and, like all other endosonographers, to regularly review the quality and outcome of the procedures. Educational activities, such as scientific meetings and hands-on workshops, should also be attended.

WHAT IS THE NUMBER OF EXAMINATIONS REQUIRED TO BECOME COMPETENT IN EUS?

The simple answer to this difficult question is "we do not know". Therefore, the competence of an EUS-trainee can hardly be assessed only by the numeric count of performed procedures.

Basic EUS

According to guidelines published in 2001, there are a suggested, minimum number of 125 supervised procedures to be performed before acceptable competence in EUS can be expected[7]. For comprehensive competence in all aspects of EUS, the same guidelines recommend a minimum of 150 supervised trainee-performed EUS-procedures. Out of these 150 procedures at least 75 procedures should have a focus on the pancreaticobiliary area and at least 50 procedures should include EUS-guided sampling (EUS-FNA)[7]. These recommended numbers should be considered to be an absolute minimum and not a guarantee that the necessary skills will be acquired.

A few clinical studies[1,8,22] have investigated the number of training procedures required to become a competent endosonographer. These publications are summarized in Table 1. As is discussed below, there is a significant variation in the methodologies of the studies, in the variables measured, and in the criteria for competence, when comparing the studies included in Table 1. This variation makes the results of these studies somewhat difficult to compare to each other.

In the early era of EUS, examinations were mainly performed with the purpose of tumor staging without sampling. Today a majority of EUS-procedures include diagnostic sampling of lesions (EUS-FNA/B) or therapeutic interventions such as drainage of pancreatic pseudocysts. Therefore, to a large extent, radial echo-endoscopes have been replaced by linear ones[11]. Consequently, the number of required cases for competence in EUS that were recommended many years ago should be interpreted with some caution since it might not be completely valid today.

EUS with EUS-FNA

Before independent performance of EUS-FNA, the ESGE and the ASGE both recommend a minimum of 50 supervised, trainee-performed EUS-FNAs of which 25-30 should be pancreatic EUS-FNA[7,9]. No specific number of EUS-FNA-procedures has been identified before full competence can be expected[9], but the learning curve most likely continues long after the initial period of supervised training[23]. In a retrospective study by Mertz *et al*[21], the sensitivity for the detection of pancreatic cancer by trainee-performed EUS-FNAs was compared in quintiles of procedures. A significant increase in sensitivity after the third quintile was detected. Consequently, the authors concluded that the ASGE guideline of 25 supervised EUS-FNA procedures in solid pancreatic lesions seemed reasonable.

In a prospective, Japanese study including only subepithelial lesions[24] the accuracy and safety of EUS-FNA performed by two trainees were compared with those of two experts. Before the study period, both trainees had performed 50 EUSs without sampling and attended 20 EUS-FNAs performed by experts. In the study, a total of 51 cases were performed alternately by the trainee and the expert, and there was no difference in the acquisition of an adequate specimen. No major complications were recorded.

In a study by Wani *et al*[1], five EUS-trainees performing a total of 1412 examinations were assessed with regards to both basic EUS and EUS-FNA. The number of examinations required for acceptable competence varied significantly among the trainees. In one trainee 255 procedures were required while another trainee was still in need of continued training after 402 procedures (Table 1). The authors concluded that, compared with the recommended minimum of 150 supervised cases, all five trainees needed much larger number of training procedures to be competent[7]. Consequently, it is likely that > 200 procedures are required for the majority of trainees. This estimation is supported by others who argue that the number of recommended EUS-procedures may be a significant underestimation of the true number of procedures that are needed[25].

WHAT IS COMPETENCE AND QUALITY IN EUS?

Logically, the competence of the trainee is reflected by the quality of the EUS being performed. Consequently, in EUS, what is good quality and what quality is good enough? One definition of adequate competence is suggested in the following guidelines by the ASGE: "The minimum level of skill, knowledge, and/or expertise derived through training and experience, required to safely and proficiently perform a task or procedure"[7]. Nevertheless, there is no consensus on the exact definition of competence in EUS or with what tools, and on what scale, it should be measured[1]. It also remains to be agreed upon what the specific indicators to be used as quality measures are in EUS.

In 2006, the American College of Gastroenterology

Table 1 Number of trainee-performed endosonography-procedures required for the adequate performance of the different steps of a diagnostic endosonography-examination not including fine needle aspiration

Ref.	Procedural step or scanning position						
	Intubation[1]	**Esophageal view**		**Gastric view**		**Duodenal view**	
Meenan *et al*[8] 2003	NA[2]	25–CNR[3]		35–CNR		78–CNR	
	Intubation	**Mediastinum**	**Celiac axis**	**Gastric wall**	**Pancreas (body)**	**Pancreas (head)**	**CBD**
Hoffman *et al*[22] 2005	1–23	1–33	8–36	1–47	1–34	15–74	13–134
	Intubation	**AP window**	**Celiac axis**		**Pancreas (body)**	**Pancreas (head)**	**CBD**
Wani *et al*[1] 2013	245–CNR	315–CNR	235–CNR		226–CNR	166–CNR	CNR–CNR[4]

Each range indicates the number of procedures required for the fastest learning trainee (low end) and the number of procedures required for the slowest learning trainee (high end). Competency not reached means that at least one trainee had not yet reached adequate competence by the end of training period. In the study by Meenan *et al*[8] five trainees were assessed; in the study by Hoffman *et al*[22] twelve trainees were assessed; and in the study by Wani *et al*[1] five trainees were assessed. [1]Intubation of the esophagus with the echoendoscope; [2]Not assessed; [3]Competency not reached at the end of the training period; [4]No trainee reached adequate competence. CBD: Common bile duct; CNR: Competency not reached.

(ACG)/ASGE task force aimed to establish quality indicators in EUS to aid in the recognition of high-quality examinations[26]. An updated and extended version including 23 quality indicators was published in 2015[27]. The 23 indicators were divided into three categories – Preprocedure (n = 9), Intraprocedure (n = 5), Postprocedure (n = 9). The three most prioritized indicators should be the frequency of adequate staging of GI malignancies, the diagnostic sensitivity of EUS-FNA in pancreatic masses, and the frequency of adverse events post-EUS-FNA[27]. However, these documents are basically intended for trained endosonographers working in clinical practice and not specifically for the situation of evaluating trainees in EUS. Naturally, the fully-trained endosonographer should ultimately aim to meet these quality indicators. Interestingly, the authors stressed that a subject for future research is the amount of training required for obtaining "diagnostic FNA yields comparable to those of published literature".

The European Society of Gastrointestinal Endoscopy (ESGE), has published technical guidelines on EUS[28], however these guidelines do not include any quality indicators. As such, a recent initiative launched by the ESGE aims to address this specific issue. A working group has been formed[29,30] but to date no report has been published.

ASSESSING THE ADVANCED ENDOSCOPY TRAINEE – HOW AND WHAT TO MEASURE?

Thus, one way of assessing endosonographers in training would be to apply some of the quality indicators for EUS and to record the outcome on an arbitrary scale over time. However, the assessment of endoscopy trainees should not necessarily only focus on the quality indicators, but also focus on other parameters. The sensible approach would be to use the pre-defined and validated assessment criteria as well as the direct observation of an expert[11].

There are several validated assessment tools for measuring the learning curve in endoscopy such as the Mayo Colonoscopy Skills Assessment Tool (MCSAT)[31], the Competency in Endoscopy (ACE)[32], the British Direct Observation of Procedural Skills (DOPS)[33], and the Global Assessment of Gastrointestinal Endoscopic Skills (GAGES)[34]. Technical skills such as scope navigation, tip control, and loop reduction together with cognitive skills such as pathology identification and management of patient discomfort are assessed and scored to a varying degree. However the above tools were primarily designed for colonoscopy and not for EUS, which is why the ASGE has encouraged the development of objective criteria for the assessment of endosonographers in training[35].

The ASGE standards of practice committee has authored guidelines for credentialing and for granting privileges for EUS[7], with these guidelines stating that the competence in EUS should be evaluated independently from other endoscopic procedures. As further specified in this publication, the competent endosonographer should acquire skills including, among others, safe intubation of the esophagus, appropriate sonographic visualization of various organs, recognition of abnormal findings, and appropriate documentation of the EUS-procedure[7].

TOOLS FOR THE ASSESSMENT OF ENDOSONOGRAPHERS IN TRAINING

The assessment tools of trainee-performance in porcine EUS-models have been investigated[15]. However, it might be challenging to interpret trainee-competence based on their performance in an animal model, which is a quite different experience compared with the clinical everyday EUS-practice. To date, there is no clear recommendation on what parameters to include in the assessment of endosonographers in training performing EUS in humans. Although there is a lack of a uniform standard, some assessment tools, elaborated for EUS-trainees and for use in real patients, have been proposed.

The assessment tools that rate specific steps or

Table 2 Assessment form used by Meenan *et al*[8] to evaluate and assess endosonographers in training using a radial array echoendoscope

Site	Structures	Points
Esophagus	Liver, inferior vena cava/hepatic veins, crus, abdominal aorta, spine, right pleura, thoracic aorta, left atrium, aortic outflow, left pulmonary vein, azygous vein, thoracic duct, right/left bronchus, carina, aortic arch, carotids, trachea, thyroid	18 points (minimum score for competence: 12 points)
Stomach	Stomach wall layer pattern, celiac axis, left adrenal, portal confluence, splenic vein, splenic artery, follow course of splenic vein	8 points (following course of splenic vein: 2 points; minimum score for competence: 5 points)
Duodenum	Gall bladder, portal vein, pancreatic duct, abdominal aorta, inferior vena cava, uncinate process, superior mesenteric vein, superior mesenteric artery, follow course of common bile duct	11 points (following course of common bile duct: 3 points; minimum score for competence: 7.5 points)
Use of ultrasound controls	Frequency, range, brightness/contrast	3 points

Points were awarded for the ability to produce "best views with certainity" from the three different positions of scanning. The minimum score for competence in each of the positions is provided in the rightmost column. Adapted from Meenan *et al*[8] and reprinted with permission from Georg Thieme Verlag KG.

maneuvers of the EUS-procedures have been investigated by some authors. As an example, in 2012 Konge *et al*[36] presented the EUS Assessment Tool (EUSAT), designed exclusively to measure EUS-FNA-competence for the specific situation of mediastinal staging of non-small cell lung cancer. Other examples also include assessment tools for the accurate staging of esophageal cancer[37,38], for the diagnostic EUS-FNA of pancreatic masses[21] or submucosal lesions[24], and for the adequate on-site trainee-assessment of the EUS-FNA-specimens[39]. These studies are limited to a certain scenario and they do not cover the complete examination including all organs and structures within reach for upper GI EUS.

Basic EUS without EUS-FNA

Only a handful of groups have presented tools aimed at assessing the complete EUS-procedure including visualization of all the standard views. In an older study by Meenan *et al*[8], five EUS-trainees were evaluated in performing radial EUS, *i.e.,* no EUS-FNA. In the beginning of training the trainees observed supervisor-performed examinations (range: 55-170 cases). Afterwards, the trainees performed the examinations themselves (range: 25-124 cases). In this study, a study unique data collection tool (Table 2), was designed to assess the ability of the trainees to use the ultrasound controls and to visualize a number of predetermined anatomic stations via the esophagus, the stomach, and the duodenum. Esophageal intubation with the echoendoscope was not assessed. *Via* the assessment tool and a point score system (maximum score: 40 points, Table 2), each trainee was evaluated at the end of training and during five examinations. For each position (esophagus/stomach/duodenum) an arbitrary minimum score was set to determine adequate competence. The authors concluded that the assessment tool was applicable in clinical practice and could identify trainees with a need for continued training. Difficult maneuvers could be identified such as the dynamic visualization of the aortic outflow, of the splenic vein, and of the common bile duct. A drawback of the study, which limits its implications, is that linear EUS was not performed and that only five procedures per trainee were scored.

In another older study, only published in abstract form, twelve EUS-trainees were evaluated and rated by an expert[22]. According to the text of the abstract, the trainee-performed EUSs were assessed and rated with respect to the separate steps of the procedure (Table 1). Each step was scored and categorized as follows: 0 = Failed; 1 = Unsatisfactory; 2 = Satisfactory; and 3 = Excellent. Competency was defined as consistent achievement of a score of 2. Unfortunately, any further details and comments on this assessment tool cannot be provided due to the lack of a full article publication.

Basic EUS including EUS-FNA

In a more recent study by Wani *et al*[1], five EUS-trainees performing a total of 1412 EUS-examinations were assessed by an EUS-expert. Beginning at the 25th examination, every 10th examination was assessed. Similar to the work by Meenan, the authors elaborated on a standardized data collection tool including different steps of the EUS-procedure (Figure 2). Each step was scored on a 5-grade scale. Then the score of each step and the overall score were recorded. Finally, the assessment of competence was based on the trend and inclination of the score and the learning curve was calculated by a so called CUSUM (Cumulative Sum Analysis)[1]. The authors found the suggested assessment method to be both feasible and valuable for

1 = no assistance; 2 = minimal assistance (one instruction); 3 = moderate assistance (multiple instructions); 4 = significant assistance (attg manipulates scope to optimize visualization); 5 = unable to achieve

Echoendoscope: [ ] Radial [ ] Linear

Indication: [ ] Panc mass [ ] Panc cyst [ ] Bild dil [ ] PD dil
[ ] Lymphadenopathy [ ] Lumi GI cancer
[ ] Mediastinal mass [ ] Submucosal les [ ] Chron pancreatitis
[ ] Other:_____

Date: **Case No for fellow:**

Attending initials: **Fellow initials:**

EUS stations. Allow about 1 minute per station before assistance (please specify reason for NA)

Endoscopic intubation	1	2	3	4	5	NA_____
AP window	1	2	3	4	5	NA_____
Celiac axis	1	2	3	4	5	NA_____
Body of pancreas	1	2	3	4	5	NA_____
Tail of pancreas	1	2	3	4	5	NA_____
Portosplenic confluence	1	2	3	4	5	NA_____
Head/neck of pancreas	1	2	3	4	5	NA_____
CBD/CHD	1	2	3	4	5	NA_____
Gallbladder	1	2	3	4	5	NA_____
Uncinate	1	2	3	4	5	NA_____
Ampulla	1	2	3	4	5	NA_____

Characterization/Sampling of lesion

Identify lesion of interest	1	2	3	4	5	NA_____
Appropriate TNM stage	1	2	3	4	5	NA_____
Characterize subepithelial lesion	1	2	3	4	5	NA_____
Achieved EUS-FNA	1	2	3	4	5	NA_____

Procedureal complication:

Figure 2 Assessment form used by Wani *et al*[1] to evaluate and assess endosonographers in training mainly using a curvilinear or a linear array echo-endoscope. The criterion for successful performance of each step was a score of 1. Adapted from Wani *et al*[1] and reprinted with permission from Elsevier.

identifying trainees who needed continued training. The method also identified the anatomic stations, such as the pancreas and the ampulla, that were more difficult to master for trainees. A weak point of this study was that only every 10th examination was assessed.

The identical study methodology and assessment tool (Figure 2), was used in an enlarged study by Wani *et al*[40] published in 2015. This study included 17 trainees who performed a total of 4257 examinations in 15 tertiary centers. The results were similar to those presented in the first publication with the learning curves showing a high degree of inter-trainee variation.

In 2017, another study was published by the same author[41], with the study evaluating trainees in EUS and ERCP using the EUS and ERCP skills assessment tool (TEESAT). In every third trainee-performed EUS, a nearly identical assessment tool (Figure 2), as was used in the two previous studies[1,40] was used to score the trainees. Twenty-two trainees participated in the study and 3786 examinations were graded. A centralized database was used and was found feasible for the collection of data. The authors concluded that TEESAT was a more time-consuming tool than any global rating scale but that it had the clear advantage of monitoring the learning curve and providing precise feed-back to trainees. TEESAT, therefore, could facilitate the improvement of certain steps or maneuvers. Finally, this study confirmed the fact that there was significant variability among the trainees concerning the time and number of procedures to achieve competence in EUS.

CONCLUSION

The safe and competent performance of advanced endoscopy procedures such as EUS is cognitively and technically demanding. Therefore, there is a definite need for the evaluation and assessment of EUS trainees both during and at the completion of training.

Some assessment tools have been evaluated in clinical studies but only some of those tools cover all the steps and aspects of a complete, diagnostic EUS-procedure. Moreover, the few extensive assessment tools that have been studied thus far have not yet been fully validated by external and independent inves-

tigators. The small number of publications within the field is somewhat troublesome, meaning that today, there is no standardized measurement protocol and assessment tool regarding trainee-performance in EUS. Consequently, no specific recommendation can be put forward on the most appropriate assessment tool to use for the evaluation of endosonographers learning basic, diagnostic EUS[6]. The assessment of endosongraphers learning therapeutic EUS was not an aim of this article.

Nevertheless, EUS is a rapidly expanding field with a growing number of diagnostic and therapeutic indications[42-44]. Therefore, supervisors should be prepared to include new and additional parameters for assessment with respect to the type of EUS-procedure being trained. It may also be that the trainee-performed EUS-FNA should be assessed more profoundly than previously attempted and include parameters such as diagnostic accuracy. Similar tools already exist for the purpose of assessing competence in polypectomy during colonoscopy[45].

Clinical research addressing the issue of assessing endosonographers in training should be encouraged. Studies presenting new assessment tools and studies validating suggested tools would be valuable. Such initiatives could be a great support in the education and training of future endosonographers. Although attempts are not lacking[27], there is an urgent need to establish an international consensus on the benchmarks for high-quality performance and competence in EUS.

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MINIREVIEWS

Necroptosis in inflammatory bowel disease and other intestinal diseases

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Abstract

For a long time, it was believed that apoptosis and necrosis were the main pathways for cell death, but a growing body of research has shown that there are other pathways. Among these, necroptosis, a regulatory caspase-independent, programmed cell death pathway, is supposed to be of importance in the pathogenesis of many diseases. The mechanism of regulating, inducing and blocking necroptosis is a complex process that involves expression and regulation of a series of molecules including receptor interacting protein kinase 1 (RIPK1), RIPK3, and mixed lineage kinase like protein. By blocking or downregulating expression of key molecules in the necroptotic pathway, intestinal inflammation can be affected to some extent. In this paper, we introduce the concept of necroptosis, its main pathway, and its impact on the pathogenesis of inflammatory bowel disease (IBD) and other intestinal diseases, to explore new drug targets for intestinal diseases, including IBD.

Key words: Inflammatory bowel disease; Necroptosis; Inflammation; Colorectal cancer; Intestinal infectious diseases; Drug therapy; Receptor interacting protein kinase 1 inhibitor

Core tip: This minireview is based on the currently available literature about necroptosis and aims to

uncover the role of necroptosis in the pathogenesis of inflammatory bowel disease and other intestinal diseases, including colorectal cancer and intestinal infectious diseases. The main regulatory pathways for necroptosis are summarized. Drug therapy targeting of necroptosis is also described.

Li S, Ning LG, Lou XH, Xu GQ. Necroptosis in inflammatory bowel disease and other intestinal diseases. *World J Clin Cases* 2018; 6(14): 745-752 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/745.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.745

INTRODUCTION

The balance between cell death, proliferation and differentiation focuses on the maintenance of homeostasis and normal development. Cell death has long been thought to occur primarily in two ways: apoptosis and necrosis. The former refers to caspase-dependent programmed cell death. Due to the quick phagocytosis and degradation of apoptosomes by phagocytes[1], apoptosis is normally considered to be an immune silent cellular activity. The latter is mainly characterized by destruction of cell membrane integrity, release of a large number of intracellular components, and induction of inflammatory reactions in surrounding tissues[2]. However, more and more studies have proved that cell death is not only caused by apoptosis or necrosis. In 2005, Degterev *et al*[3] reported a new method of cell death: necroptosis. This new cell death pathway has similar morphological features to necrosis, but the mechanism of the regulation is caspase-independent programmed cell death. With the use of caspase inhibition, necroptosis can be triggered by the combination of death receptor and ligand.

TUMOR NECROSIS FACTOR-α PATHWAY AND OTHER PATHWAYS FOR NECROPTOSIS

Although studies have shown that there may be multiple pathways involved in necroptosis, the tumor necrosis factor (TNF)-α-mediating pathway is considered to be the most widely researched one. It can be activated by the combination of TNF-α and TNF receptor 1 (TNF-R1). Since the downstream of TNF-α and TNF-R1 pathways involves a variety of molecules that participate in several physiological processes including cell survival, apoptosis, necrosis, necroptosis, and inflammatory factor production, the combination can mediate different cell physiological processes through the formation of diverse compounds corresponding to specific physiological or pathological conditions.

Formation of Complex Ⅰ

The combination of TNF-α and TNF-R1 can raise TNF-α receptor associated death domain protein (TRADD), receptor interacting protein kinase (RIPK)1, TNFR-associated factor 2, cellular inhibitors of apoptosis (cIAP1 or cIAP2) and linear ubiquitin chain assembly complex to form Complex Ⅰ. Complex Ⅰ can activate the mitogen-activated protein kinase (MAPK) pathway and nuclear factor (NF)-κB pathway by collecting TGF–TAK1–TAB complex and IKK1–IKK2–NEMO complex, then activating the proinflammatory pathway to avoid cell death[4].

Formation of Complex Ⅱa

Complex Ⅱa is composed of TRADD, Fas-associated death domain (FADD) and caspase-8, which forms when Complex Ⅰ is unstable. Complex Ⅱa mainly mediates cell apoptosis[4,5].

Formation of Complex Ⅱb

In some particular cases, *e.g.*, cIAP inhibitors exist or IAPs are knocked out[6], TAK1 inhibitors exist or TAK1 is knocked out[7], and NEMO is knocked out[8] the MAPK pathway and NF-κB pathway induced by Complex Ⅰ cannot be activated. RIPK1, RIPK3, FADD and caspase-8 comprise Complex Ⅱb. Since caspase-8 can break the interaction sites between RIPK1 and RIPK3, which leads to inactivation of the complex, Complex Ⅱb typically activates the RIPK1-dependent apoptosis pathway rather than the necroptosis pathway mediated by the RIPK1–RIPK3 complex. Complex Ⅱb may act through the formation of necrosomes when caspase-8 activity decreases or RIPK3 and mixed lineage kinase like protein (MLKL) levels are high enough. Intracellular FADD-like interleukin (IL)-1β converting enzyme (FLICE)-inhibitory protein (FLIPL) can form caspase-8-FLIPL heteromeric compounds, which have only caspase-8 catalytic activity. So, FLIPL participates in the regulation of both cell death pathways: apoptosis and necroptosis by controlling RIPK1 and RIPK3 level through proteolysis[4].

Formation of Complex Ⅱc

When caspase-8 is inhibited or missing, Complex Ⅱb will transfer to Complex Ⅱc, forming necrosomes (the complex includes RIPK1, RIPK3 and MLKL). RIPK1 and RIPK3 interact and activate downstream MLKL to trigger the necroptosis pathways[4] (Figure 1).

Eventual executives for necroptosis

The eventual executives for necroptosis pathway are not yet clear. MLKL is one of the most widely researched molecules and a commonly used indicator assessing the effect of necroptosis in the pathogenesis of inflammatory bowel disease (IBD). MLKL is a fake kinase, which possesses a kinase domain structure but lacks kinase activity. RIPK3 can activate the corresponding threonine and serine site of MLKL and make it phosphorylate.

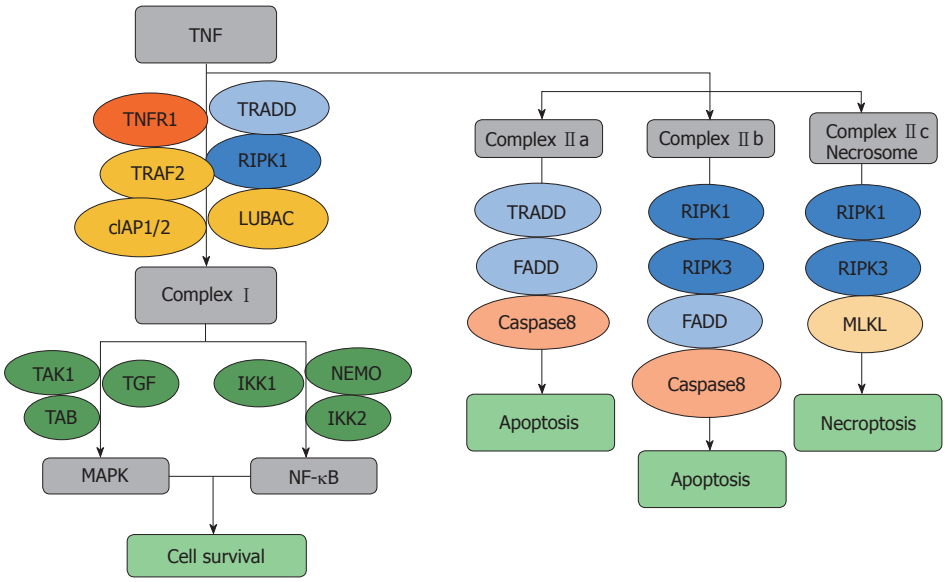

Figure 1 Tumor necrosis factor-α pathway for necroptosis. Combination of tumor necrosis factor (TNF)-α and TNF-R1 can raise TNF-α receptor associated death domain protein (TRADD), receptor interacting protein kinase 1 (RIPK1), TNFR-associated factor 2, cellular inhibitors of apoptosis (cIAP1 or cIAP2) and linear ubiquitin chain assembly complex to form Complex Ⅰ, which can activate the Mitogen-activated protein kinase and NF-κB pathways by binding the TGF–TAK1–TAB and IKK1–IKK2–NEMO complexes, leading to cell survival. Complex Ⅱa [consists of TRADD, Fas-associated death domain (FADD) and caspase-8] forms when Complex Ⅰ is unstable and mediates apoptosis independent of RIPK1. Complex Ⅱb (consists of RIPK1, RIPK3, FADD and caspase-8) forms when cIAP inhibitors are present or IAPs are knocked out, TAK1 inhibitors are present or TAK1 is knocked out, and NEMO is knocked out, and mediates apoptosis dependent on the binding of RIPK1 and RIPK3. Complex Ⅱc (consists of RIPK1, RIPK3 and MLKL) forms when caspase-8 is inhibited or missing and leads to necroptosis. TRAF2: TNFR-associated factor 2; cIAP1 or cIAP2: Cellular inhibitors of apoptosis; LUBAC: Linear ubiquitin chain assembly complex; TRADD: TNF-α receptor associated death domain protein; MAPK: Mitogen-activated protein kinase; FADD: Fas-associated death domain.

The phosphorylation of MLKL changes its conformation to form oligomers. Oligomerized MLKL exposes the N-terminal domain structure, which promotes necrosome transfer from the cytoplasm to the cell or organelle membrane. This destroys membrane integrity and leads to cell death[9,10].

Other pathways for necroptosis

TNF ligand superfamily member 10 (TRAIL) and TNF ligand superfamily member 6 (FasL)-mediated pathways share many similarities with the TNF-α pathway, and activate caspase-8 and induce apoptosis. If caspase-8 is inhibited, the necroptosis pathway is activated. However, these two pathways also have their own characteristics. First, the TNF-α pathway forms a prosurvival signaling complex first and then a death-inducing complex. The TRAIL/FasL pathways form a death-inducing signaling complex, which consists of Fas/DR4,5 (also known as TRAILR1,2), FADD and caspase-8[11] and subsequently induce apoptosis. Second, RIPK1 can directly bind to TNF-R1 through its DD domain. The binding of FasL and TRAIL receptors to RIPK1 requires FADD as a bridge[12,13]. Therefore, FADD is necessary for TRAIL and FasL signaling pathways, but is not necessary for the TNF-α associated pathway[11]. The main function of FADD is to provide binding sites for caspase-8 and caspase-10 precursors and the activated combination subsequently mediates downstream caspase-3, caspase-6 and caspase-7, and finally induces apoptosis[14,15] (Figure 2).

NECROPTOSIS AND INFLAMMATION

The relationship between necroptosis and inflammation remains unclear. Some scholars believe that cells release damage-associated molecular patterns (DAMPs) through pyrolysis in the process of necroptosis. DAMPs can activate the immune system by itself or combining with pathogen-associated molecular patterns. It can promote macrophages and dendritic cells and other sentinel cells activate and increase the level of abundant cytokines including interleukin (IL)-1 superfamily (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, and IL-36γ), which mediates the pathogenesis of various acute and chronic inflammatory diseases[4,16,17]. Duprez *et al*[18] have shown that necroptosis mediated by RIPK1–RIPK3 can increase the mortality from systemic inflammatory response syndrome induced by TNF. With *RIPK3* gene knockout or preventive use of RIPK1 inhibitors, necrostain-1 can effectively alleviate the levels of DAMPs in the circulation. In the model of myocardial ischemia/reperfusion, phosphorylation of RIPK1 and RIPK3 is always accompanied by infiltration of a large number of neutrophils. Necrostain-1 dramatically reduces inflammation. It presents a lower level of TNF-α and oxidative stress, reduction of adverse myocardial remodeling, and improvement of cardiac function[19]. In addition, in the liver injury model induced by ethanol, the loss of RIPK3 can avoid the pathogenesis of liver cirrhosis, the increase in inflammatory factors, and therefore prevent liver tissue injury[20]. The dual deletion

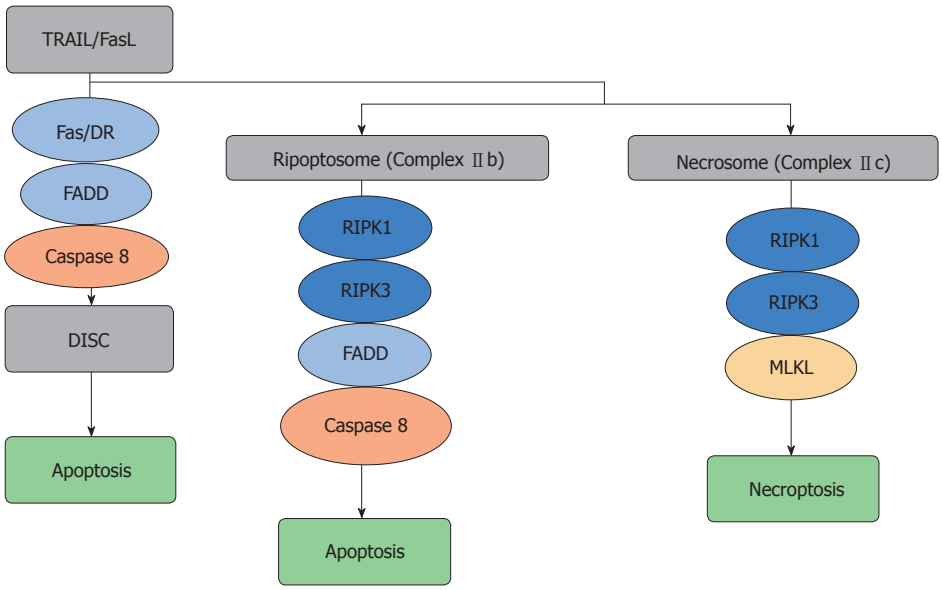

Figure 2 Tumor necrosis factor ligand superfamily member 10/tumor necrosis factor ligand superfamily member 6 pathways for necroptosis. Tumor necrosis factor (TNF) ligand superfamily member 10 and TNF ligand superfamily member 6 pathways induce apoptosis independent of receptor interacting protein kinase 1 (RIPK1) with the formation of death-inducing signaling complex [consists of Fas/DR, Fas-associated death domain (FADD) and caspase-8]. Ripoptosome (consists of RIPK1, RIPK3, FADD and caspase-8) forms in particular situations such as presence of cellular inhibitors of apoptosis (IAP) antagonists or IAP knock out and leads to apoptosis. Necrosomes (consists of RIPK1, RIPK3 and mixed lineage kinase like protein) form when caspase-8 is inhibited or blocked, and induces necroptosis. DISC: Death-inducing signaling complex; MLKL: Mixed lineage kinase like protein; TRAIL: TNF ligand superfamily member 10; FasL: TNF ligand superfamily member 6; FADD: Fas-associated death domain.

of RIPK1 and FADD induces necroptosis, which is dependent on RIPK3 in colon intestinal epithelial cells, decreases the number of Paneth cells, and causes localized inflammatory damage[21].

However, there are also researchers who consider that some pathogens may terminate the signaling cascade of proinflammatory factors through necroptosis to limit the cytokine storm. Necroptosis can inhibit excessive release of inflammatory factors induced by TNF/Toll-like receptor (TLR) in a specific environment and therefore plays an anti-inflammatory role[16]. The TNF-α pathway, for example, participates in inflammation, apoptosis and necroptosis, but has different outcomes under disparate physiological conditions. Therefore, the result of transformation from an inflammatory response dependent on TNF to necroptosis is not just cell death (although DAMPs released during the process can also promote inflammation), but the cascade induced by TNF itself, a powerful inflammatory factor. The end of the cascade avoids stimulation of cell synthesis and the release of more cytokines and chemokines, which limit the inflammatory response[22]. According to the study of Alvarez-Diaz *et al* [23], mice with FADD/MLKL or caspase-8/MLKL double knockout develop severe systemic autoimmune diseases and die within a short period of time due to the dramatic increase in a variety of cytokines and chemokines. In addition, Newton *et al*[24] have shown that RIPK3 deficiency does not improve sepsis induced by lipopolysaccharide (LPS), colitis induced by dextran sulfate sodium (DSS), pancreatitis induced by frosin, and brain injury induced by hypoxia. The absence of MLKL cannot protect against kidney injury caused by ischemia–reperfusion[24]. Bozec *et al*[25] have shown that expression of RIPK3 decreases in colorectal cancer (CRC) patients with IBD, which further demonstrate the anti-inflammatory effect of necroptosis.

NECROPTOSIS AND IBD

IBD is a kind of chronic, nonspecific intestinal inflammatory disease whose pathogenesis is unclear. The main pathological types of IBD are ulcerative colitis (UC) and Crohn's disease (CD). Despite the lack of epidemiological data for IBD in developing countries, the prevalence of IBD is on the rise globally[26]. Although the cause of IBD remains unknown, environmental, infectious, immune and genetic factors are involved in the pathogenesis of excessive apoptosis of intestinal epithelial cells, damage to the intestinal mucosal barrier, and higher permeability of intestinal epithelial cells, which are considered to contribute to the development of IBD[27]. Necroptosis is a new mode of cell death. The process of necroptosis is regulated as well as apoptosis. So, some scholars think that necroptosis plays an important role in the pathogenesis of IBD.

In situ end labeling technology cannot distinguish between apoptosis and necroptosis, and early research about the effect of apoptosis in the pathogenesis of IBD cannot prove whether necroptosis plays the same role[4]. Recent studies based on animal models and patients with IBD have suggested that necroptosis plays a role in the development of intestinal inflammation.

Welz *et al*[28] found in mice that intestinal epithelial cells with FADD gene knock out presented with necrosis dependent on RIPK3, reduced Paneth cells, enteritis

and severe colitis. The absence of RIPK3 or the use of CYLD inhibitors can inhibit this spontaneous pathological process. Mice with intestinal epithelial cell caspase-8 gene knock out also had inflammatory lesions in the terminal ileum (increased Paneth cell death and reduced goblet cells), and high susceptibility to colitis. These findings were related to increased levels of RIPK3[29]. RIPK3 knock down can reduce intestinal inflammation in caspase-8 knockout mice to a certain extent[30]. All these studies based on mouse models have shown that necroptosis of intestinal epithelial cells induces intestinal inflammation.

Günther *et al*[29] have confirmed that in adult CD patients, the level of RIPK3 expressed by Paneth cells increases along with necroptosis in the terminal ileum. By comparison between adult penetration type CD patients, adult narrow type CD patients and healthy controls, serum level of TNF-α and mucosal tissue level of RIPK3 are obviously increased in both types of CD[10]. Pierdomenico *et al*[31] investigated biopsy samples from 33 children with CD and 30 with UC and found increased expression of RIPK3 and MLKL in inflammatory tissue and dramatically decreased expression of caspase-8. There was no significant difference in expression of all three proteins in non-inflammatory tissues, which confirm that necroptosis can magnify the inflammatory response and induce pathological conditions in the intestine. Negroni *et al*[32] have confirmed that necroptosis induced by RIPK3 can activate MLKL and increase expression of IL-8, IL-1β, IL-33 and high-mobility group protein 1. Necroptosis then induces the translocation of NF-κB p65 and the assemblage of inflammasome NLRP3. At the same time, the integrity of the intestinal epithelial barrier induced by various intercellular connective proteins, including Cadherin E and occludin can also be influenced, which mediates the occurrence of intestinal inflammation[32].

NECROPTOSIS AND CRC

Incoercible proliferation of intestinal epithelial cells and decreased cell death are the main pathological processes of CRC. Therefore, necroptosis plays an important role in the occurrence and development of CRC. Expression levels of RIPK1 and RIPK3 were lower in mucosal tissue of CRC patients compared to normal mucosal tissues, which indicates that necroptosis plays a role in the induction of cell death and inhibition of CRC development. Bozec *et al*[25] have shown that RIPK3 has a suppressive effect on CRC, while tumor cells without RIPK3 are often more invasive. *RIPK3* knockout mice are more susceptible to CRC related enteritis. The lack of *RIPK3* gene leads to excessive activation of the NF-κB, signal transducer and activator of transcription (STAT) 3, AKT and Wnt-β–catenin pathways, which results in abnormal proliferation of intestinal epithelial cells and the occurrence of tumor.

The induction of TNF-α-related necroptosis by RIPK1 and NF-κB can overcome the apoptosis tolerance in CRC and significantly suppress tumor growth[33]. *In vivo* experiments have confirmed that combination of a new type of pan-caspase inhibitor IDN-7314 and 5-fluorouracil (5-FU) is beneficial in CRC patients with 5-FU resistance, through increased cell necroptosis[33]. Induction of necroptosis also increases intestinal epithelial cell death in CRC patients with apoptosis tolerance induced by absence of caspase-8[34]. Sun *et al*[35] have shown that 3-bromine pyruvate (hexokinase inhibitor) causes organelle swelling, damaged cell membrane integrity, exudation of cell contents and increased necroptosis in SW480 and HT29 colon cancer cells. Necrostin-1 significantly recovers cell survival. A recent study also showed that resibufogenin suppresses growth and metastasis of CRC through RIPK3-mediated necroptosis. This kind of effect can be reduced by RIPK3 deficiency rather than the use of z-VAD, a pan-caspase general inhibitor, which confirms the role of necroptosis in the treatment of CRC[36].

NECROPTOSIS AND INTESTINAL INFECTIOUS DISEASES

The balance between death and survival of intestinal epithelial cells is essential to maintain integrity of the intestinal barrier and intestinal homeostasis. Excessive death of intestinal epithelial cells damages the function of the intestinal barrier, leading to weakened resistance to pathogenic bacteria. Hefele *et al*[37] have shown that caspase-8 knockout mice present with more severe mucosal injury and intestinal epithelial cell death after infection with *Salmonella typhimurium* compared to wild-type mice. Knock out of *RIPK3* or *MLKL* can significantly relieve the mucosal injury and intestinal epithelial cell death. Qi *et al*[38] have also shown that infection with *S. typhimurium* without sopB induces phosphorylation of MLKL and therefore promotes necroptosis of goblet cells. This induces more severe intestinal damage, including increased levels of cytokines and chemokines and decreased mucus and mucin-2. However, this kind of physiological or pathological process can be effectively alleviated in MLKL knockout mice. TLRs expressed on the surface of intestinal epithelial cells can promote the identification of microorganisms. Stimulation of TLRs leads to intestinal epithelial cell loss, which mediates epithelial antibacterial and antiviral activity in the host and helps to remove exogenous pathogens.

Caspase-8 knockout mice show more severe injury of intestinal epithelial cells with the activation of the necroptosis pathway induced by RIPK3 rather than the extrinsic apoptotic pathway after stimulation of TLRs. TLR-3 mediate necroptosis through TRIF and TLR-4 mediates necroptosis through TNF-α. RIPK inhibitor can improve intestinal injury induced by LPS and maintain the function of the intestinal barrier. These results provide new ideas for the treatment of intestinal inflammation and infectious diseases[39] (Table 1).

Table 1 Effects of necroptosis in intestinal diseases

Disease	Expression of necroptosis moleculars	Pathological processes may involve after the activation of Necroptosis
IBD	RIPK3 upregulated MLKL upregulated, caspase-8 downregulated	(1) Impair intestinal epithelial barrier and membrane permeability (2) Commensal bacteria invade the mucosa through TLR signaling (3) Reduce number of Paneth cell (4) Increase expression of cytokines (*e.g.*, IL-8, IL-1β, IL-33, HMGB1) (5) Translocation of NF-κB p65 and assembly of inflammasomes NALRP3
CRC	RIPK3 downregulated, RIPK1 downregulated	(1) Suppress excessive activation of NF-κB, STAT3, AKT and Wnt-β-catenin pathways (2) Overcome the apoptosis tolerance in CRC and suppress tumor growth and metastasis
Intestinal infectious diseases	RIPK3 and MLKL upregulated when caspase-8 is deficient	(1) Impair the integrity of intestinal epithelial barrier (2) Increase levels of cytokines and chemokines, and decrease levels of mucus and mucin-2 (3) TLR-3 mediate necroptosis through TRIF and TLR-4 mediates necroptosis through TNF-α

IBD: Inflammatory bowel disease; CRC: Colorectal cancer; RIPK: Receptor interacting protein kinase; IL: Interleukin; MLKL: Mixed lineage kinase like protein; TLR: Toll-like receptor; TNF: Tumor necrosis factor; STAT: Signal transducer and activator of transcription.

DRUG THREAPY TARGETING IN NECROPTOSIS

Since necroptosis may play a partial role in the pathogenesis of IBD, regulation of the key molecules during necroptosis may provide a new target for the treatment of IBD. The most frequently studied among these is necrostatin-1, an RIPK1-specific inhibitor whose protective effect in IBD has been widely reported[29,32,40]. Liu *et al*[40] have confirmed that when the structure of RIPK1–RIPK3 complex is destroyed[41,42] by necrostatin-1, expression of RIPK1 and RIPK3 is decreased and expression of caspase-8 is increased in a mouse model of intestinal inflammation induced by DSS. The use of necrostatin-1 thus restores weight loss, decreased colon length, damage to the intestinal mucosa, and excessive release of inflammatory factors like IL-6. As an effective necroptosis inhibitor, necrostatin-1 has the following characteristics: inhibition of necroptosis without affecting apoptosis and autophagy; no effect on the physiological function of normal cells[43].

Apart from necrostatin-1, autophagy protein ATG16L1 reported by Matsuzawa-Ishimoto *et al*[44] also alleviates necroptosis in an IBD model induced by virus infection, through TNF-α and RIPK1, and maintains integrity of the intestinal barrier. Dong *et al*[45] have confirmed that necrosulfonamide reverses the histological abnormality induced by TNF-α and Z-VAD-fmk and reduces the degree of necroptosis.

Other recent studies also reported drug therapy targeting necroptosis in other diseases. Nikseresht *et al*[46] revealed that ex-527, a selective inhibitor of Sirt1, reduced expression of critical regulators of necroptosis in a model of cerebral ischemia–reperfusion injury, which resulted in alleviation of infarction volume and increased survival. Rats with cognitive impairment induced by severe acute pancreatitis show increased levels of RIPK3 and RIPK1, and berberine can partly treat this cognitive impairment through attenuation of neuronal necroptosis[47]. Oliveira *et al*[48] have found that Oxa12, a new oxazolone, can reduce TNF-α-induced necroptosis in mouse L929 fibrosarcoma cells and zVAD-fmk-induced necroptosis in murine BV2 microglial cells. They have confirmed that Oxa12 disturbs the phosphorylation of MLKL and formation of necrosome complexes, which provides a new insight into the treatment of other inflammatory diseases. Another interesting study has shown that AdipoRon, an antidiabetic adiponectin receptor agonist, can lead to the death of MIAPaCa-2 cells (human pancreatic carcinoma cell line) through necroptosis *via* the activation of RIPK1 and extracellular signal-regulated kinase 1/2[49].

CONCLUSION

Although current research has confirmed that necroptosis is an important pathway of programmed cell death, many problems remain to be explored and resolved. How cells select survival, apoptosis, necrosis and necroptosis according to different physiological and pathological conditions is unclear. The interaction between various

terminal states also needs to be further explored. In the necroptosis pathway, how RIPK3 induces necroptosis and inhibits apoptosis at the same time, the molecular mechanisms of MLKL, and the regulation of RIPK family activity and its substrates are still controversial. In the pathogenesis of IBD, the role of necroptosis in the process of initiation, amplification and extension of inflammation needs to be confirmed. The TNF-α pathway is the most widely studied necroptotic pathway, but which downstream effects are activated, necroptosis, apoptosis or inflammation, in the pathogenesis of IBD needs further investigation. TNF monoclonal antibody is currently the main drug for the treatment of IBD, although up to 50% of patients show no response, and an increased risk of infection[50]. This suggests that there is an urgent need to explore new treatments for IBD. We believe that with further investigation of the molecular mechanism of necroptosis, we will be more aware of cell death and develop new ideas for exploration of the pathogenesis of various human diseases.

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ORIGINAL ARTICLE

Case Control Study

Benefits of the Seattle biopsy protocol in the diagnosis of Barrett's esophagus in a Chinese population

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Abstract

AIM

To investigate the benefits of the Seattle protocol in the diagnosis of Chinese individuals with Barrett's esophagus.

METHODS

Subjects enrolled were patients from one center with endoscopically-suspected esophageal metaplasia. These patients first received narrow-band imaging-targeted biopsy, and later, the Seattle protocol-guided biopsy, within a period from October 2012 to December 2014. Those cases without initial pathologic patterns of intestinal metaplasia (IM) and then appearance or loss of IM tissue were designated as Group A or B, respectively. Those with initial pathologic patterns of

IM, which then persisted or were lost were designated as Group C or D, respectively.

RESULTS

The number of cases for each group was as follows: A: 20, B: 78, C: 31 and D: 14. The distribution of the Prague criteria M levels of Group A was significantly higher than Group B (P = 0.174). Among these groups, Group C had the highest proportions of hiatus hernia (54.8%), long segment Barrett's esophagus (29%), and also the highest Prague criteria M levels. The sensitivity of IM detection was 69.2% for the narrow-band imaging-targeted biopsy and 78.5% for the Seattle protocol-guided biopsy. The difference was not significant (P = 0.231). The number of detectable dysplasias increased from one case *via* the NBI-target biopsy to five cases *via* the Seattle protocol-guided biopsy, including one case of adenocarcinoma.

CONCLUSION

The Seattle protocol improved the IM detection in our subjects with higher Prague criteria M levels and disclosed more cases with dysplastic tissues.

Key words: Barrett's esophagus; Dysplasia; Intestinal metaplasia; Seattle protocol; Chinese

Core tip: While comparing the diagnosis of Barrett's esophagus in a Chinese population *via* narrow-band imaging-targeted biopsy or the Seattle protocol-guided biopsy, the sensitivity of intestinal metaplasia detection was 69.2% and 78.5%, respectively. The number of detectable dysplasias increased from one case *via* the narrow-band imaging-targeted biopsy to five cases *via* the Seattle protocol-guided biopsy. These results concluded that the Seattle protocol identified more cases with dysplastic tissues.

Lee SW, Lien HC, Chang CS, Lin MX, Chang CH, Ko CW. Benefits of the Seattle biopsy protocol in the diagnosis of Barrett's esophagus in a Chinese population. *World J Clin Cases* 2018; 6(14): 753-758 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/753.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.753

INTRODUCTION

Endoscopically, the current definition of Barrett's esophagus (BE) includes the presence of an area of salmon-colored mucosa in the distal esophagus, plus the histological finding of intestinal metaplasia (IM) in the esophagus[1]. BE is clinically important because it is a major risk factor for the development of esophageal adenocarcinoma (EAC), and the number of EAC cases has been growing in Western countries[2]. EAC is typically diagnosed at an advanced stage when it also has a poor prognosis, as its 5-year survival rate is low (17%)[3]. Therefore, early detection of BE, especially those with dysplastic tissue, attracted recent research interests. Regarding the choice of biopsy methods in detecting BE, the use of narrow band imaging (NBI) has been compared with traditional white light endoscopy (WLE), and results showed its superiority over WLE[1,3]. According to the American Gastroenterological Association guidelines, the standard for diagnosing BE is the endoscopic evaluation performed with 4-quadrant biopsy specimens taken every 1-2 cm, which is described as the Seattle biopsy protocol[1,4]. However, some in this field considered disadvantages of the Seattle protocol as being relatively inefficient, time-consuming and providing a low diagnostic rate[5-7]. In Europe, reportedly only half of endoscopists follow the Seattle protocol for biopsy of BE patients[8,9].

Our present study was aimed to evaluate the benefits of the Seattle protocol on BE cases in a Chinese population of Taiwan.

MATERIALS AND METHODS

Subject collection

We collected data from subjects who had endoscopically-suspected esophageal metaplasia followed by NBI-targeted biopsy conducted at the Medical Screening Center at Taichung Veteran General Hospital. Over a period from October 2012 to December 2014, these patients were asked to repeat another open-access transoral upper gastrointestinal endoscopy together with the Seattle protocol-guided biopsy. NBI-target biopsy was defined as surveillance of the gastroesophageal junction (GEJ) with NBI, and a biopsy was taken according to the individual endoscopist's expertise. Seattle protocol-guided biopsy was performed with 4-quadrant biopsy specimens taken every 1-2 cm at the GEJ. We recorded the general patient data, which included their age, gender, and body mass index (BMI). In addition, we collected their endoscopic findings, including hiatus hernia, erosive esophagitis (EE), short segment BE (SSBE, extending < 3 cm into the esophagus) and long segment BE (LSBE, extending $\geqslant$ 3 cm into the esophagus)[10], the Prague C and M criteria[11], and pathologic dysplasia appearances, including low-grade dysplasia (LGD), high grade dysplasia and EAC.

Exclusion criteria

Exclusion criteria included total esophagectomy, severe cardiopulmonary deficiency, malignancy, other unsuitable conditions for upper gastrointestinal scope, and segments of metaplastic columnar epithelium < 1 cm, which were classified as "specialized IM of the esophagogastric junction".

Table 1 General data and endoscopic appearances of groups A and B

	Group A (n = 20)		Group B (n = 78)		P-value
	mean ± SD	n (%)	mean ± SD	n (%)	
Age (yr)	60.95 ± 17.29		55.19 ± 13.28		0.189[1]
Gender (male)		9 (45.0)		35 (44.9)	0.992[2]
BMI (kg/m^2)	25.76 ± 4.52		23.69 ± 3.59		0.079[1]
EE		7 (35.0)		15 (19.2)	0.132[2]
Hiatus hernia		8 (40.0)		15 (19.2)	0.051[2]
LSBE		2 (10.0)		3 (3.8)	0.269[2]
Biopsy pieces	4.58 ± 1.57		3.39 ± 1.74		0.009[1]

[1]P-values were analyzed with t-test; [2]P-values were analyzed with Pearson's χ^2 test. BMI: Body mass index; EE: Erosive esophagitis; LSBE: Long segment Barrett's esophagus.

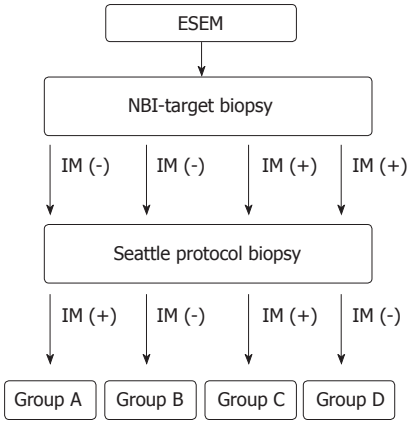

Figure 1 The flow-chart of stratified groups in this study. ESEM: Endoscopically-suspected esophageal metaplasia; NBI: Narrow-band imaging; IM: Intestinal metaplasia.

Seattle protocol

The flow-chart of the study is shown in Figure 1. Subjects without initial pathologic patterns of IM, but with IM tissue detected later by the Seattle protocol were classified into "Group A". Subjects without initial pathologic patterns of IM and without IM tissue detected later by the Seattle protocol were classified into "Group B". Subjects with initial pathologic patterns of IM and again confirmed by the Seattle protocol later were classified into "Group C". Subjects with initial pathologic patterns of IM that were not detected later by the Seattle protocol were classified into "Group D". After grouping, inter-group differences were analyzed statistically as described below.

Statistical analysis

Data of each measured parameter were first expressed as mean and standard deviation. Gender, hiatus hernia, endoscopic and pathologic findings of BE tissue of the stratified groups were expressed as percentages of patients in their respective groups. Comparisons were made using Pearson's chi-square test to evaluate the contributions of gender and positive ratio of each stratified group. Independent t-tests were used to analyze age, BMI, and numbers of biopsy pieces. A P-value < 0.05 was considered statistically significant.

RESULTS

From the total of 143 enrolled subjects, the number of patients in each group was as follows: A: 20 (14%), B: 78 (54.5%), C: 31 (21.7%) and D: 14 (9.8%).

First, for Groups A and B, their general data and endoscopic appearances are shown in Table 1. The levels of age, gender and BMI were similar between the two groups. Compared to Group B, Group A had slightly higher proportions of EE (35% *vs* 19.2%, P = 0.132), hiatus hernia (40% *vs* 19.2%, P = 0.051), and LSBE (10% *vs* 3.8%, P = 0.269), but none of the differences were statistically significant. However, we found significantly more endoscopic biopsy pieces at the GEJ in Group A than in Group B (mean 5.69 *vs* 4.00, P = 0.039). The Prague C and M criteria of these subjects in Groups A and B are shown in Figure 2A. The distributions of "C" levels were similar between groups (P = 0.174), but the "M" levels were significantly higher in Group A (P = 0.021).

The general data, endoscopic appearances and the Prague C and M criteria for Groups C and D are shown in Table 2 and Figure 2B. Group C had, among all groups, the highest proportion of hiatus hernia (54.8%), LSBE (29%) and the highest Prague criteria "M" levels. Group D, compared to Group C, had a significantly higher proportion of EE (57.1% *vs* 19.4%, P = 0.011) and fewer biopsy pieces (mean 4 *vs* 5.69, P = 0.039).

The results of the two different biopsy protocols in terms of sensitivity of IM detection are listed in Table 3. Among all subjects with pathologic appearance of IM at the GEJ (n = 65 in Groups A, C and D), 45 of them (in Groups C and D) yielded positive IM results *via* NBI-target biopsy at a sensitivity of 69.2%. In comparison, 51 subjects (in Groups A and C) yielded positive IM results *via* the Seattle protocol-guided biopsy, with a higher sensitivity of 78.5%. However, the difference of IM detection rates between these two biopsy protocols was not significant (P = 0.231).

As shown in Table 3, the number of detectable dysplasias in the GEJ of all the enrolled subjects was only one case at the beginning with NBI-target biopsy, which later increased to five cases using the Seattle protocol. Among the five subjects, four were LGD and

Table 2 General data and endoscopic appearances of groups C and D

	Group C (n = 31)		Group D (n = 14)		P-value
	mean ± SD	n (%)	mean ± SD	n (%)	
Age (yr)	66.53 ± 12.47		65.79 ± 14.18		0.860[1]
Gender (male)		25 (80.6)		12 (85.7)	0.518[2]
BMI (kg/m^2)	25.65 ± 3.70		23.14 ± 3.64		0.051[1]
EE		6 (19.4)		8 (57.1)	0.011[2]
Hiatus hernia		17 (54.8)		6 (42.9)	0.457[2]
LSBE		9 (29.0)		2 (14.3)	0.287[2]
Biopsy pieces	5.69 ± 2.82		4.00 ± 2.18		0.039[1]

[1]P-values were analyzed with t-test; [2]P-values were analyzed with Pearson's χ^2 test. BMI: Body mass index; EE: Erosive esophagitis; LSBE: Long segment Barrett's esophagus.

Table 3 Results of the two different biopsy protocols n (%)

	NBI-targeted biopsy	Seattle protocol-guided biopsy	P-value
IM (n = 65)	45 (69.2)	51 (78.5)	0.231[2]
Dysplastic tissue			
Group A (n = 20)	0 (0.0)	2 (10.0)[2]	0.487[1]
Group B (n = 31)	1 (3.2)[2]	3 (9.6)[1]	0.612[1]
Group C (n = 14)	0 (0.0)	0 (0.0)	1.000[1]

[1]P-values were analyzed with Fisher's exact test; [2]P-values were analyzed with Pearson's χ^2 test. All dysplastic tissues were low-grade dysplasia except one adenocarcinoma in Group B detected *via* Seattle protocol guided biopsy. IM: Intestinal metaplasia; NBI: Narrow-band imaging.

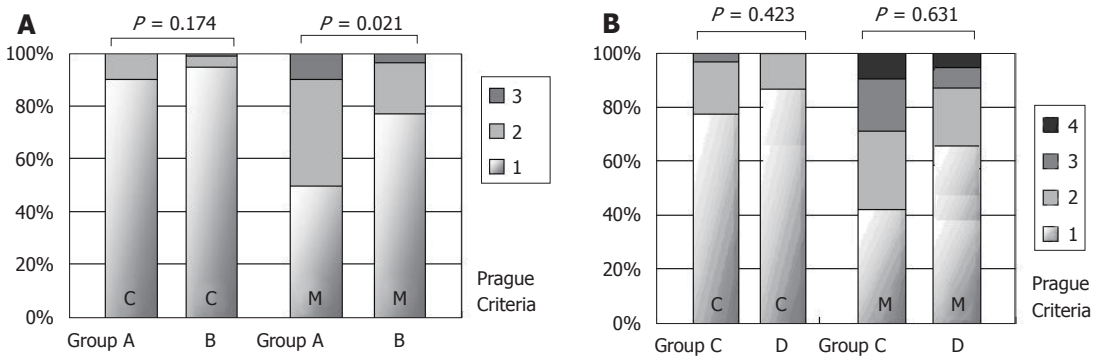

Figure 2 Endoscopic appearances of the patients in Groups A and B (A), Groups C and D (B) according to the Prague C and M criteria.

one was EAC arising from the BE tissue.

DISCUSSION

BE, a condition in which the squamous epithelium of the distal esophagus is replaced by columnar epithelium with IM, is a well-established precursor of EAC. Regarding the risk of EAC, BE has a > 40-fold increase over the general population. Although BE has been a disease primarily found in the Western world, it has become more frequently reported in Asian countries[12]. The underlying etiology of BE is still unclear. In the majority of cases, BE is associated with a combined reflux of acid and bile, even in the absence of symptoms. The prevalence of BE has been estimated at 1%–2% in patients undergoing endoscopy for any indication, and the prevalence rises to 5%–15% in patients with gastroesophageal reflux disease (commonly known as GERD) symptoms[13]. Risk factors for BE include older ages, male gender, Caucasian race, GERD symptoms, central abdominal obesity, and possibly tobacco smoking[14].

Due to the extremely poor outcome of EAC, the early and accurate diagnosis of BE, especially with the presentation of dysplastic tissue, is particularly important. Currently, the use of electronic chromoendoscopy, like NBI, is a standard protocol for detecting BE. According to previous reports, NBI, compared to WLE, could better detect dysplasia in BE, and higher grades of dysplasia with fewer biopsy samples[3,15]. It is the recommendation of the American Gastroenterological Association guidelines that 4-quadrant biopsy specimens be obtained at intervals of 1-cm in BE patients with known or suspected dysplasia, and this is consistent with the Seattle protocol[1]. However, the Seattle protocol is considered by some as relatively inefficient, requiring additional biopsy procedures, longer procedure times, and higher operating costs. This technique is

also vulnerable to sampling errors, consequently lower diagnostic rates, suboptimal disease management, and poorer adherence to the practice guidelines[5-9].

In a multicenter, randomized, crossover trial of 123 BE patients, the NBI-targeted biopsy was compared with the 4-quadrant biopsy with WLE. No difference was found between the two techniques in terms of the frequency of detecting IM tissues (both 85%) and dysplasia (71% for NBI *vs* 55% for WLE; $P = 0.15$)[3]. However, the procedure of "4-quadrant biopsy" in that study is not fully compatible with the Seattle protocol. As a result, the IM or dysplasia detection rate might have been underestimated. Another study enrolling 2245 BE patients from the U.S. pathology database reported that only 51.2% of cases had adhered to the Seattle protocol, and more cases of LSBE were associated with poorer adherence. Furthermore, non-adherence was associated with fewer detections of dysplasia (OR = 0.53, 95%CI: 0.35-0.82)[5].

For our patients, the Seattle-protocol guided biopsy, when compared with NBI-target biopsy, slightly improved the sensitivity rate of IM at the GEJ (78.5% *vs* 69.2%), although the difference was not significant ($P = 0.231$). Further analysis showed that the Seattle-protocol-guided biopsy had improved IM detection in those cases with higher "M" levels, according to the Prague criteria. On the contrary, the Seattle biopsy protocol had limitations regarding the correct diagnoses of BE in those individuals with EE. Unsurprisingly, the more biopsy samples were obtained during endoscopy, the better the diagnosis of IM became. This could account for the lack of difference between these two biopsy protocols in detecting IM in most of our cases with LSBE, and support that the more biopsy pieces that were taken, the less likely sampling errors occurred.

The mean biopsy pieces obtained per patient in our study ranged between 3.39 and 5.69. The majority of cases with fewer biopsy pieces were SSBE (89.5%). This finding is compatible with previous studies on Asian patients[12]. According to one study, biopsies of at least eight pieces at the GEJ was required for an adequate detection of IM[16]. However, it is technically difficult to obtain as many as eight samples per SSBE patient.

One study in the UK enrolling 220 BE subjects reported a significant increase in the detection rate of all types of dysplasia when the Seattle Protocol was adapted (LGD: 12% *vs* 3.6%, advanced dysplasia: 5.2% *vs* 0.8%, $P < 0.00001$)[17]. In our study, the number of cases with dysplastic tissue over the GEJ increased from one *via* the NBI-target biopsy to five *via* the Seattle protocol-guided biopsy, although the increment was not significant. For the one patient with EAC detected early by the Seattle protocol-guided biopsy, treatments were started promptly with curative therapy, like the endoscopic submucosal dissection.

Recently, other advanced endoscopic techniques have been introduced to improve the detection of IM and dysplastic tissue in BE. These techniques include cytosponge, esophageal capsule endoscopy, dye-based chromoendoscopy, and confocal laser endomicroscopy[18,19]. However, they have not yet reached routine clinical application due to their higher costs and uncertain efficacies.

There are some limitations in our study. Firstly, the endoscopic and pathologic appearance were diagnosed or confirmed by individual endoscopists and pathologists, with inevitable inter-observer and intra-observer variations. Secondly, this study was hospital-based and data were derived from a single tertiary care center. Selection bias of cases could not be ruled out. Thirdly, some BE-associated variables, like reflux symptom, smoking habit and *Helicobacter pylori*, were not analyzed. Finally, most of our cases belonged to SSBE, and this may not reflect populations in the Western countries. Further work is still needed to confirm or reinforce our present results.

In conclusion, we found that the Seattle protocol showed improvements in IM detection in subjects with high Prague criteria "M" levels, and disclosed more cases, including EAC, with dysplastic tissue.

ARTICLE HIGHLIGHTS

Research background

According to the American Gastroenterological Association guidelines, the definition of Barrett's esophagus (BE) includes the histological finding of intestinal metaplasia (IM) in the esophagus. BE is clinically important because it is a major risk factor for the development of esophageal malignancy. Therefore, early detection of BE, especially those with dysplastic tissue, attracted recent research interests.

Research motivation

The standard for diagnosing BE is endoscopic evaluation performed with the Seattle biopsy protocol. However, some in this field consider disadvantages of the Seattle protocol as being relatively inefficient, time-consuming and providing low diagnostic rates. In Western countries, reportedly only half of endoscopists follow the Seattle protocol for biopsy of BE patients.

Research objectives

The aim of this study is to investigate the benefits of the Seattle protocol in the diagnosis of Chinese individuals with BE.

Research methods

Subjects enrolled were cases of Taichung Veterans General Hospital with endoscopically-suspected esophageal metaplasia. These patients first received the narrow-band imaging (NBI)-targeted biopsy and later the Seattle protocol-guided biopsy, within a period from October 2012 to December 2014. Cases without initial pathologic patterns of IM and then appearance or loss of IM tissue were designated as Group A or B, respectively. Those with initial pathologic patterns of IM, which then persisted or were lost were designated as Group C or D, respectively.

Research results

The number of cases for each group was as follows: A: 20, B: 78, C: 31 and D: 14. The distribution of the Prague criteria M levels of Group A was significantly higher than Group B ($P = 0.174$). The sensitivity of IM detection was 69.2% for the NBI-targeted biopsy and 78.5% for the Seattle protocol-guided biopsy. The difference was not significant ($P = 0.231$). The number of detectable dysplasia increased from one case *via* the NBI-targeted biopsy to five cases *via* the Seattle protocol-guided biopsy, including one case of adenocarcinoma.

Research conclusions

The Seattle protocol improved the IM detection in the subjects with higher Prague criteria M levels, and it disclosed more cases with dysplastic tissues.

Research perspectives

In the future, the prospective studies in the selected BE patients should be conducted to evaluate the usefulness of the Seattle protocol in clinical practice.

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ORIGINAL ARTICLE

Retrospective Study

Modified laparoscopic Sugarbaker repair of parastomal hernia with a three-point anchoring technique

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Abstract

AIM

To retrospectively evaluate the safety and feasibility of a new modified laparoscopic Sugarbaker repair in patients with parastomal hernias.

METHODS

A retrospective study was performed to analyze eight patients who underwent parastomal hernia repair between June 2016 and January 2018. All of these patients received modified laparoscopic Sugarbaker

hernia repair treatment. This modified technique included an innovative three-point anchoring and complete suturing technique to fix the mesh. All procedures were performed by a skilled hernia surgeon. Demographic data and perioperative outcomes were collected to evaluate the safety and efficacy of this modified technique.

RESULTS

Of these eight patients, two had concomitant incisional hernias. All the hernias were repaired by the modified laparoscopic Sugarbaker technique with no conversion to laparotomy. Three patients had *in-situ* reconstruction of intestinal stoma. The median mesh size was 300 cm^2, and the mean operative time was 205.6 min. The mean postoperative hospitalization time was 10.4 d, with a median pain score of 1 (visual analog scale method) at postoperative day 1. Two patients developed postoperative complications. One patient had a pocket of effusion surrounding the biologic mesh, and one patient experienced an infection around the reconstructed stoma. Both patients recovered after conservative management. There was no recurrence during the follow-up period (6-22 mo, average 13 mo).

CONCLUSION

The modified laparoscopic Sugarbaker repair could fix the mesh reliably with mild postoperative pain and a low recurrence rate. The technique is safe and feasible for parastomal hernias.

Key words: Parastomal hernia; Three-point anchoring and suturing; Sugarbaker repair; Mesh; Enterostomy

Core tip: Parastomal hernia is a common complication after enterostomy. We introduce a new modified laparoscopic Sugarbaker repair technique with three-point anchoring to repair the parastomal hernia. The findings confirm the safety and feasibility of the modified method and support the application of this technique to parastomal hernias.

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INTRODUCTION

Parastomal hernia (PSH) is an incisional hernia at the site of the surgical wound. It is a common complication following enterostomy with an incidence rate as high as 48%[1]. Surgery is the only treatment to repair PSH. Similar to the repair of an abdominal wall hernia, the recurrence rate of postoperative PSH has decreased significantly with the development of mesh technology[2]. However, given the existence of intestinal stoma PSH, repair is always a challenge for the surgeons.

Similar to other incisional hernias, PSH could be safely and effectively repaired by the laparoscopic approach. The laparoscopic Sugarbaker technique is the most effective method to reduce the recurrence rate[3] and is recommended by the International Endohernia Society[4]. However, consensus does not exist regarding the mesh selection procedure, the method of mesh fixation, and other operative technical details for this technique. These issues require further investigation.

One of the technical details most difficult to determine during the laparoscopic Sugarbaker technique is a strategy for reliably fixing the mesh to construct a funnel that can hold the ostomic intestine inside not only to avoid injury and compression to the intestine but also to reduce the hernia recurrence rate. We focused on this aspect to improve the technical details of the laparoscopic Sugarbaker technique[5-7]. In our hospital, we applied an innovative three-point anchoring and suturing technique to fix the mesh during the laparoscopic Sugarbaker technique. We retrospectively review our techniques and the outcomes of our patients.

MATERIALS AND METHODS

Our research was a single-center retrospective study performed between June 2016 and January 2018. Eight patients with the diagnosis of primary PSH who underwent a modified laparoscopic Sugarbaker technique were included. Inclusion criteria were clinical symptoms consistent with PSH with no acute bowel obstruction or strangulation. All the operations were performed by the same surgeon. The study protocol was approved by the hospital ethics committee.

Surgical technique

All patients underwent preoperative abdominal computed tomography (CT) imaging to evaluate the size of the PSH defect, the contents of the hernia, and the length of the ostomic intestine. Routine bowel preparation was performed before the operation. After successful general anesthesia, patients were placed in the supine position. Gauze and polyurethane film dressing tape were used to cover the intestinal stoma after routine disinfection. Based on the location of the stoma, the first incision was made on the opposite side of the abdomen as far as possible away from the stoma and the previous incision site. For example, in patients with stoma on the left lower quadrant of the abdomen, the first incision was made to the right upper quadrant of the abdomen. The puncture incision was performed using the Verssel technique to establish and maintain a 15-mmHg carbon dioxide pneumoperitoneum. The abdominal cavity was explored after the placement of

the laparoscopic lens. Under direct visualization, two or three incisions were made on both sides of the first incision followed by the placement of 5-mm or 12-mm Trocars. Adhesiolysis was performed to separate the intestine and omentum from the abdominal wall by cold and sharp instruments, such as scissors. An ultrasound knife and coagulation were only used for hemostasis. Adhesiolysis was performed in the hernia sac to reduce the hernia contents as much as possible. After adhesiolysis, the size of the defect was assessed to confirm whether the defect could be closed under laparoscopy (a defect larger than 5 cm was typically difficult to close using the laparoscopic approach) (Figure 1A). Then, the dressing covering the stoma was removed, and the area around the stoma was disinfected again. The defect was closed by interrupted suturing with PDS™ (Ethicon®) with assistance from a suture grasping device (Figure 1B). Under the following conditions, we performed the reconstruction of stoma using the Lap-Re-Do technique, which was previously published in detail by Yang *et al*[8]: The hernia contents could not be reduced completely laparoscopically, there was a large defect that was unlikely to be closed laparoscopically, and there was a long and twisted stoma in the hernia sac. The loop of ostomic intestine was also evaluated to ensure that the Sugarbaker technique could be applied. If the loop was not long enough for the Sugarbaker technique, the keyhole technique was used.

Then, the first anchoring point for the mesh was determined under laparoscopic visualization. A 5-cm-long suture thread was placed into the abdominal cavity. One end of the suture thread was placed at the innermost point of the stoma, and the thread was straightened to be perpendicular to the midline of the abdomen. The abdominal wall, which was reached by the other end of the suture thread, was marked. Based on the actual operating conditions, we selected one of two types of mesh. If the operative field might be contaminated, a biologic mesh (Biodesign™, Surgsis®) was selected. Otherwise, a synthetic mesh (Sepramesh™, Bard®) was used if no signs of contamination were present. The mesh was trimmed to the appropriate size to cover the defect by at least 5 cm in all directions. One stitch with PDS thread was placed and tied at the middle point of the long edge on the inner side of the mesh. Pneumoperitoneum was re-established. The mesh was rolled up, placed inside the abdominal cavity, and then expanded. A small incision was made at the site on the abdominal wall marked previously. The PDS thread tied to the mesh was pulled out with a suture-grasping device and knotted. Two pairs of clamps were used to adjust the mesh to attach to the peritoneal wall to place the stoma in the middle position on the outside surface of the mesh (Figure 1C). Stitches with a 2-0 Prolene™ (Ethicon®) thread were placed in the upper and lower part of the mesh to anchor the mesh to the peritoneal wall at the site close to the stoma. The mesh was folded to form a funnel to accommodate the ostomic intestine passing inside. Positioning of the mesh was completed after the abovementioned three-point anchoring and suturing (Figure 1D). Then, four edges of the mesh were fixed to the peritoneal wall with continuous suturing using 2-0 Stratifix™ (Ethicon®) thread (Figure 1E). Care was taken not to injure the underlying peritoneal vessels during the suturing. The same stitches were placed in the upper and lower edges of the ostomic intestine to suture the mesh to the peritoneal wall. Stitches were placed from the lateral side of the mesh to the inside of the stoma to construct a funnel to allow the passage of the ostomic intestine (Figure 1F). Finally, we performed the transfascial suture with a purse-string needle (ST-70, Prolene™, Ethicon®) to puncture the abdominal wall corresponding to the four corners of the mesh (Figure 1G). Two tips of the purse-string needle entered the skin at the same site and passed through the mesh at two different points 1 cm apart. The thread was cut and knotted inside the abdominal cavity. The mesh was then fixed to the peritoneal fascia (Figure 1H). We did not use any tack or glue to fix the mesh. Before the end of the operation, the stoma was examined manually to ensure there was no stenosis.

Postoperative pain intensity was assessed by a visual analog scale. Intravenous analgesic medication was administered for pain relief up to the postoperative day 3. Patients who did not undergo the Lap-Re-Do procedure were given a semi-liquid diet from postoperative day 1. They did not receive any intravenous antibiotics or total parenteral nutrition, and they were discharged when stool passed normally from the stoma. For patients undergoing the Lap-Re-Do procedure, intravenous antibiotics were administered for 3 d postoperatively to prevent any infection near the incisional site. The patients fasted, and total parenteral nutrition was given until postoperative day 5. A liquid diet was started on day 5 and changed to a semi-liquid diet on day 7. Patients were discharged when no infection was observed, and the stool passed through the stoma.

RESULTS

Patients' preoperative conditions are listed in Table 1. None of the patients received emergent surgery. Two patients had diabetes, and preoperative blood glucose levels were well controlled. One patient had a long smoking history and quit smoking 3 years ago. All the ileostomies were located in the right lower quadrant of the abdomen. All the colostomies were located in the left lower quadrant of the abdomen. Two patients had a concomitant incisional hernia, which was located in the midline of the lower abdominal wall.

Patients' intraoperative conditions and postoperative follow-up outcomes are presented in Table 2. All laparoscopic procedures were successful, and none of the patients required laparotomy. Three patients received the Lap-Re-Do procedure to remove the extra ostomic intestinal segment and the hernia sac to

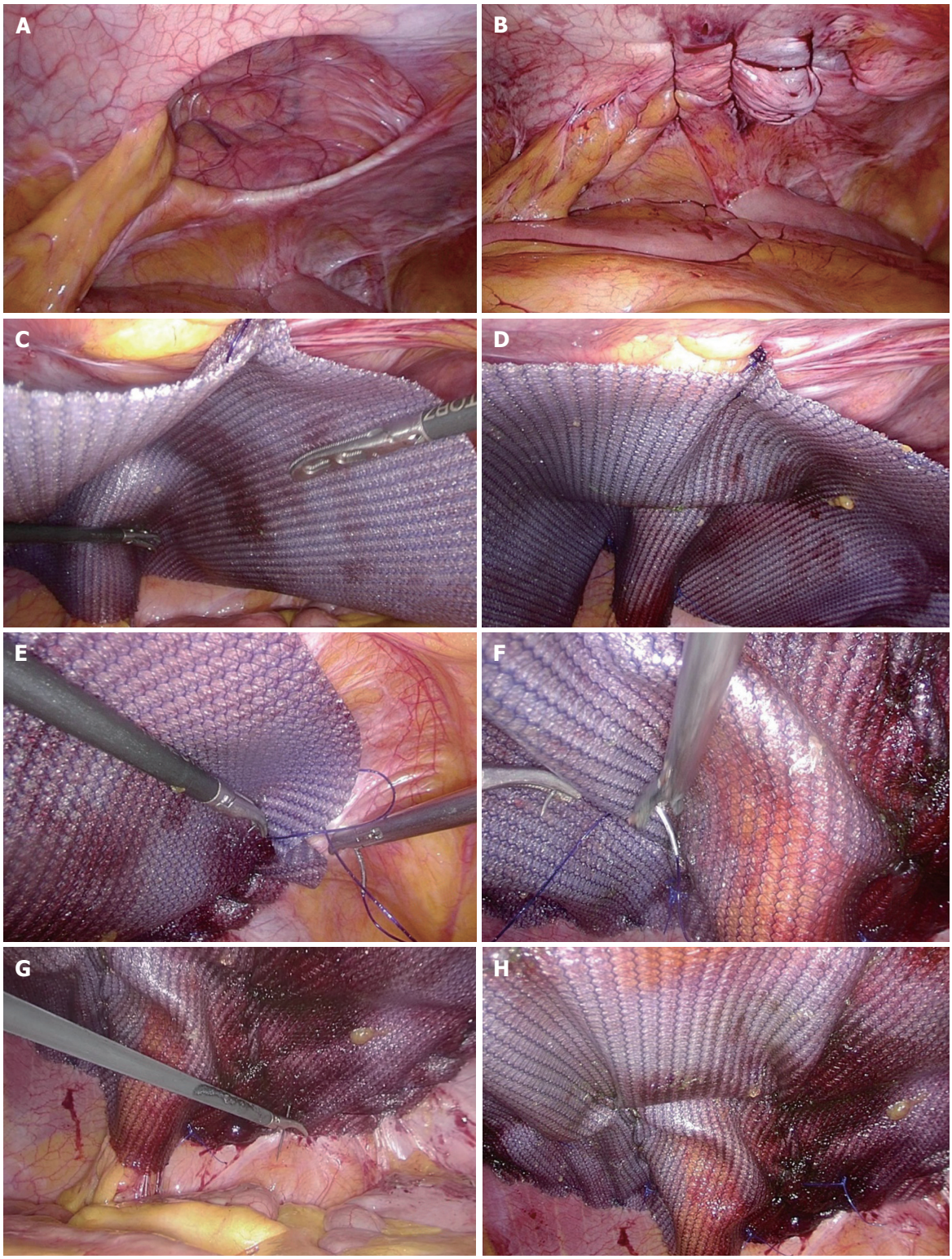

Figure 1 Keynotes for the surgical technique. A: The parastomal defect is exposed after adhesiolysis; B: The defect was closed by interrupted stitches under laparoscopy; C: The mesh was fixed at the first point, which also covers the ostomic intestine; D: Completion of three-point anchoring; E: The mesh was fixed by continuous suturing; F: The funnel was constructed by continuous suturing; G: The transfascial suture with a purse-string needle; H: The mesh was finally fixed to the peritoneal wall.

facilitate the reconstruction of the stoma *in situ*. Two patients with concomitant incisional hernias received simultaneous incisional hernia repairs with the same mesh to cover the incision and parastomal defects. In these procedures, no additional mesh was used, and no additional incisions were made. Two patients had potential postoperative contaminations around the surgical field. One patient underwent the Lap-Re-Do procedure. Another patient had an ileal PSH after the radical cystectomy for bladder cancer. The ostomic

Table 1 Demographic data

No. of patients	8
Age (yr)	65.3 ± 7.4
Gender (male/female)	5/3
BMI (kg/m^2)	24.5 ± 3.8
ASA	
I	0
II	7
III	1
Comorbidity	Two cases of diabetes
Smoker (yes/no)	1/7
Type of stoma	
Colostomy	4
Ileostomy	4
Size of defect (cm^2)	17.9 ± 10.3
EHS classification of PSHs	
EHS 1	3
EHS 2	1
EHS 3	3
EHS 4	1

BMI: Body Mass Index; EHS: European Hernia Society; PSH: Parastomal hernia.

Table 2 Outcomes

Outcomes	Results
Time spent for operation (min), mean ± standard deviation	205.6 ± 66.7
No. of patients undergoing Lap-Re-Do (yes/no)	3/5
Concomitant incisional hernia (yes/no)	2/6
Types of mesh (biologic/Sepramesh)	2/6
Intraoperative complication (yes/no)	1/7
Size of mesh (cm^2), median (range)	300 (221.3-300)
Pain score on postoperative day 1 (VAS)	
Median (range)	1 (1-2)
VAS = 1	6 patients
VAS = 2	2 patients
Number of days of postoperative stay, mean ± standard deviation	10.4 ± 6.3
Follow-up period (mo), mean (min, max)	12.9 (6, 22)
Number of hernia recurrences	0
Postoperative complication (yes/no)	2/6

VAS: Visual analog scale.

intestine was injured when separating the adhesion between the bowels. This injury was immediately repaired under the laparoscope. We used a biologic mesh in these two patients. The remaining six patients received a synthetic mesh.

On the first postoperative day, the pain score was 1–2 points with a mean of 1.4 ± 0.5. No patient reported a pain score greater than 3 points or required additional analgesic treatments. All patients were able to ambulate on postoperative day 1. Two patients developed complications during the postoperative hospital stay. One patient with ileal PSH had an intraoperative ileal injury that was repaired by the biologic mesh. He suffered from a cloudy fluid leakage from the left side of the Trocar incision site on postoperative day 7. Ultrasound examination revealed a pocket of fluid around the mesh. CT-guided puncture and aspiration were performed, and a drainage catheter was placed. The aspirated fluid was turbid effusion with no intestinal fluid. The patient had no fever, abdominal pain or distension and could eat and defecate normally. Fluid drainage gradually decreased and finally disappeared. The catheter was removed, and the patient was discharged. Another patient undergoing the Lap-Re-Do procedure developed a postoperative parastomal abscess, which was superficial with no connection to the peritoneal cavity after opening the incision. The abscess gradually resolved after dressing changes and intravenous antibiotic treatments. The incision healed with no requirement for a secondary repair.

The mean follow-up time was 13 mo, ranging from 6 to 22 mo. No evidence for hernia recurrence was found during the clinic visits. Only one patient underwent repeated CT scans, which confirmed that there was no recurrence of the hernia.

DISCUSSION

PSH is a common complication after surgeries for colon or small intestine stoma reconstruction. Some patients with no clinical symptoms can be treated conservatively[9]. However, between 30%–70% patients eventually require surgical treatment for various reasons. Similar to a ventral hernia, PSH can be repaired by simple suturing, which is an easy operation. However, simple suturing commonly results in a high recurrence rate and is not appropriate for most patients[10]. Mesh repair is the most effective surgical method in this situation. Peritoneal mesh placement through the laparoscopic approach has many advantages for abdominal wall hernia repair. It can shorten the operation time and has a low recurrence rate[3]. The laparoscopic approach has become one of the most commonly used methods to repair PSH. Based on the position of the mesh and its distance to the ostomic intestine, laparoscopic PSH repair employs three main surgical techniques: the keyhole, Sugarbaker, and sandwich methods. According to previous publications, the Sugarbaker method has a lower recurrence rate compared with the keyhole method and is significantly less expensive compared with the sandwich method[3,11,12].

The Sugarbaker method was first proposed in 1980. The Sugarbaker method was performed during the laparotomy, and a nonslit prosthesis was placed to the lateral side of the bowel. The prosthesis was fixed to the peritoneal fascia by suturing at 1-cm intervals. Advantages of this method are that the stoma is not affected and the intestinal function recovers quickly after the operation. In addition, the colon passes through the funnel formed by the prosthesis, and recurrent herniation around the stoma is prevented[13]. In 2000, Voitk performed the Sugarbaker technique through the laparoscopic approach for the first time[14]. He used the tack to anchor the mesh without transfascial sutur-

ing. Since then, many researchers have made various improvements in the placements and fixations of the mesh[5-7,15].

The main technical difficulty during the Sugarbaker procedure involves how to fix the mesh to the abdominal wall to establish an appropriate funnel to allow the passage of ostomic intestine and its content without causing any stenosis or obstruction. The mesh should also prevent other intestines from entering the funnel, which could lead to incarceration and hernia recurrence. At the same time, the mesh should be fully flattened along the peritoneal wall. In the cases reported previously, the mesh was fixed to the peritoneal wall *via* transfascial suturing, a tack, or a combination of the two, which is similar to the method used during ventral hernia repair. We believe that transfascial suturing is necessary for the Sugarbaker technique given that transfascial suturing is critical to prevent hernia recurrence. However, unlike the ventral hernia, the final shape of the mesh around the PSH is not flat but rather a complex curved surface. From the outside of the peritoneal cavity, it is difficult to predict the final position for the mesh inside the peritoneal cavity for transfascial suturing. Mesh fixation *via* the simple technique similar to ventral hernia repair often causes the mesh to be distorted and not flattenable[5]. In addition, inappropriately positioned and tensional transfascial sutures could cause significant postoperative pain[16,17]. Therefore, we believe that the placement of the mesh during the Sugarbaker technique should be improved. Ideally, the mesh should be placed in the peritoneal cavity at the most appropriate location with initial anchoring, and then the final fixation is performed by transfascial suturing.

Currently, there is no uniform standard for meshes used in the Sugarbaker procedure. Meshes reported in the literature include polypropylene, expanded polytetrafluoroethylene (ePTFE), polyvinylidene fluoride (PVDF), polyester and biological meshes[18]. Sepramesh™ and Biodesign™ were used in our study. Sepramesh™, a synthetic mesh with coating, is safe and effective in parastomal hernia repair[19]. The advantage of biological meshes is that they can be used safely in herniorrhaphy with minimal risk of contamination; however, the recurrence rate is high[20,21]. Therefore, we only apply this mesh to cases where the surgical area is suspected to be contaminated. In our study, no mesh-related complications were found.

Our procedure to shape and fix the mesh inside the peritoneal cavity includes four steps. The first step is to determine the initial three anchoring points. One is the midpoint of the inside surface of the mesh, which is anchored through the transfascial suturing. The other two anchoring points, which are located on the outside surface of the mesh, are used to form the funnel and are sutured to the peritoneal wall with Prolene thread. After this first step, the position of the mesh and the shape of the funnel are determined in the peritoneal cavity. The second step is to flatten the mesh and place continuous stitches at the edges of the mesh to suture it to the peritoneal wall. The third step is to construct the funnel by continuous stitches through suturing from the outer edges of the mesh until the site of the stoma is reached. Given that this step is performed without tension and along the natural course of the intestine, it avoids bowel twisting and obstruction after the Sugarbaker procedure as reported by some authors[22,23]. After these three steps, the mesh is completely flattened and fixed on the peritoneal wall without distortion. The final step to fix the mesh in our procedure is transfascial suturing. Our method is different from the traditional method. A double-ended needle is inserted through the skin and passed into the peritoneal cavity to reach the mesh at two different locations 1 cm apart. Then, the needle is removed, and a loose knot is placed. Given that the mesh is already fixed inside the peritoneal cavity, this step is easy and does not cause any tension. Therefore, our procedure is tension free. Our patients suffered minimal postoperative pain, even with activity.

Although a tack is the most common choice by other physicians, we do not use a tack to fix mesh. A tack is easy to use but can cause some potential risks, including acute and chronic postoperative pain[24,25], volvulus, and bowel injury[26,27]. The length of the commonly used metal tack is 4 mm. When considering the thickness of the mesh, the actual depth of the tack nailed into the tissue is less than 3 mm, potentially cause its unreliability to fix the mesh to the peritoneal wall. In addition, the tack is placed close to the PSH, which could cause tension to both sides of the funnel formed by the mesh. When intestinal peristalsis or passage of the intestinal contents occurs, mesh failure and hernia recurrence could result[28]. Thus, the effect of fixation of the mesh to the peritoneal wall through the tack remains unclear. In addition, the tack device is relatively expensive. It was reported that continuous suturing to fix the mesh to the peritoneal wall during ventral hernia repair could avoid complications from the tack placement[29]. Our fixation technique is reliable, and the procedure is inexpensive. Patients also had minimal pain postoperatively. Our patients had minimal pain postoperatively, and none of them suffered hernia recurrence. One of the reasons for this finding might be attributed to the use of continuous suturing instead of a tack. Although continuous suturing requires higher technical skills and longer operation times than tack placement, it should be acceptable when considering its better outcomes.

In patients with long and twisted ostomic intestine in the hernia sac, we followed the Lap-Re-Do procedure reported by Yang *et al*[8], which involves the resection of the original stoma, opening of the fascia, and reconstruction of the stoma *in situ*. We believe that this procedure could improve stoma function and restore the normal contour of the abdominal wall. Three of our patients underwent the Lap-Re-Do procedure. One of them had a postoperative infection around the stoma, which did not spread to the deep tissues and the

mesh. The infection was resolved after drainage and intravenous antibiotic administration.

In summary, our modified laparoscopic Sugarbaker technique could repair the PSH. In addition to being tension free, it is easy to operate inside the peritoneal cavity. It also has the advantages of fewer postoperative complications and minimal postoperative pain. We did not observe any hernia recurrence during the follow-up period; however, long-term studies should be conducted to confirm our results.

ARTICLE HIGHLIGHTS

Research background

Parastomal hernia (PSH) is a common complication following enterostomy. The laparoscopic Sugarbaker technique has been shown to be the most effective method and is recommended by the International Endohernia Society. However, no consensus exists regarding the mesh selection procedure, the method of mesh fixation, and other operative technical details for this technique.

Research motivation

One of the technical details most difficult to determine during the laparoscopic Sugarbaker technique is a strategy for reliably fixing the mesh to construct a safe funnel. We applied a modified Sugarbaker technique to PSH in our center to try to reduce the technical difficulty.

Research objectives

To assess the safety and feasibility of the modified laparoscopic Sugarbaker repair in patients with PSH.

Research methods

A total of 8 patients received modified laparoscopic Sugarbaker hernia repair treatment. This modified technique included an innovative three-point anchoring and complete suturing technique to fix the mesh. Perioperative outcomes, including operative and postoperative complications, were collected to retrospectively evaluate the safety and efficacy of this modified technique.

Research results

All the hernias were repaired using the modified laparoscopic Sugarbaker technique with no conversion to laparotomy. The mean operative time was 205.6 min, and the mean postoperative hospitalization time was 10.4 d, with a median pain score of 1 (visual analog scale method) at postoperative day 1. Two patients experienced mild postoperative complications and recovered after conservative management. No recurrence occurred during the follow-up period.

Research conclusions

The modified laparoscopic Sugarbaker repair with three-point anchoring technique could fix the mesh reliably with mild postoperative pain and a low recurrence rate. The technique is safe and feasible for PSH.

Research perspectives

Our study demonstrates that the modified laparoscopic Sugarbaker repair is safe and efficient *via* three-point anchoring for PSH. Surgeons can use our method to repair PSH.

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SYSTEMATIC REVIEWS

Safety of laparoscopic surgery in digestive diseases with special reference to antithrombotic therapy: A systematic review of the literature

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Abstract

AIM

To elucidate the effect of antithrombotic therapy (ATT) on bleeding and thromboembolic complications during or after laparoscopic digestive surgery.

METHODS

Published articles or internationally accepted abstracts between 2000 and 2017 were searched from PubMed, Cochrane Database, and Google Scholar, and studies involving laparoscopic digestive surgery and antiplatelet therapy (APT) and/or anticoagulation therapy (ACT) were included after careful review of each study. Data such as study design, type of surgical procedures, antithrombotic drugs used, and surgical outcome (both bleeding and thromboembolic complications) were extracted from each study.

RESULTS

Thirteen published articles and two internationally accepted abstracts were eligible for inclusion in the systematic review. Only one study concerning elective laparoscopic cholecystectomy in patients with peri-operative heparin bridging for ACT showed that the risk of postoperative bleeding was higher compared with those without ACT. The remaining 14 studies reported no significant differences in the incidence of bleeding complications between the ATT group and the group without ATT. The risk of thromboembolic events (TE) associated with laparoscopic digestive surgery in patients receiving ATT was not significantly higher than those with no ATT or interrupted APT.

CONCLUSION
Laparoscopic digestive surgery in ATT-burdened patients for prevention of bleeding and TE showed satisfactory results. The risk of hemorrhagic complication during or after these procedures in patients with continued APT or heparin bridging was not significantly higher than in patients with no ATT or interrupted APT.

Key words: Thromboembolic complication; Bleeding complication; Laparoscopic surgery; Anticoagulation therapy; Digestive surgery; Antithrombotic therapy; Antiplatelet therapy

Core tip: In total, 15 published articles and abstracts concerning laparoscopic digestive surgery and antithrombotic therapy were systematically reviewed. These articles demonstrated that the risk of bleeding and thromboembolic complications during or after these procedures in patients with continued antiplatelets or heparin bridging was not significantly higher than in patients with no antithrombotics or interrupted antiplatelets.

Fujikawa T, Ando K. Safety of laparoscopic surgery in digestive diseases with special reference to antithrombotic therapy: A systematic review of the literature. *World J Clin Cases* 2018; 6(14): 767-775 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/767.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.767

INTRODUCTION

Following cancer, heart disease and cerebrovascular disease are the major causes of death worldwide. With the arrival of an aging society in recent years, the number of patients with heart disease and/or cerebrovascular disease who require non-cardiac surgery is increasing. For the purpose of preventing thromboembolic events (TE), most of them receive antithrombotic therapy (ATT), including antiplatelet therapy (APT) and anticoagulation therapy (ACT). Perioperative management of these patients is challenging for surgeons, and they are often at high risk of bleeding and thromboembolic complications[1-4].

Many digestive operations are currently performed laparoscopically. Several reports have shown advantages of laparoscopic digestive surgery, including early recovery of digestive function, reduction of body wall destruction, reduction of postoperative pain, less postoperative complications, and rapid return to daily life[5-9]. During laparoscopic surgery, minimizing surgical blood loss to maintain a dry operative field is exclusively important. Improvement of several techniques and new surgical devices, such as ultrasonic coagulating shears or saline-linked soft-coagulation system, led us to perform various types of advanced laparoscopic digestive operations including colorectal resection, esophagogastrectomy, and hepato-biliary-pancreas surgery. However, optimal management of patients receiving ATT during laparoscopic digestive surgery is still controversial.

The purpose of the current systematic review study is to elucidate the effect of ATT on bleeding and thromboembolic complications during or after laparoscopic digestive surgery.

MATERIALS AND METHODS

Articles written in English and published between 2000 and 2017 were collected from PubMed, Cochrane Database and Google Scholar. We also used PubMed and Google Scholar to search internationally accepted English abstracts. The following key words were used for the search: Clopidogrel, aspirin, antiplatelet, anticoagulant, warfarin, bleeding, hemorrhage, gastrointestinal, gastroenterological, digestive and laparoscopic surgery. Articles or abstracts were included when published in peer reviewed journals or when accepted at internationally renowned medical conferences. Types of eligible studies included randomized clinical trials, prospective or retrospective cohort studies, or case-control studies; guidelines, review articles, or case series/reports were not included.

After removing duplicates, articles were systematically excluded by careful review of each study. The quality of each study was assessed depending on study design, and eligible articles and abstracts were determined. Complete data were extracted from each study, which included study design, year of publication, sample size, type of surgical procedures, type of antithrombotic drugs, and surgical outcome (both bleeding and thromboembolic complications).

RESULTS

Characteristics of included studies

Research collection and screening was conducted from January 2018 to February 2018. In all, 13 articles and two abstracts were included[10-24]. Among them, there were no randomized clinical trials or prospective cohort studies, and only retrospective cohort studies or case-control studies were seen. Among 15 studies, nine studies examined only APT use, two studies focused on ACT, and four studies investigated both. Concerning APT, patients who had continued preoperative APT were compared with those who did not receive APT. In patients with continued APT, only single antiplatelet agents, such as aspirin, were usually continued. One study focused on clopidogrel alone, and one study investigated aspirin alone. In studies regarding ACT, only warfarin was used, and most patients received heparin bridging perioperatively.

Only one retrospective cohort study used a large number of cases (over 1000 cases), but various types of laparoscopic surgery (mostly laparoscopic cholecystectomy) were included. This is the largest study to date, examining the effects of APT on outcome of abdominal laparoscopic operations. This study demonstrated that there was no significant difference in postoperative bleeding events between patients who continued APT and other patients.

We classified the type of surgery into two categories based on previous reports[10]: Basic laparoscopic surgery (*e.g.*, cholecystectomy, appendectomy, adhesiolysis, hernia repair) and advanced laparoscopic surgery (*e.g.*, colorectal resection, gastrectomy, liver/pancreas resection). The results of basic surgery and advanced surgery are shown in Tables 1 and 2, respectively. Bleeding events included two categories: intraoperative bleeding complications (IBCs; increased surgical blood loss), and postoperative bleeding complications (PBCs; intraabdominal bleeding, gastroenterology bleeding, or abdominal wall hematoma).

Basic laparoscopic surgery

In basic laparoscopic surgeries, only two types of surgery (cholecystectomy and appendectomy) were included. Laparoscopic cholecystectomy was the most commonly reported overall, and a total of eight studies were included[11-15,17,18,24]. Research on laparoscopic appendectomy included two case-control studies[19,20].

For laparoscopic cholecystectomy, warfarin was described in three studies. With only one study, the risk of PBC in ACT patients was significantly higher than those without ACT[11]. In the remaining two studies, the proportion of IBC or PBC did not increase, even with heparin bridging[14,18]. In terms of APT, seven studies focusing on aspirin and/or thienopyridine were included[12-14,17,18,24,25]. IBC was examined as an outcome in six of them, and PBC was analyzed in four studies. None of the studies demonstrated an increase in IBC or PBC when APT (mostly aspirin monotherapy) was continued preoperatively. In two laparoscopic appendectomy studies[19,20], they were exclusively performed in an emergency setting. Both studies focused on preoperative APT continuation and showed that neither IBC nor PBC increased with continued APT.

These findings suggested that when basic laparoscopic digestive operations were performed, the risk of either IBC or PBC in patients undergoing preoperative continued monotherapy for APT or heparin bridging for ACT was not significantly higher than in those without ATT or interrupted APT.

Advanced laparoscopic surgery

Concerning advanced laparoscopic surgery, only limited numbers of studies were found in three types of surgery; one study on laparoscopic liver resection[16], two studies on laparoscopic colorectal cancer resection[12,21], and two studies regarding laparoscopic gastrectomy[22,23].

Fujikawa *et al*[16] conducted a retrospective cohort study using liver resection cases (including laparoscopic and open surgery). The authors found that neither IBC nor PBC increased in the case of laparoscopic liver resection, even with aspirin monotherapy for APT and/or heparin bridging for ACT. In two studies of laparoscopic colorectal cancer resection, the effect of APT on IBC or PBC was assessed, and the authors found that APT continuation did not significantly affect hemorrhagic complications[12,21].

Among two papers regarding laparoscopic gastrectomy, Takahashi *et al*[22] examined the difference in IBC and PBC between the ATT group and the group without ATT. The ATT group included preoperative APT continuation and heparin substitution for ACT, but there was no significant difference in IBC or PBC between the groups. Finally, Gerin *et al*[23] examined the difference in PBC during laparoscopic sleeve gastrectomy between the warfarin group and the group without warfarin. PBC occurred in 6.7% of patients who received ACT, whereas 3.3% of patients without ACT experienced PBC ($P = 0.60$).

Perioperative thromboembolic events and mortality

Among 15 included studies, the incidence of perioperative TE and the mortality rate was described in eight and 14 studies, respectively. In basic laparoscopic surgeries, the TE rate was 0%-2.2% in the continued APT group and 0%-0.2% in the control group. Six out of eight studies showed no mortality in the entire cohort. In the remaining two studies, there was no difference in mortality between the groups. In advanced laparoscopic surgery, the incidence of TE was identical between the groups, with only one expired case (1% of the ATT group). Overall, the risk of TE associated with laparoscopic digestive surgery for patients receiving ATT was not significantly higher than those without ATT or interrupted APT.

DISCUSSION

To the best of our knowledge, this is the first systematic review that assesses the effect of ATT on bleeding and thromboembolic complications during and after laparoscopic digestive surgery. The present review summarized results of various types of laparoscopic digestive surgery in patients receiving ATT for the prevention of thromboembolism. The risk of hemorrhagic or thromboembolic complications during or after these procedures in patients with continued APT or heparin bridging was not significantly higher than in patients with no ATT or interrupted APT. There are some promising results for both basic and laparoscopic surgery. However, in terms of advanced laparoscopic surgery, such as colorectal resection or liver resection, there is scarce evidence.

ATT includes two types of medications, classified as antiplatelets and anticoagulants. Antiplatelets

Table 1 Reported data concerning bleeding complications of "basic" abdominal surgery in patients with antithrombotic therapy (antiplatelet therapy and/or anticoagulation therapy)

First author of the reports	Year	Surgery type	Drug use and exposure	Bleeding events	TE, mortality
Laparoscopic surgery (overall)					
Fujikawa[10]	2013	Abdominal laparoscopic surgery (cholecystectomy (mostly), appendectomy, surgery for GI malignancy, liver resection, splenectomy *etc*)	Patients with continued use of ASA (n = 52) Patients with discontinuation of APT (n = 160) Patients not on APT (control, n = 863)	PBC 0% in continued ASA *vs* 2.5% in discontinuation *vs* 0.7% in control (P = 0.987)	TE 0% in continued ASA *vs* 0.6% in discontinued ASA *vs* 0.2% in control (P = 0.625) Only one mortality in continued ASA group (1.9%)
Laparoscopic cholecystectomy					
Ercan[11]	2010	Laparoscopic cholecystectomy (only elective)	Patients with ACT (w/ bridging, n = 44) Patients without ACT (control, n = 1377)	PBC 25% in ACT *vs* 1.5% in control (P < 0.001) One mortality due to severe bleeding	(not mentioned)
Ono[12]	2013	Laparoscopic cholecystectomy (n = 270) or Laparoscopic colorectal cancer resection (n = 218)	Patients with continued ASA (n = 52) Patients without ASA (control, n = 436)	SBL 27 mL in continued ASA *vs* 17 mL in control (P = 0.430)	No mortality in both groups
Anderson[13]	2014	Laparoscopic cholecystectomy (elective and emergency)	Patients with continued clopidogrel (n = 36) Matched patients without clopidogrel (control, n = 36)	No difference in SBL (49 g *vs* 47 g, P = 0.85) PBC 0% in clopidogrel *vs* 2.8% in control (P = 0.31)	No TE in both groups No mortality in both groups
Noda[14]	2014	Early laparoscopic cholecystectomy for acute cholecystitis	Patients with continued use of ATT (n = 21) Patients without ATT (n = 162)	No conversion to open surgery No PBC in both groups	No mortality in both groups
Joseph[15]	2015	Emergency laparoscopic cholecystectomy	Patients with continued use of APT (n = 56), including those with preop Plt transfusion (n = 12) Patients without APT (control, n = 56)	SBL ⩾ 100 mL 14.3% in continued ASA *vs* 9% in control (P = 0.50)	No difference in the rates of overall postop complications (8.9% *vs* 7.1%, P = 0.80) No mortality in both groups
Fujikawa[16]	2017	Emergency cholecystectomy including 106 laparoscopic surgery for acute cholecystitis	Patients with continued use of APT (n = 89) Patients without APT (control, n = 154)	SBL ⩾ 500 mL 12% in continued APT *vs* 5% in control (P = 0.240) PBC 7% in multiple APT *vs* 3% in single APT *vs* 0.6% in control (P = 0.027)	TE 1.1% in continued APT *vs* 0% in control (P = 0.37) No mortality in both groups
Sakamoto[17]	2017	Laparoscopic cholecystectomy (only elective operation)	Patients with continued single APT (n = 49) Patients with discontinuation of APT (n = 106) Patients not on APT (control, n = 653)	SBL ⩾ 200 mL 4.7% in continued APT *vs* 4.7% in discontinued APT *vs* 1.5% in control (P = 0.064) PBC 0% in continued APT *vs* 0.9% in discontinued APT *vs* 0.2% in control (P = 0.022)	TE 0% in continued APT *vs* 0.9% in discontinued APT *vs* 0.2% in control (P = 0.296) No mortality in any group
Yun[18]	2017	Laparoscopic cholecystectomy (elective *vs* emergency) for acute cholecystitis	Patients with continued use of ATT (almost APT, n = 22) Patients with discontinued ATT (almost APT, control, n = 45)	SBL ⩾ 100mL 13.6% in continued ATT *vs* 22.2% in control (P = 0.613)	One case of TE (2.2%) in control Mortality 4.6% in continued ATT *vs* 2.2% in control (P > 0.999)
Laparoscopic appendectomy					
Chechik[19]	2011	Appendectomy including laparoscopic appendectomy (n = 78)	Patients with continued APT (n = 39) Patients without APT (control, n = 140)	No difference in SBL or PBC between the groups	No mortality in both groups
Pearcy[20]	2017	Laparoscopic appendectomy (urgent only)	Patients with continued APT (n = 287) Matched patients without APT (control, n = 287)	No difference in SBL (31 g *vs* 26 g) or blood transfusion rate (1% *vs* 0%) between the groups	Two cases of TE (MI) in continued APT (0.7%) No difference in the rates of mortality (1% *vs* 0%, P = 0.12)

ATT: Antithrombotic therapy; APT: Antiplatelet therapy, ACT: Anticoagulation therapy; TE: Thromboembolism; SBL: Surgical blood loss; PBC: Postoperative bleeding complications; ASA: Aspirin; GE: Gastroenterological; MI: Myocardial infarction.

Table 2 Reported data concerning bleeding complications of "advanced" abdominal surgery in patients with antithrombotic therapy (antiplatelet therapy and/or anticoagulation therapy)

First author of the reports	Year	Surgery type	Drug use and exposure	Bleeding events	TE, mortality
Laparoscopic liver resection					
Fujikawa[24]	2017	Laparoscopic liver resection *vs* open liver resection	Patients with ATT (n = 100) Patients without ATT (control, n = 158)	SBL ⩾ 500 mL 23% in those with ATT *vs* 27% in control (P = 0.468) PBC 4.6% in those with ATT *vs* 4.3% in control	TE 1% in ATT *vs* 1.3% in control (P = 0.310) Mortality 1% in ATT *vs* 0% in control (P = 0.350)
Laparoscopic colorectal cancer resection					
Ono[12]	2013	Laparoscopic colorectal cancer resection (n = 218) or laparoscopic cholecystectomy (n = 270)	Patients with continued ASA (n = 52) Patients without ASA (control, n = 436)	SBL 27 mL in continued ASA *vs* 17 mL in control (P = 0.430)	No mortality in both groups
Shimoike[21]	2016	Colorectal cancer surgery including laparoscopic surgery (n = 191)	Patients with APT (n = 148) Patients without APT (control, n = 343)	PBC 0.7% in those with APT *vs* 0.9% in control (P = 1.000)	TE 0.7% in APT *vs* 0% in control (P = 0.301) No mortality in both groups
Laparoscopic gastrectomy					
Takahashi[22]	2017	Laparoscopic gastrectomy	Patients with ATT (continued in high risk, n = 12) Patients without ATT (n = 34)	No difference in SBL or PBC between the groups	No difference in overall complications between the groups No mortality in both groups
Gerin[23]	2015	Laparoscopic sleeve gastrectomy	Patients with ACT (n = 15) Matched patients without ACT (control, n = 30)	PBC 6.7% in ACT *vs* 3.3% in control (P = 0.60)	No mortality in both groups

ATT: Antithrombotic therapy; APT: Antiplatelet therapy; ACT: Anticoagulation therapy; TE: Thromboembolism; SBL: Surgical blood loss; PBC: Postoperative bleeding complications; ASA: Aspirin; HBP: Hepatobiliary and pancreas.

decrease platelet aggregation and prevent thrombus formation, and they are generally used for primary and secondary prevention of cardiovascular and cerebrovascular diseases, such as myocardial infarction or cerebral infarction. Antiplatelets include thienopyridine (*e.g.*, clopidogrel, ticlopidine, or prasugrel), type Ⅲ phosphodiesterase inhibitor (*e.g.*, cilostazol), acetylsalicylic acid (aspirin), and other non-steroidal anti-inflammatory agents[10,26]. On the other hand, anticoagulants interfere with the native clotting cascade and prevent blood clotting, and they are generally used for atrial fibrillation, deep vein thrombosis, cardiac endoprostheses, and acute coronary syndrome. These include vitamin K antagonists (*e.g.*, warfarin), heparin derivatives (*e.g.*, fondaparinux), direct thrombin inhibitors (*e.g.*, dabigatran), and factor Xa inhibitors (*e.g.*, rivaroxaban, apixaban, edoxaban)[26,27]. The two latter types are now increasingly used and are referred to as direct-acting oral anticoagulants (DOACs) or non-vitamin K antagonist oral anticoagulants (NOACs). The types of antithrombotics, specific agents, and duration of action are summarized in Table 3.

So far, there has been scarce evidence concerning the definite protocols or guidelines for each specific gastroenterological surgical procedure, including laparoscopic surgery. Thanks to the development of techniques and various energy devices, indication of laparoscopic digestive surgery is now expanded not only to basic procedures but also relatively advanced digestive operations[6,8,9]. During laparoscopic surgery, minimizing surgical blood loss to maintain a dry operative field is required, and thus, this procedure results in less surgical blood loss and a lower incidence of postoperative complications[16]. Although the optimal management of patients receiving ATT during laparoscopic digestive surgery is still controversial, rigorous antithrombotic management, such as continued aspirin monotherapy for APT or heparin bridging for ACT, is considered to be safe and feasible.

Using several recently updated guidelines concerning antithrombotics as references[26-30], the recommended protocol of perioperative management for patients undergoing ATT in the case of elective open or laparoscopic digestive surgery is shown in Figure 1. The management generally consists of three approaches according to types of ATT; APT, warfarin, and DOACs. In patients with thromboembolic risks, aspirin monotherapy is continued in patients with APT, and warfarin is substituted by heparin bridging 3-5 d before surgery. In the case of DOACs, ATT is stopped 1-2 d before surgery (with some modification needed if decreased renal function exists); if the thromboembolic risk is very high, heparin bridging might be considered. Postoperatively, every antithrombotic agent is reinstituted as soon as possible (POD1-2).

Table 3 Types, specific agents, and acting duration of commonly used antithrombotic drugs

Class of agents	Type	Specific agents	Duration of action
Antiplatelets			
	Thienopyridines	Clopidogrel (Plavix), Ticlopidine (Panardine), Prasugrel (Effient)	5-7 d[1]
	Type Ⅲ PDE inhibitor	Cilostazol (Pretal)	2 d
	Acetylsalicylic acid	Aspirin	7-10 d
	Other NSAIDs	Ibuprofen (Brufen, Advil), Loxoprofen (Loxonin), Diclofenac (Voltaren), *etc*	Varies
Anticoagulants			
	Vitamin K antagonist	Warfarin (Coumadin)	5 d
	Heparin derivatives	Fondaparinux (Arixtra)	1.5-2 d
		DOACs	
	Direct thrombin inhibitor	Dabigatran (Pradaxa)	1-2 d
	Factor Xa inhibitors	Rivaroxaban (Xarelto), Apixaban (Eliquis), Edoxaban (Lixiana)	1-2 d

[1]In ticlopidine, duration of action is 10-14 d. PDE: Phosphodiesterase; NSAID: Non-steroidal anti-inflammatory drug; DOAC: Direct-acting oral anticoagulant.

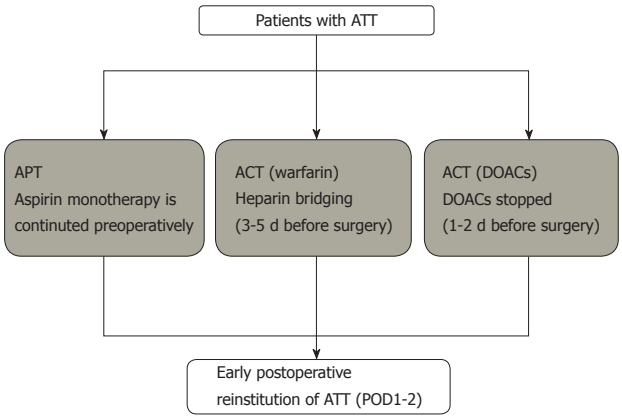

Figure 1 Recommended perioperative management protocol for patients undergoing antithrombotic therapy in the case of elective laparoscopic digestive surgery. The management generally consists of three ways according to the types of antithrombotic therapy (ATT); antiplatelet therapy (APT), warfarin, and Direct-acting oral anticoagulants (DOACs). In patients with thromboembolic risks, aspirin monotherapy is continued in patients with APT, and/or warfarin was substituted by heparin bridging 3-5 d before surgery. In the case of DOACs, ATT is stopped 1-2 d before surgery (with some modification needed if decreased renal function exists); if the thromboembolic risk is very high, heparin bridging might be considered. Postoperatively, every antithrombotic agent is reinstituted as soon as possible (POD1-2). ATT: Antithrombotic therapy; APT: Antiplatelet therapy; TE: Thromboembolism; ACT: Anticoagulation therapy; DOAC: Direct-acting oral anticoagulant.

Recent updated guidelines concerning antithrombotic management during non-cardiac surgery[26,27,31-33] showed that the prevention of TE is more important than bleeding complications, as it might cause death or severe sequelae. Concerning implantation of a coronary stent, recent American College of Cardiology/American Heart Association (commonly known as ACC/AHA) and European Society of Cardiology (commonly known as ESC) guideline state that we should continue antiplatelet medications, at least aspirin monotherapy, in the perioperative period for patients with high risk of thromboembolism[30], but most institutions practically choose to discontinue APT in the case of major digestive surgery with bleeding risks. Discontinuing aspirin or clopidogrel may lead to an increased risk of acute myocardial infarction, cerebral infarction, and subsequent death[34,35]. Although some studies, including the POISE-2 study, have reported that a modest increase in bleeding risk was observed in continued APT patients during non-cardiac surgery[36,37], most studies have shown that there was no increase in significant bleeding events[38,39]. Thus, sufficient consideration and emphasis should be placed on the prevention of thromboembolism caused by cessation of antithrombotic drugs, rather than the risk of perioperative bleeding.

Concerning patients with ACT, heparin bridging is a common management for warfarin[40]. Recently, a large-scale randomized controlled trial (BRIDGE study) showed that heparin bridging was not recommended in the case of low bleeding risk surgery due to increased bleeding risks[25]. However, this study included relatively small numbers of major digestive surgery, and it could not conclude that heparin bridging is unnecessary in major general or abdominal surgery. In the current review, only one study concerning warfarin use and laparoscopic cholecystectomy showed an elevated risk of postoperative bleeding when heparin bridging was used[11]. The remaining studies demonstrated the safety of ACT bridging without an increase in severe bleeding complications. Especially in patients with high thromboembolic risks, heparin bridging might be considered to avoid critical thromboembolic complications.

In the present review, there was no report regarding patients who received DOACs during laparoscopic digestive surgery. Currently, DOACs are increasingly prescribed for the purpose of preventing arterial or venous thromboembolism. In large clinical trials, DOACs have been shown to have lower rates of intracranial hemorrhage compared to warfarin[41-44]. Furthermore, in cases of intracranial bleeding, there are reports that hematoma sizes were small in patients receiving DOACs compared to those with warfarin administration[45,46]. This difference is mainly due to the difference in mechanism of action in the blood clotting cascade. A sufficient understanding of these pharmacological characteristics, which is remarkably

different from warfarin, is of paramount importance for surgeons. A recently published review and an ongoing prospective study[47,48] suggests safety and feasibility of perioperative management of DOACs during noncardiac surgery, which is rather simple compared with those of warfarin. Still, the detailed assessment of perioperative management protocol, such as the necessity of bridging anticoagulation, has not yet conducted and should be investigated further. In addition, these reports or reviews did not show results according to the procedure types. Safety of every surgical type, including laparoscopic digestive surgery, should be assessed in the future.

Summary and recommendations for future studies

Currently, there are only limited numbers of studies concerning the management of ATT-prescribed patients during laparoscopic digestive surgery. As the population ages and the morbidity of cardiovascular disease increases, this patient population is expanded further. Definite protocols or guidelines should be established using reliable studies with good design. In the future, a well-designed prospective randomized study or multicenter cohort study is mandatory to elucidate the safety and feasibility of laparoscopic digestive surgery.

In conclusion, laparoscopic digestive surgery in ATT-burdened patients for the prevention of bleeding and TE showed satisfactory results. The risk of hemorrhagic complication during or after these procedures in patients with continued APT or heparin bridging was not significantly higher than in patients with no ATT or interrupted APT.

ARTICLE HIGHLIGHTS

Research background

Recently, many digestive surgical procedures are being performed laparoscopically. However, the effect of antithrombotic therapy (ATT) on perioperative bleeding complications during laparoscopic surgery is still largely unclear.

Research motivation

The risk of bleeding complications in ATT is related to the perioperative use of antiplatelet therapy (APT) or anticoagulation therapy (ACT). To safely perform laparoscopic digestive surgery in patients with ATT, optimal perioperative management of antithrombotic drugs should be established.

Research objectives

The main objective of the present study is to elucidate the effect of ATT on bleeding and thromboembolic complications during or after laparoscopic digestive surgery.

Research methods

Published articles or internationally accepted abstracts between 2000 and 2017 were searched, and studies involving laparoscopic digestive surgery and ATT were included after careful review of each study. Data including study design, type of surgical procedures, type of antithrombotic drugs, and surgical outcome were analyzed.

Research results

In total, 15 studies were included. Only one study concerning laparoscopic cholecystectomy showed that patients with heparin bridging for ACT had a higher risk of postoperative bleeding. The remaining 14 studies reported continued APT or that heparin bridging for ACT did not affect the incidence of bleeding complication. The risk of thromboembolic events after laparoscopic digestive surgery in patients receiving ATT was not significantly higher than those with no ATT or interrupted APT.

Research conclusions

The risk of hemorrhagic complication during or after these procedures in patients with continued APT or heparin bridging was not significantly higher than in patients with no ATT or interrupted APT.

Research perspectives

The definite protocol or guidelines should be established using reliable studies with good design. In the future, a well-designed prospective randomized study or multicenter cohort study is mandatory to elucidate the safety and feasibility of laparoscopic digestive surgery.

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CASE REPORT

Epstein–Barr virus-associated hemophagocytic syndrome in a patient with ulcerative colitis during treatment with azathioprine: A case report and review of literature

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Author contributions: Miyaguchi K was involved in data collection, data analysis, and writing up the first draft of the paper; Tsuzuki Y contributed towards data analysis, and patient follow-up in the out-patient unit; Yamaoka M contributed to medical treatment; Imaeda H supervised, and finalized the manuscript; all authors approved the final manuscript.

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Abstract

A 19-year-old female was diagnosed with ulcerative colitis when she presented with persistent melena, and has been treated with 5-aminosalicylic acid for 4 years, with additional azathioprine for 2 years at our hospital. The patient experienced high-grade fevers, chills, and cough five d prior to presenting to the outpatient unit. At first, the patient was suspected to have developed neutropenic fever; however, she was diagnosed with Epstein-Barr virus-associated hemophagocytic syndrome (EB-VAHS) upon fulfilling the diagnostic criteria after bone marrow aspiration. When patients with

inflammatory bowel disease treated with immunomodulators, such as thiopurine preparations, develop fever, EB-VAHS should be considered in the differential diagnosis.

Key words: Inflammatory bowel disease; Azathioprine; Virus-associated hemophagocytic syndrome; Ulcerative colitis; Case report

Core tip: A 19-year-old female was diagnosed with ulcerative colitis, and has been receiving treatment with 5-aminosalicylic acid for 4 years, with additional azathioprine for 2 years. The patient experienced high-grade fever five d prior to presenting to the outpatient unit. She was diagnosed with Epstein-Barr virus-associated hemophagocytic syndrome (VAHS). VAHS is one of the rare and life-threatening pathophysiological conditions induced by thiopurine treatment. In such cases, early diagnosis is necessary, along with management of therapy, and related complications. When patients with inflammatory bowel disease, treated with immunomodulators such as thiopurine preparations, demonstrate high fever, VAHS should be considered in the differential diagnosis.

Miyaguchi K, Yamaoka M, Tsuzuki Y, Ashitani K, Ohgo H, Miyagawa Y, Ishizawa K, Kayano H, Nakamoto H, Imaeda H. Epstein–Barr virus-associated hemophagocytic syndrome in a patient with ulcerative colitis during treatment with azathioprine: A case report and review of literature. *World J Clin Cases* 2018; 6(14): 776-780 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/776.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.776

INTRODUCTION

Virus-associated hemophagocytic syndrome (VAHS) is an extremely rare and life-threatening complication, sometimes induced by viral infection. It is characterized by high-grade fever, hepatosplenomegaly, pancytopenia, and disseminated intravascular coagulation (DIC). The syndrome is diagnosed by the presence of histiocytosis in the lymphoreticular network (*i.e.,* the bone marrow)[1]. The etiological agent is a virus, such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes zoster virus, human herpesvirus 6, rubella, measles virus, or influenza virus. Among them, Epstein-Barr VAHS (EB-VAHS) tends to be severe[2].

Thiopurine formulations are reported to be effective for the long-term remission of inflammatory bowel disease (IBD)[3]. However, side effects such as myelosuppression, hepatic dysfunction, pancreatitis, hair loss, and gastrointestinal symptoms are observed in approximately 3% of patients. In particular, myelosuppression is reported to occur within 2 mo of drug administration[4]. A recent report also suggested that patients with IBD receiving thiopurine treatment are at an increased risk of developing lymphoproliferative disorders[5]. Therefore, it is necessary to consider the adverse effects of thiopurine treatment when fever, leukopenia, hepatic dysfunction, *etc.* are observed.

Here we report a case of EB-VAHS during the treatment of ulcerative colitis with drugs including azathioprine (AZA).

CASE REPORT

A 19-year-old female with frequent bloody stools presented to our hospital in 2017. She was diagnosed with ulcerative colitis (pancolitis) by total colonoscopy in 2013. The patient was treated with 3600 mg/d of 5-aminosalicylic acid (5-ASA) and went into remission. She experienced recurrence of bloody stools in 2015, and was treated with 50 mg/d of AZA. Although AZA treatment was initiated, the patient occasionally experienced bloody stools and prednisolone (PSL) was administered, after which her condition improved. The AZA dose was increased to 100 mg/d in 2016. Although she occasionally experienced bloody stools, her symptoms were relieved by additional administration of 5-ASA suppositories.

The patient was admitted to our hospital with fever, ocular pains, chills, and cough for 5 d prior to admission in 2017. Her neutrophil count had decreased to 589/μL, and leukocyte reduction was not evident in blood results 2 d before her symptoms started. The patient developed a fever of 38.8 ℃, but showed no abnormalities in the chest and abdomen, with no observed cervical lymph node swelling.

The patient presented with fever, along with mild anemia [hemoglobin (Hb), 11.1 g/dL], mild thrombocytopenia (13.0 × 10^4/μL), mildly elevated C-reactive protein (CRP) (1.32 mg/dL), and neutropenia [white blood cell (WBC), 940/μL; neutrophils, 589/μL].

Colonoscopy revealed that the mucosa was mildly inflamed only on the left side of the colon; the endoscopic subscore was Mayo score 1 (Figure 1). The patient was treated with 2 g/d of cefepime and granulocyte-colony stimulating factor (G-CSF), but her WBC and neutrophil counts improved only to 2650/μL, and 1661/μL, respectively. The fever persisted, and her condition was complicated by the appearance of right cervical lymphadenopathy. Splenomegaly and splenic infarction were observed *via* thoracoabdominal contrast computed tomography scanning (Figure 2). In addition, liver dysfunction (Aspartate transaminase, 225 IU/L; alanine aminotransferase, 200 IU/L), and increases in lactate dehydrogenase (LDH) (589 IU/L), ferritin (740 ng/mL), and soluble interleukin 2 receptor (sIL-2R) (5210 IU/mL) were observed on biochemical examination. Aggravated anemia (Hb, 9.4 g/dL), thrombocytopenia (8 × 10^4/μL), and the appearance of atypical lymphocytes (Aty-Lym, 2%) were also

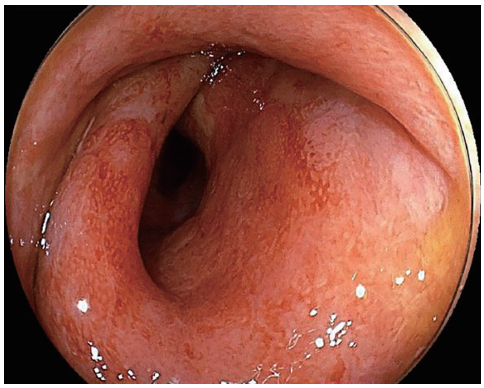

Figure 1 Colonoscopy showing diffuse redness, disappearance of vasculature, and mucosal edema in the descending colon–rectum, suggesting a Mayo Endoscopic Subscore of 1.

observed on peripheral blood examination. Bone marrow smear examination showed an increase in foamy macrophages, and blood cell phagocytosis (Figure 3), but no chromosomal abnormalities. Furthermore, antibody test results, were suggestive of primary acute EBV infection, as follows: EB immunoglobulin M (EB-IgM) positive, EB-IgG positive, EB nuclear antigen (EBNA) negative, and EB deoxyribonucleic acid (EB-DNA) positive (1.0×10^4 copies/mL). CMV IgG was negative. The diagnostic criteria for VAHS are as follows: (1) blood cell phagocytosis, myelocyte phagocytosis; (2) elevated ferritin; and (3) elevated sIL-2R levels ($\geqslant$ 2400 IU/mL). Taken together, the patient was diagnosed with EB-VAHS. The patient was treated with steroid pulse therapy (methylprednisolone 1000 mg/d for 3 d), and her symptoms and examination findings improved. After pulse therapy, PSL was tapered gradually from 60 mg/d. The follow-up lab examination data after improvement from VAHS was as follows: WBC 6720/μL, Hb 13.4 g/dL, platelet 16.2×10^4, LDH 175U/L, Aty-Lym negative, EB-virus capsid antigen (EB-VCA) IgM negative, EB-VCA IgG positive (× 40), EBNA 1.3C.I, EB-DNA positive, ferritin 18 ng/mL, sIL-2R 290 IU/mL. The patient was discharged after a couple of weeks and was followed-up in the outpatient unit.

DISCUSSION

The initial diagnosis was neutropenic fever accompanied by bone marrow suppression, probably due to AZA administration. However, bone marrow suppression by AZA often occurs within 2 mo of initiation, however here, 1 year had passed since AZA was increased from 50 mg to 100 mg before bone marrow suppression was evident. In addition, the patient showed only minor improvement to white blood cell, and neutrophil counts, while fever persisted during G-CSF treatment. The diagnosis of VAHS was made based on symptoms such as cervical lymph node swelling, splenomegaly, hepatic dysfunction, pancytopenia, elevated LDH, elevated ferritin, elevated sIL-2R, and the appearance of Aty-Lym. However, a bone marrow biopsy was required to make a definite diagnosis. Although the mechanism of VAHS is yet to be completely elucidated, it is reported that activation of T-cells, as well as macrophage proliferation, and the production of cytokines triggered by viral infection such as EBV are responsible for characteristic symptoms like high-grade fever, hepatosplenomegaly, pancytopenia, and DIC[1]. These symptoms could be related to disease severity[6]. Therefore, when VAHS is strongly suspected by clinical findings, it is recommended that treatment should be initiated before fulfilling the diagnostic criteria[7]. The treatment for VAHS is divided into four steps[1]. First, steroid such as cyclosporine and etoposide are administered to control the resultant hypercytokinemia, and plasma exchange may be considered if hypercytokinemia is resistant to initial treatment. Second, if there is a virus-specific treatment, the etiological virus should be targeted. Third, if the virus is refractory to treatment, removal of virus-infected lymphocytes by CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisone), according to treatment for malignant lymphoma, should be considered. Fourth, supportive therapy for secondary infection, DIC, and central nervous symptom and hepatic disorders may be considered.

Eight cases of CMV infection and five of EBV infection have been reported to be VAHS cases after AZA administration during ulcerative colitis treatment[8-15]; however, the etiological virus is unknown in most cases. There have also been reports that it is unknown whether the syndrome is caused due to acute or chronic infection, however, most cases are positive for both IgM and IgG. Therefore, the pathology of VAHS is thought to be mainly caused by reactivation of chronic viral infection, although VAHS could also occur due to acute viral infection. In the present case, EB-IgM was positive and EBNA was negative; therefore, this case of VAHS was caused by primary acute infection. It is difficult to diagnose VAHS in many cases, and the syndrome occurrs during remission rather than immediately after AZA administration. Prognosis greatly differs between EBV-, and non-EBV-associated cases and 70% of non-EBV-associated cases are reported to be cured only by supportive therapy[2]. In contrast, in EBV-associated cases, a more severe course was observed and 4 of 16 patients with VAHS died during IBD therapy[9,12,14,15]. Old age, DIC, elevated ferritin, thrombocytopenia, anemia, jaundice, and chromosomal abnormalities are frequently observed, and are poor prognostic factors[15]. Some studies reported chromosomal abnormalities after chromosome analysis of bone marrow cells revealed an abnormal karyotype, although none were specific. In the present case, no DIC or chromosomal abnormalities were observed, and the clinical course was well controlled. The factors responsible for VAHS in patients with IBD are as follows: (1) mucosal immune systems, such as immune tolerance in the intestinal tract, are destroyed due to IBD; (2) immunomodulating drug therapy increases susceptibility too many infections

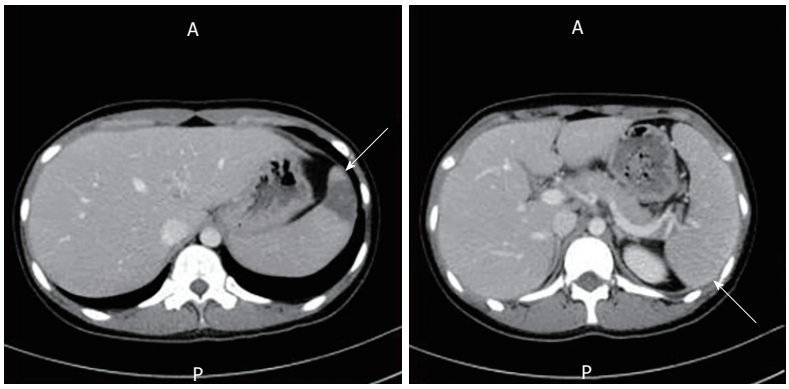

Figure 2 Thoracoabdominal contrast computed tomography scanning. Computed tomography scan showing an area of low density in the spleen, suggesting splenic infarction (left arrow) and splenomegaly (right arrow).

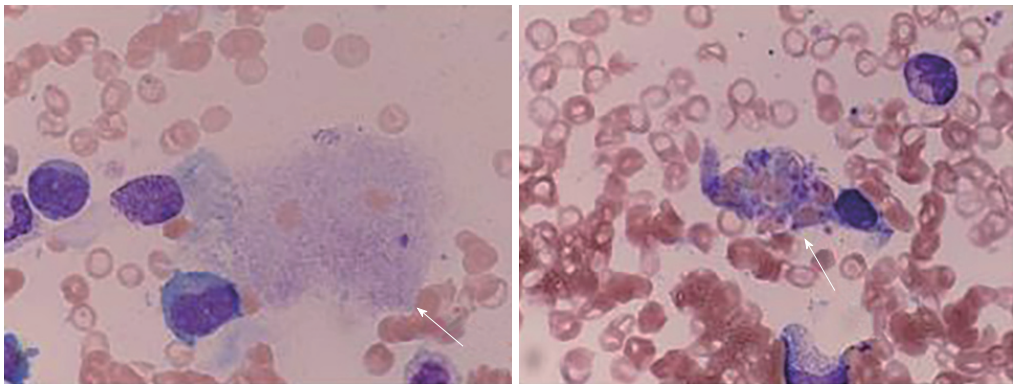

Figure 3 Hematoxylin and Eosin staining (400 × magnification) in the specimen of bone marrow smear. It shows the increase in macrophages (left arrow) and hemophagocytosis (right arrow).

including opportunistic infections; (3) once viral infection occurs, the pathogen-exclusion mechanism does not function well, and the immune response loses efficacy.

Therefore, long-term AZA administration might trigger EB infection and induce VAHS. However, to prove this theory, one needs to demonstrate an immunosuppressive state at the time of EB infection, and the subsequent exponential cytokine storm after EB infection, leading to VAHS.

VAHS is a rare but potentially life-threatening complication of EBV infection. Although this syndrome is also rare in patients with IBD treated with thiopurine preparations, administration of immunosuppressants or immunomodulators may increase the risk of viral infection.

Thererfore, when high-grade fever, cytopenia, and elevated liver enzyme, ferritin, and LDH levels are observed in patients with ulcerative colitis treated with thiopurine preparations, VAHS should be considered in the differential diagnosis if CMV or EBV infection is confirmed. In addition, it should be remembered that hemophagocytosis is a fatal disease and caution should always be implemented to avoid this fatal consequences.

ARTICLE HIGHLIGHTS

Case characteristics

19-year-old female presented high-grade fevers, chills, and cough five d prior to presenting to the outpatient unit.

Clinical diagnosis

Patient was diagnosed with Epstein-Barr virus-associated hemophagocytic syndrome upon fulfilling the diagnostic criteria after bone marrow aspiration, during the treatment with azathioprine (AZA) for UC.

Differential diagnosis

Febrile neutropenia.

Laboratory diagnosis

Pancyopenia (white blood cell, 2650/μL; hemoglobin, 9.4 g/dL; platelet, 8.0 × 10^4); lactate dehydrogenase, 589 U/L; atypical lymphocytes, 2.0%; Epstein-Barr virus capsid antigen immunoglobulin M (EB-VCA-IgM), positive; EB-VCA-IgG, positive; EB nuclear antigen, negative; EB deoxyribonucleic acid, positive (1.0 × 10^4 copies/mL); blood cell phagocytosis; myelocyte phagocytosis; ferritin elevation; and elevated soluble interleukin 2 receptor (≥ 2400 IU/mL).

Imaging diagnosis

Contrast computed tomography showed spleen swelling and spleen infarction.

Pathological findings

Bone marrow examination confirmed blood cell phagocytosis.

Treatment
Steroid pulse therapy and post-steroid therapy.

Related reports
A case report by N'guyen *et al*[11] suggests that EBV-specific clinical and virological management should be considered when treating a patient with IBD with AZA.

Term explanation
VAHS is a rare pathophysiological condition induced by thiopurine treatment for IBD, caused by excessive lymphocytic cytokine production during viral infection.

Experience and lessons
VAHS should be included in the differential diagnosis during thiopurine treatment for IBD.

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CASE REPORT

Acquired hemophilia A in solid cancer: Two case reports and review of the literature

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Author contributions: Saito M, Ogasawara R, Izumiyama K, Mori A, Kondo T, Tanaka M, Morioka M and Ieko M collected the patient's clinical data; Saito M designed and wrote the report.

Informed consent statement: Consent was obtained from each patient or family (wife) for publication of this report and any accompanying images.

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Abstract

Acquired hemophilia A (AHA) is a rare, hemorrhagic autoimmune disease, whose pathogenesis involves reduced coagulation factor Ⅷ (FⅧ) activity related to the appearance of inhibitors against FⅧ. Common etiological factors include autoimmune diseases, malignancy, and pregnancy. We report two cases of AHA in solid cancer. The first case is a 63-year-old man who developed peritoneal and intestinal bleeding after gastrectomy for gastric cancer. He was diagnosed with AHA, and was treated with prednisone, followed by cyclophosphamide. In the second case, a 68-year-old man developed a subcutaneous hemorrhage. He was diagnosed with AHA in hepatocellular carcinoma on CT imaging, and treated with rituximab alone. Hemostasis was achieved for both patients without bypassing agents as the amount of inhibitors was reduced and eradicated. However, both patients died within 1 year due to cancer progression. Successful treatment for AHA in solid cancer can be difficult because treatment of the underlying malignancy is also required.

Key words: Acquired hemophilia A; Coagulation factor Ⅷ; Solid cancer; Gastric cancer; Hepatocellular carcinoma; Case report

Core tip: Acquired hemophilia A (AHA) is a rare hemorrhagic disease usually affecting the elderly, involving reduced coagulation factor Ⅷ activity. Malignancies are reported to occur in association with 10%-15% of patients with AHA. We report two cases of AHA in solid cancer, namely, gastric cancer and hepatocellular carcinoma. Hemostasis was fully achieved owing to eradication of inhibitor against factor Ⅷ, however, both patients died within 1 year due to cancer progression. Successful treatment for AHA in solid cancer can be difficult because not only active hemorrhage management and inhibitor eradication but also treatment of the underlying malignancy is required.

Saito M, Ogasawara R, Izumiyama K, Mori A, Kondo T, Tanaka M, Morioka M, Ieko M. Acquired hemophilia A in solid cancer: Two case reports and review of the literature. *World J Clin Cases* 2018; 6(14): 781-785 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/781.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.781

INTRODUCTION

Acquired hemophilia A (AHA) is a hemorrhagic disease with a decrease in coagulation factor Ⅷ (FⅧ) activity due to the appearance of autoantibodies (inhibitors) against FⅧ[1,2]. The breakdown of the immune control mechanism is speculated to cause this disease[1]. AHA is very rare, and the annual incidence is about 1.48/million/year[2]. Elderly patients (age ⩾ 60 years) account for over 80%[2]. In the majority of patients with AHA, hemorrhage is sudden and spontaneous, although it occurs in approximately 25% of patients after trauma or invasive procedures[3].

Approximately 50% of patients have no underlying AHA-associated condition. Common etiological factors include autoimmune diseases (14.1%), malignancy (11.5%), and pregnancy (8.9%)[4]. The most common cause of solid cancers in AHA is prostate cancer, followed by lung cancer[5,6]. A recent study demonstrated that malignancy at baseline was associated with reduced overall survival for patients with AHA[7]. In addition, a systematic review described a large number of AHA patients with cancer[8]. However, evidence to confirm AHA in association with solid cancers needs to be obtained in more patients. In this study, we performed a retrospective analysis of the clinical characteristics of two AHA patients with solid cancers, namely, gastric cancer and hepatocellular carcinoma (HCC) at our institution.

CASE REPORT

Case 1 (Clinical course in Figure 1)

A 63-year-old man had been diagnosed with gastric cancer and had undergone a gastrectomy at his nearby hospital. Bleeding within the intraperitoneal drainage tube was observed 5 d after surgery. Intraperitoneal cytology identified gastric cancer cells and a diagnosis of stage Ⅳ gastric cancer was confirmed. He developed hematemesis and melena 2 d following the removal of the drainage tube. His anemia worsened and his hemoglobin (Hb) level reached 6.3 g/dL, requiring red blood cell (RBC) transfusions for 5 d consecutively. Endoscopic examination revealed intestinal bleeding from the site of the anastomosis (Figure 2), and endoscopic hemostasis was performed. Subcutaneous hemorrhage became apparent in both lower extremities over several days. Transfusion with a total of 7 units of packed RBC was performed. The activated partial thromboplastin time (APTT) was prolonged to 74.2 s compared to 23.1 s measured preoperatively, and the patient was transferred to our hospital.

On admission, the patient presented with anemia, an Hb level of 9.0 g/dL and a prolonged APTT of 93.7 s. FⅧ activity was reduced to 3.18%, the inhibitor titer was 7.59 BU/mL, and he was diagnosed with AHA. Prednisone (PSL 1 mg/kg per day) and tranexamic acid were administered. Although the patient had developed an intramuscular hematoma in the right iliacus muscle approximately 1 mo after treatment, bypassing agents had not been administered because the hemorrhage was not persistent. As the inhibitor titer had increased to 11.7 BU/mL, 1 g of cyclophosphamide (CPA) was additionally administered and chemotherapy for gastric cancer with TS1 (tegafur/gimeracil/oteracil) was initiated. The inhibitors were eradicated, and the patient was discharged 9 wk after treatment for AHA. Because the patient remained in remission for AHA, the PSL dose was reduced and stopped. Treatment for gastric cancer was administered repeatedly; however, the patient died 9 mo after gastrectomy due to carcinomatous peritonitis.

Case 2

The second patient was a 68-year-old man with a history of cerebral infarction who had developed dementia (ECOG performance status, 3-4), in addition to arteriosclerosis obliterans, diabetes mellitus (DM), and hypertension. He had been taking a small amount (5 mg) of PSL for nephrotic syndrome. He was admitted to the local hospital having developed a non-traumatic subcutaneous hemorrhage in his right forearm. An abdominal computed tomography scan revealed hepatocellular carcinoma (file size 5.5 cm in diameter) (Figure 3). The anemia had progressed and his Hb levels had reduced from 12.7 to 8.1 g/dL, and 1 unit of packed RBC had been transfused. The APTT was prolonged to between 70 and 80 s, and he was transferred to our hospital.

On admission, the patient had anemia lasting, with an Hb of 7.8 g/dL and a prolonged APTT of 94.0 s. FⅧ activity was reduced to 3.1%, the inhibitor titer had

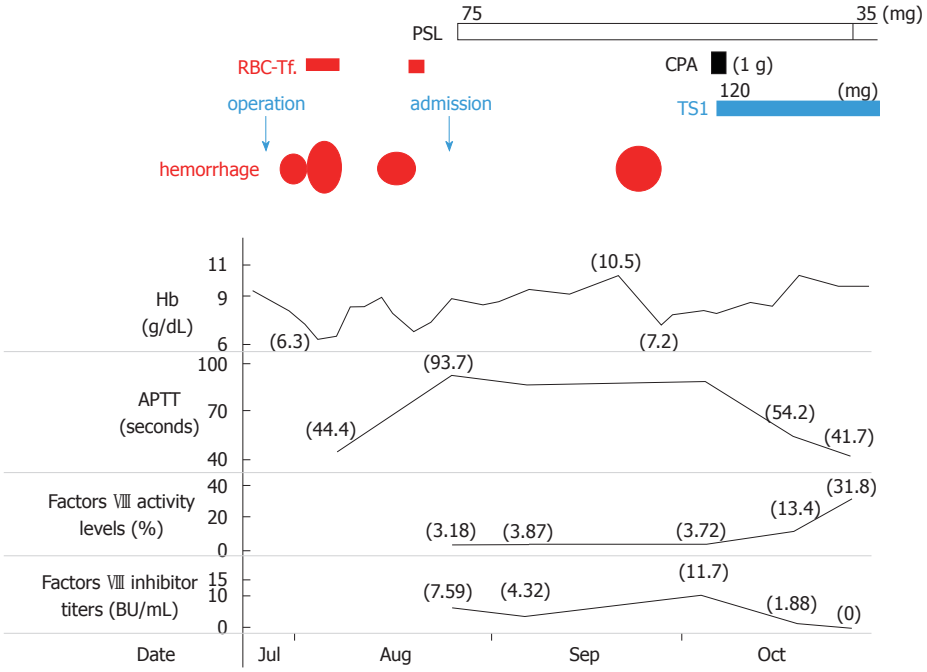

Figure 1 Clinical course in case 1. RBC-Tf: Red blood cell transfusion; Hb: Hemoglobin; APTT: Activated partial thromboplastin time; PSL: Prednisone; CPA: Cyclophosphamide; TS1: Tegafur/gimeracil/oteracil.

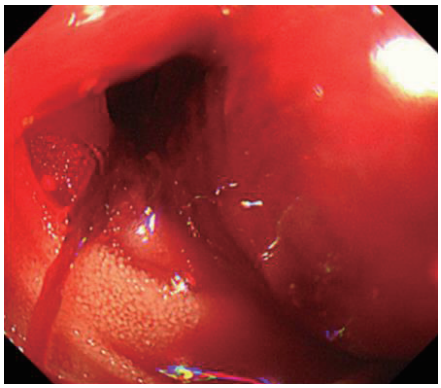

Figure 2 Esophagogastroduodenoscopy imaging (Case 1). Intestinal bleeding was detected from the site of anastomosis.

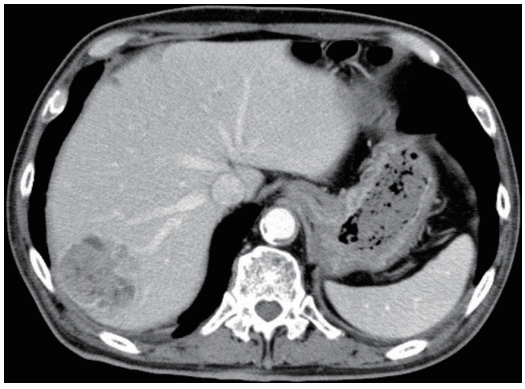

Figure 3 Abdominal computed tomography imaging (Case 2). HCC (5.5 cm in diameter) was noted in segment 7 of the liver.

increased to 57.1 BU/mL, and he was diagnosed with AHA. Although his liver function tests were normal, he tested positive for hepatitis C virus antibodies, and the values of alpha-fetoprotein and protein induced by vitamin K absence-Ⅱ were significantly higher at 1862 ng/mL and 210 mAU/mL, respectively. His anemia had worsened (Hb level, 6.8 g/dL), and 1 unit of packed RBC was transfused. Bypassing agents were not used as the bleeding was not considered to be severe at that time. In addition to continuing PSL administration (5 mg/d), rituximab (RTX 375 mg/m^2) was administered 5 times every week in order to eradicate the inhibitors without eliciting side effects. As a result, the inhibitor titer was reduced to 3.5 BU/mL after 3 wk and hemostasis was achieved. The patient was transferred back to his previous hospital to continue treatment for HCC. At this hospital, eradication of the inhibitors was confirmed approximately 1 mo after RTX treatment had terminated. Although transcatheter arterial chemoembolization was performed for HCC, the treatment was not effective, and the HCC continued to progress aggressively. The patient died at the hospice 7 mo after the HCC diagnosis.

DISCUSSION

Control failure of Treg cell line against autoimmune response to FⅧ is considered to be one of the onset factors of AHA[9]. More intense antibody responses, that is, higher inhibitor titers (10 BU or more) to FⅧ correlated with a predominance of Th2-driven subclasses IgG$_4$[10].

Malignancies have been reported to occur in 11.5% of patients with AHA[4]. This pathological condition can

be attributed to an imbalance in the immune system associated with the onset of solid cancer. However, the true causality and the underlying mechanism by which cancer cells induce autoantibodies to FⅧ have not been elucidated yet[8]. Iatrogenic bleeding may be the initial sign in AHA patients[11]. In case 1, since the APTT before gastrectomy was normal, surgical procedure may be a trigger for the development of an acquired inhibitor against FⅧ.

Regardless of the presence or absence of underlying disease, the treatment for AHA is divided into hemostatic therapy for hemorrhage[4] and immunotherapy aimed at eradicating inhibitors[12]. Bypass hemostatic agents, recombinant activated factor Ⅶ and activated prothrombin complex concentrate, are considered to the first-line approach for the treatment of bleeding episodes[4,13]. In the study of the European Acquired Haemophilia Registry (EACH 2), 144 of the 482 AHA patients (30%), especially for "non-severe" patients, hemostatic treatment was not required[4]. The two patients in our study did not develop life-threatening bleeding after they were transferred to our hospital. Therefore, immunological treatments were administered instead of bypassing agents to achieve hemostasis through reducing the inhibitor titer against FⅧ. The EACH2 study demonstrated that among the immunological treatments for AHA, the combination of PSL and CPA was more effective than PSL alone, with remission rates of 80% and 58%, respectively[12]. In our first patient, PSL alone was not effective, but the combination of PSL and CPA was effective. Our second patient had DM and was almost bedridden, and could not use either original PSL (1 mg/kg day) or CPA because he was considered to have a high risk of developing fatal infectious diseases. According to Japanese and Italian guidelines[14,15], RTX alone was selected, which is suggested as an alternative treatment, and our patient was successfully treated.

In the recent review based on the histories of 105 cases of AHA in cancers, prostate (25.3%) and lung (15.8%) cancer were more frequent, followed by colon cancer (9.5%)[8]. There were 3 cases of gastric cancer[16-18] and 2 cases of HCC[19,20]. Another case report for AHA with HCC has also been published[21]. Compared with the patients with idiopathic AHA, patients with cancer are more likely to show recurrent bleeding and are less likely to achieve a complete response with eradication of the inhibitors[8]. As with our two patients, gastric cancer and HCC were both identified as advanced cancers in these studies and patients generally had a poor prognosis. Regarding hemostasis, AHA in our patients was successfully treated, however, both patients died of cancer within 1 year. As noted by Casadiego-Peña *et al*[22], in the case of AHA with cancer, it is recommended to combine immunological treatment to eradicate the inhibitor with therapy for the malignancy. In our patients, cancer progression may not have occurred due to immunosuppression resulting from the administration of immunological treatments, but it is more likely that the cancers were already highly advanced at the time of AHA onset.

In conclusion, AHA remission was achieved in both patients despite cancer progression until their deaths. Besides hemostatic therapy and immunological treatments, successful treatment of AHA patients with cancer requires the concurrent treatment of the underlying malignancy. As opposed to hematological malignancies for which chemotherapy is often effective, solid cancers in AHA patients are typically detected at advanced stages. Thus, these patients are likely to have a poor prognosis.

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ARTICLE HIGHLIGHTS

Case characteristics

60s two Japanese men with solid cancer [one is gastric cancer, the other is hepatocellular carcinoma (HCC)] had a marked bleeding tendency.

Clinical diagnosis

Progressed anemia due to severe hemorrhage, requiring blood transfusion.

Differential diagnosis

Hemorrhagic disease, such as immune thrombocytopenia or disseminated intravascular coagulation.

Laboratory diagnosis

In both patients, hemoglobin level reached < 7 g/dL, prolonged APTT of 94 s, and FⅧ activity was reduced to 3.1%. The inhibitor titer was 7.59 and 57.1 BU/mL respectively, compatible with acquired hemophilia A (AHA). In the second patients, hepatitis C virus antibodies were positive and the levels of alpha-fetoprotein and protein induced by vitamin K absence-Ⅱ were 1862 ng/mL and 210 mAU/mL, respectively.

Imaging diagnosis

Endoscopic examination in the first case revealed intestinal bleeding from the site of the anastomosis. Abdominal computed tomography scan in the second patients revealed HCC (5.5 cm in diameter).

Pathological diagnosis

In the first case, resected stomach and intraperitoneal cytology identified gastric cancer.

Treatment

Immunological treatments (prednisone and cyclophosphamide in case 1, and rituximab alone in case 2) were administered instead of bypassing agents. Oral tegafur/gimeracil/oteracil was administered in case 1, and transcatheter arterial chemoembolization was performed in case 2.

Related reports

Recently, a systematic review described a large number of AHA patients with cancer.

Term explanation

AHA patients with cancer are more likely to exhibit recurrent hemorrhage and are less likely to achieve a complete response with eradication of the neutralizing autoantibodies.

Experiences and lessons

Besides hemostatic therapy and immunological treatments, successful treatment of AHA patients with cancer requires the concurrent treatment of the underlying malignancy.

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CASE REPORT

Glutaric acidemia type Ⅱ patient with thalassemia minor and novel electron transfer flavoprotein-A gene mutations: A case report and review of literature

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Author contributions: Saral NY, Aksungar FB, Aktuglu-Zeybek C and Coskun J conceived and gathered data for the case report; Aktuglu-Zeybek C obtained written informed consent from the patient; Demirelce O and Serteser M were involved in literature search and data analysis; Saral NY and Aksungar FB wrote the manuscript; all authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Informed consent statement: Written informed consent from the patient was obtained in the clinic.

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Abstract

Glutaric acidemia type Ⅱ (GAⅡ), also known as multiple acyl-CoA dehydrogenase deficiency, is an autosomal recessive inborn error of amino acid and fatty acid metabolism. We report a case of GAⅡ with novel electron transfer flavoprotein (ETF)-A mutations in a 2-year-old female with thalassemia minor. The patient developed an episode of hypoglycemia and hypotonicity

on the postnatal first day. Laboratory investigations revealed elevations of multiple acyl carnitines indicating glutaric acidemia type Ⅱ in newborn screening analysis. Urinary organic acids were evaluated for the confirmation and revealed a high glutaric acid excretion. Genetic analysis revealed two novel mutations in the ETF-A gene, which are considered to be compound heterozygote. At the 8 mo of life ketone therapy was added, which significantly increased the neuromotor development. The patient had been closely followed for two years with carnitine, riboflavin, coenzyme Q10, and ketone supplementation in addition to a high carbohydrate diet. Although the patient had comorbidity like thalassemia minor, her neuromotor development was normal for her age and had no major health problems. This specific case expands the previously reported spectrum of this disease.

Key words: Electron transfer flavoprotein-A mutation; Newborn screening; Glutaric acidemia type Ⅱ; Inborn error of metabolism; Ketone bodies; Case report

Core tip: Multiple acyl-CoA dehydrogenase deficiency (GAⅡ) is an autosomal recessive inborn error of amino acid and fatty acid metabolism. We report a case of GAⅡ with novel electron transfer flavoprotein (ETF)-A mutations in a 2-year-old female with thalassemia minor. Genetic analysis revealed two novel mutations in the ETF-A gene, which are considered to be the etiology for the disease. Most neonatal-onset patients of GAⅡ may not survive due to progressive deterioration despite aggressive treatment. However, at 8 mo of age our patient, with the experimentally added ketone therapy, had no major health problems, and neuromotor development was normal for her age. The present case report is the only one reporting a patient with both GAⅡ and thalassemia minor.

Saral NY, Aksungar FB, Aktuglu-Zeybek C, Coskun J, Demirelce O, Serteser M. Glutaric acidemia type Ⅱ patient with thalassemia minor and novel electron transfer flavoprotein-A gene mutations: A case report and review of literature. *World J Clin Cases* 2018; 6(14): 786-790 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/786.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.786

INTRODUCTION

Glutaric acidemia type Ⅱ (GAⅡ), also known as multiple acyl-CoA dehydrogenase deficiency, is an autosomal recessive inborn error of amino acid and fatty acid metabolism[1]. GAⅡ is caused by a defect in the electron transfer flavoprotein (ETF) or ETF dehydrogenase (ETFDH) resulting in deficiencies in multiple acyl-CoA dehydrogenases[2]. The ETF/ETFDH deficiencies are responsible for multiple defects of the dehydrogenation system because they block not only fatty acid oxidation, but also the oxidation of branched-chain amino acids and of glutaryl-CoA on the catabolic pathway of lysine, hydroxylysine, and tryptophan[3].

There are three clinical phenotypes in GAⅡ: neonatal form with congenital anomalies (most commonly cystic or dysplastic kidneys)[1]; neonatal form without congenital anomalies; and late onset form with myopathic phenotype and rarely metabolic acidosis[4]. All forms of GAⅡ can be caused by defects in the genes encoding the ETF α and β subunits (ETF-A and ETF-B, respectively) or in the gene encoding ETF-QO (ETFDH). The majority of patients with ETF deficiency are found to have mutations in the ETF-A gene[1].

Neonatal onset form is usually fatal and characterized by severe non-ketotic hypoglycemia, metabolic acidosis, excretion of large amounts of fatty acid, and amino acid-derived metabolites with congenital anomalies[5]. In addition to hypoglycemia and metabolic acidosis, routine laboratory findings may include hyperammonemia and elevated liver transaminases. Cardiomyopathy may be present in some cases. Pathologic abnormalities include fatty infiltration of the liver, heart, and kidneys[1].

Treatment consists of a diet low in protein and fat together with carnitine, ubiquinone, and riboflavin supplementation. However, most neonatal-onset patients may not survive due to progressive deterioration despite aggressive treatment[1]. We hereby present a case of GAⅡ, a neonatal form without congenital anomalies with a novel ETF-A mutation in a 2-year-old female with thalassemia minor.

CASE REPORT

The patient was born at full-term to nonconsanguineous parents after an uneventful pregnancy as the first child of the family with no history of metabolic diseases. The birth weight was 3192 g and height was 50 cm. Initial physical examination revealed a healthy infant with no dysmorphic features. An episode of hypoglycemia and hypotonicity occurred on the postnatal first day, and the infant was admitted to the neonatal intensive care unit. Initial laboratory results revealed significant hypoglycemia with elevated transaminase levels.

An expanded newborn screening (NBS) sample obtained in the first week was reported to be positive for glutaric acidemia type Ⅱ with elevations of multiple acylcarnitines. In particular, C4 butyrylcarnitine levels were extremely high, accompanied by elevated C5, C6, C8, C10, C14, and C5-DC glutaryl carnitine levels. Second-tier testing was carried out for NBS and urinary organic acids were evaluated for confirmation. Glutaric acid excretion was extremely high with increased levels of lactic acid, adipic acid, 5-hydroxyhexanoic acid, 2-hydroxy glutaric acid, and suberic acid. Radiological examinations revealed normal cranial Doppler

Table 1 Laboratory tests on the 22nd day after birth

Biochemical data	Patient results	Reference range
ALT (IU/L)	55 ↑	13-45
AST (IU/L)	63	18-69
ALP (IU/L)	252	107-474
CK (IU/L)	139	43-474
Urea (mg/dL)	14	2.1-34
CRE (mg/dL)	0.3	0.3-0.8
Lactate (mmol/L)	23.4	17-24
Ammonia (μmol/L)	103 ↑	16-68
HCO_3 (mmol/L)	18.3	17-24
Ca (mg/dL)	10.7	8.4-11.9
P (mg/dL)	5.9	3.1-7.7

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; CK: Creatine kinase; CRE: Creatinine.

Table 2 Dried blood spot acylcarnitine results

Blood acylcarnitine concentrations (μmol/L)	Patient	Reference range
Free carnitine (C0)	5.46 ↓	8.60-90.0
Acetylcarnitine (C2)	3.86 ↓	8.00-73.4
Propionylcarnitine (C3)	0.20 N	< 6.800
Butyrlycarnitine (C4)	2.25 ↑	< 1.200
Isovalerylcarnitine (C5)	0.18 N	< 0.600
Glutarylcarnitine (C5DC)	0.27 ↑	< 0.210
Hexanoylcarnitine (C6)	0.52 ↑	< 0.210
Octanoylcarnitine (C8)	2.77 ↑	< 0.320
Decanoylcarnitine (C10)	2.18 ↑	< 0.480
Dodecanoylcarnitine (C12)	1.37 ↑	< 0.690
Tetradecanoylcarnitine (C14)	0.57 N	< 0.800
Hexadecanoylcarnitine (C16)	0.69 N	< 8.700
Octadecenoylcarnitine (C18)	0.76 N	< 2.240

ultrasonography (USG) and normal cranial magnetic resonance findings. There were no pathologic findings aside from minimal hepatomegaly in the liver in USG (craniocaudal length 79.6 mm) and peripheral pulmonary stenosis was detected in echocardiographic evaluation.

The patient was transferred to the department of nutrition and metabolism of the university hospital with GA Ⅱ pre-diagnosis on the 22nd day after birth and was followed up for further examination and treatment regimen. Her general condition was good, and no abnormality was identified during the physical examination upon arrival at the university hospital. The laboratory findings and acylcarnitine profile are shown in Tables 1 and 2, respectively.

At the university hospital, a nasogastric tube was inserted and the patient was started on a diet of 6 mg/kg/min glucose with total parenteral nutrition containing 13% protein, 63% carbohydrate, 23% lipid, with totally 116 kcal/kg per day energy balance. After a week nutritional education was provided to the caregivers, the patient was discharged on carnitine (50 mg/kg per day), coenzyme Q10 (100 mg/d) and riboflavin (100 mg/d) supplementation with a high carbohydrate oral diet. At a follow-up after six months, ammonia levels were found to be high and sodium benzoate therapy was initiated. Meanwhile, a genetic analysis revealed, two different novel mutations in the ETF-A gene [NM_000126.3 p.L67P (c.200T>C) and Q285L (c.854A>T), compound heterozygote] and these mutations were considered to be the cause of the disease according to SIFT, PolyPhen-2, and PROVEAN databases[6-8].

At the sixth month follow-up, although the Denver test had revealed normal findings in terms of neuromotor development before, a slight delay in neuromotor development was observed. At the age of eight months, sodium 3-hydroxybutyrate (NaHB) administration was started and gradually increased from 360 mg/kg to 1400 mg/kg by the end of the 12th month, together with the high carbohydrate diet. Diet challenge was undertaken according to the plasma acylcarnitine and ketone body levels. After the diet alignments, the patient's neuromotor development was noted to increase significantly.

In the second year, follow-up laboratory tests identified low mean corpuscular volume (< 65 fl) and high red blood cell (5.5 × 10^6/μL). A hemoglobin electrophoresis was performed and results confirmed the diagnosis of thalassemia minor. Following these diagnostic tests, a percutaneous endoscopic gastrostomy (PEG) tube was inserted. The patient has been closely followed with carnitine, riboflavin, coenzyme Q10, and 1600 mg/kg per day ketone treatment in addition to a high carbohydrate diet. Patient is followed with routine controls and infections are monitored and treated immediately. Although she is slightly overweight, her neuromotor development is normal for her age and she has no major health problems.

DISCUSSION

Glutaric acidemia type Ⅱ is among the severe inborn errors of metabolism and it may be associated with significant morbidity and mortality, particularly in the neonatal-onset patients[1]. Neonatal-onset form patients may develop severe respiratory failure, cardiomyopathy, hypotonia, metabolic acidosis, and profound hypoglycemia soon after birth, which corresponds with short life expectancy[2].

The patient in the present case report had severe hypoglycemia on the postnatal first day, and diagnosis was achieved by the expanded newborn screening analysis. Acylcarnitines in dried blood spots were analyzed using a tandem mass spectrometry after butyl-derivatization. Urine organic acids were analyzed by gas chromatograph mass spectrometer and showed increased excretion of GA Ⅱ characteristic compounds, such as adipate, suberate, glutarate, 2-hydroxyglutarate, ethylmalonate, or isovalerylglycine, which are the corresponding metabolites derived from defective acyl-CoA dehydrogenase reaction steps[9]. As a result of these findings, together with those of genetic analysis, our patient was diagnosed with GA Ⅱ, neonatal-onset form without congenital anomalies.

The most important goal of newborn screening for inborn errors of metabolism is to reduce morbidity and mortality by early interventions such as dietary and pharmacologic treatments[1]. In recent years, expanded NBS using tandem mass spectrometry eased the detection of many inborn errors of metabolism in asymptomatic newborns. Screening for GAⅡ, which is estimated to have a prevalence of 1/200000, is also very important given the potential for early detection and intervention such as our case. The patient in the present study was diagnosed through the use of advanced technologies and the timely application of therapies enabled the patient to reach the second year of life without major health problems.

Our patient was diagnosed with thalassemia minor in the second year of life. In thalassemia minor (Tm), hemoglobin synthesis is decreased, but individuals are generally considered healthy. However, Tm is thought to be a potential risk for cardiovascular, neurological, metabolic, and vascular complications[10], and as a result of increased iron absorption, ineffective erythropoiesis, erythroid hyperplasia, and decreased antioxidant capacity, Tm affects health expectations[10]. Coexistence of GAⅡ and thalassemia minor in our patient may make her prone to infections and a decreased tolerance to complications may be expected.

Pharmacological therapy for GAⅡ is based on the administration of L-carnitine, Coenzyme Q10, and riboflavin (vitamin B2)[11]. Unfortunately, response is often poor to these treatments. Although ketone therapy is still at the experimental stage, sodium 3-hydroxybutyrate (NaHB) administration has emerged as a promising form of treatment, enabling the replacement of the deficient endogenous ketone body production needed not only for energy supply, but also for the synthesis of complex cell and tissue components such as myelin in the central nervous system[12]. Studies have shown that NaHB treatment results in the improvement of cardiomyopathy, hypotonia, and feeding tolerance in GAⅡ patients[13].

In our patient, in addition to routine therapy, ketone supplementation was started at eight months and the dose was increased gradually from 360 mg/kg/d to 1600 mg/kg/d, which significantly increased neuromotor development in a short time. Ketone body treatment is also thought to increase resistance to infection in GAⅡ patients[12-14]. Moreover a PEG tube insertion was another advantage for the patient because it allowed the family and caregivers to easily apply the planned diet and medications and prevent hypoglycemia attacks.

In conclusion, expanded NBS by tandem MS has made it possible to diagnose GAⅡ in this particular patient and enabled us to take measures and make early interventions for the patient who additionally had thalassemia minor. To our knowledge the present case report is the only one reporting a patient with both GAⅡ and thalassemia minor. Ketone body treatment should be considered to be part of routine therapy in GAⅡ patients with existing comorbidities, such as in our case. Finally, this patient's genetic analysis added two novel mutations of the ETF-A gene to the literature.

ARTICLE HIGHLIGHTS

Case characteristics

An episode of hypoglycemia and hypotonicity occurred on the postnatal first day, and the patient was admitted to neonatal intensive care unit.

Clinical diagnosis

Patient's general condition was good. No abnormality was identified during the physical examination.

Differential diagnosis

Metabolic diseases were investigated with tandem mass spectrometry.

Laboratory diagnosis

Tandem mass spectrometry, high pressure liquid chromatography, and mass spectrometry measurements in newborn screening enabled us to diagnose the patient very early.

Imaging diagnosis

Cranial Doppler ultrasonography (USG) and cranial magnetic resonance findings were normal, and there were no pathologic findings aside from minimal hepatomegaly in the liver.

Treatment

Patient was treated with carnitine, riboflavin, Coenzyme Q10, and ketone treatment in addition to a high carbohydrate diet.

Related reports

Glutaric academia type Ⅱ (GAⅡ) was first described in 1976 and is estimated to have a prevalence of 1/200000 live births. There are a few case reports describing the neonatal-onset form of the disease in the literature since the life-expectancy is short. There are also some cases reports describing adult-onset forms, which are mild with the patients living until adulthood.

Term explanation

Tandem mass spectrometer: High pressure liquid chromatography and mass spectrometry.

Experiences and lessons

Expanded new born screening by tandem mass spectrometry has made it possible to detect GAⅡ in this particular patient and enabled us to make early interventions for the patient. Moreover ketone treatment seems to be advantageous in GAⅡ patients, particularly in cases with comorbidities.

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CASE REPORT

Meckel's diverticulum diagnosis by video capsule endoscopy: A case report and review of literature

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Diego García-Compeán, Alan R Jiménez-Rodríguez, Ángel N Del Cueto-Aguilera, Gilberto Herrera-Quiñones, José A González-González, Héctor J Maldonado-Garza, Gastroenterology Service and Department of Internal Medicine, Faculty of Medicine, University Hospital "Dr. José E. González", Universidad Autónoma de Nuevo León, Monterrey 64700, Nuevo León, México

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Author contributions: García-Compeán D designed the research, analyzed the results and wrote the paper; Jiménez-Rodríguez AR performed the bibliographic research; Del Cueto-Aguilera AN performed the bibliographic research and reviewed the research data; Herrera-Quiñones G collected the data; González-González JA analyzed the data; Maldonado-Garza HJ analyzed the final results.

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Abstract

BACKGROUND

Meckel's diverticulum (MD) occurs predominantly in children and adolescents. It is rarely diagnosed in adults. Preoperative diagnosis is difficult due to low sensitivity of the radiological imaging studies. The role of video capsule endoscopy (VCE) in the diagnosis of MD is unknown, and the endoscopic patterns are not defined. We will describe four of our cases of MD evaluated with VCE and make a review of the literature focusing on the endoscopic characteristics.

CASE SUMMARY

We present four cases of MD confirmed by surgery. They were all adult males with ages going from 18 to 50 years, referred to our service from 2004 to 2018, due to obscure gastrointestinal bleeding (OGIB). They

had a history of 1 mo to 10 years of overt and occult bleeding episodes. Laboratory blood test showed an iron-deficiency anemia from 4 to 9 g/dL of hemoglobin that required multiple hospitalizations and blood transfusions in all cases. Repeated upper digestive endoscopies and colonoscopies were negative. Small bowel was examined with VCE, which revealed double lumen images in all cases, one with polyps and three with circumferential ulcers in the diverticulum. However, based on VCE findings, preoperative diagnosis of MD was suggested only in two patients. Capsule was retained in one patient, which was recovered with surgery. The anatomopathological report revealed ulcerated ectopic gastric mucosa in all cases.

CONCLUSION

VCE is useful for the diagnosis of MD. However, endoscopic characteristics must be recognized in order to establish preoperative diagnosis.

Key words: Meckel's diverticulum; Endoscopic features; Video capsule endoscopy; Wireless capsule endoscopy; Review; Case report

Core tip: Preoperative diagnosis of Meckel's diverticulum (MD) is practically nonexistent due to the low sensitivity of imaging studies. Video capsule endoscopy (VCE) allows direct examination of the small bowel. However, few publications report evaluating the role of VCE on diagnosis of MD, and the endoscopic characteristics have not been defined. For the above-mentioned, it is highly probable that this disease is under-diagnosed. In this literature review, we focus on the endoscopic features of MD by VCE, and in its clinical and pathological characteristics. Recognition of endoscopic features will increase preoperative diagnosis of this disease.

García-Compeán D, Jiménez-Rodríguez AR, Del Cueto-Aguilera ÁN, Herrera-Quiñones G, González-González JA, Maldonado-Garza HJ. Meckel's diverticulum diagnosis by video capsule endoscopy: A case report and review of literature. *World J Clin Cases* 2018; 6(14): 791-799 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/791.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.791

INTRODUCTION

Meckel's diverticulum (MD) is the most frequent gastrointestinal malformation. This condition arises from the incomplete involution of the omphalomesenteric duct[1] and is located in the antimesenteric region, in the last 60 to 100 cm of the ileum. Prevalence of MD has been estimated at 2% in the general population[1,2]. It predominates in male children and adolescents and is rarely diagnosed in adults[3]. This prevalence, however, could be significantly underestimated, since MD is asymptomatic in most cases. Only about 16% of cases may present clinical manifestations, with gastrointestinal bleeding (GIB) being the most frequent one[4]. On the other hand, most radiological studies, such as computerized tomography (CT) or magnetic resonance imaging, abdominal ultrasound, barium intestinal transit and mesenteric angiography, have poor diagnostic sensitivity[5]. It has been reported that technetium-99m pertechnetate scintigraphy (Meckel's Scan) has moderate diagnostic sensitivity in children and adolescents, and poor sensitivity in adults[5]. Therefore, the preoperative diagnosis of MD is practically nonexistent in most cases.

Currently, it is expected that the use of new techniques enabling the direct revision of small intestine mucosa, such as video capsule endoscopy (VCE) and balloon enteroscopy, can increase preoperative diagnosis of MD. Despite the fact that VCE was approved for clinical use in 2000, nowadays there is scarce literature regarding its usefulness in the diagnosis of MD and endoscopic characteristics of this entity.

In view of the foregoing, we decided to report a case series of MD evaluated with VCE and to analyze clinical, demographic and anatomopathological characteristics, together with similar published cases through a review of the literature, emphasizing the endoscopic findings.

CASE PRESENTATION

Case 1

Chief complaints: A 20-year-old male who was referred to our unit in 2004 with a 3-year history of anemic syndrome.

History of present illness: He had suffered anemic syndrome for 3 years, treated with blood transfusions and intravenous iron. He did not have abdominal symptoms.

History of past illness: He had no history of past comorbidities.

Physical examination upon admission: On physical examination, he was pale and did not show hemodynamic instability.

Laboratory examinations: The laboratory blood tests showed an iron-deficiency anemia (hemoglobin: 4 g/dL).

Imaging examinations: Previously, the patient had undergone four upper digestive endoscopies (UDEs), one colonoscopy and one barium intestinal transit, with non-relevant results. It was decided to examine the small intestine with a VCE, which showed an image

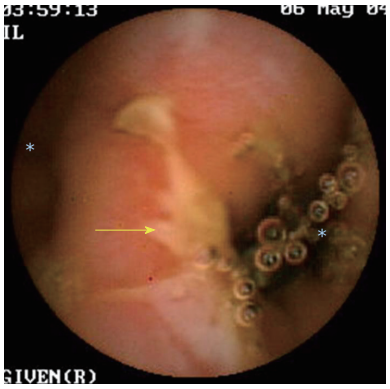

Figure 1 Image of ileum with video capsule endoscopy. Presence of double lumen is shown (asterisks), with one having a circumferential ulcer with irregular border (arrow).

with circumferential ulcers in the ileum. A diagnosis of ulcerated enteropathy of undetermined etiology was suggested. The retrospective review of the VCE images showed typical images of the MD (double lumen), which had gone unnoticed by the endoscopist (Figure 1). A Meckel's Scan was then performed, which was positive. A surgical intervention was decided by laparoscopy.

Case 2

Chief complaints: A 50-year-old male was referred to our unit in 2011 due to one-month history of hematochezia.

History of present illness: He had suffered hematochezia for 1 mo. He did not complain of abdominal pain.

History of past illness: He had no history of relevant comorbidities. He denied the use of nonsteroid anti-inflammatory drugs.

Physical examination upon admission: He presented only paleness of teguments and no hemodynamic instability.

Laboratory examinations: Laboratory blood tests showed an iron-deficiency anemia (hemoglobin: 9 g/dL).

Imaging examinations: UDE and colonoscopy performed during current hospitalization were both negative. It was considered adequate to evaluate the small intestine with VCE, which showed ulcerated polyps in a circumferential structure in the ileum (Figure 2A). Images with double lumen (Figure 2B) were found through retrospective review of VCE study; the gastrointestinal endoscopist before surgery had not noticed such images.

Since there was no conclusive diagnosis, a laparotomy was performed.

Case 3

Chief complaints: An 18-year-old male was referred to our unit in 2017 with a 9-year history of recurrent episodes of hematochezia and anemia (hemoglobin: 4 g/dL).

History of present illness: He had suffered recurrent episodes of hematochezia and anemia for 9 years, which required multiple hospitalizations and blood transfusions. Two UDEs, two colonoscopies and one CT-enterography, which were performed in the last 3 years, showed negative results.

History of past illness: He did not present past comorbid conditions.

Physical examination upon admission: On examination, he was pale and did not show hemodynamic instability. He did not have abdominal complaints.

Laboratory examinations: Laboratory blood tests showed an iron-deficiency anemia (hemoglobin: 4 g/dL).

Imaging examinations: A review of the small intestine with VCE was performed, which showed a double lumen image with circumferential ulcerations (Figure 3). The capsule was retained in this place until the battery was consumed after 10 h from the beginning of the procedure. The probable diagnosis of MD was suggested. A plain abdominal radiography, which was performed 7 d later, showed VCE retention. An abdominal CT scan showed the presence of a diverticulum in the ileum, with the capsule lodged inside it. Meckel's Scan was negative. The patient underwent laparoscopy.

Case 4

Chief complaints: A 24-year-old male was referred to our unit in 2018 with a 10-year history of iron-deficiency anemia and hematochezia.

History of present illness: He had suffered iron-deficiency anemia and hematochezia. His plasma hemoglobin values varied during this period, from 5 g/dL to 8 g/dL; the patient underwent blood transfusions and intravenous infusions of iron repeatedly.

History of past illness: He did not show past relevant comorbidities.

Physical examination upon admission: On examination, he was pale and did not show hemodynamic instability. He did not have abdominal pain.

Laboratory examinations: Laboratory blood tests showed an iron-deficiency anemia (hemoglobin: 9 g/dL).

Imaging examinations: Two UDEs and two colo-

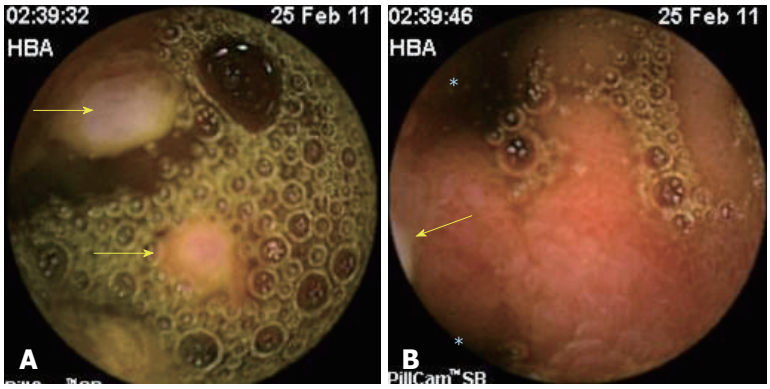

Figure 2 Image of ileum with video capsule endoscopy. A: Ulcerated polyps in the intestinal lumen (arrows); B: Double lumen (asterisks), with the lower lumen containing the polyps (arrow).

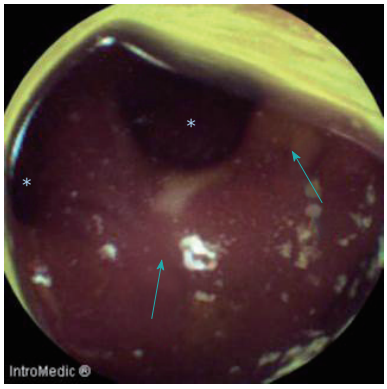

Figure 3 Image of ileum with video capsule endoscopy. Double lumen (asterisks) with ulcerations in the diverticulum (arrows).

noscopies, which were previously performed, were negative. It was decided to examine the small intestine with VCE, which showed a double lumen image in the ileum (Figure 4A). A severe circumferential ulcer with intense edema and recent bleeding evidence were identified in one of the lumens (Figure 4B). The findings were reported as suggestive of MD. CT-enterography revealed a diverticulum in the ileum. A Meckel's Scan was not performed, and surgical intervention was decided by laparoscopy.

FINAL DIAGNOSIS

Final diagnosis was GIB due to MD in all patients.

TREATMENT

Specific treatment in all cases was surgical resection of intestinal diverticulum with primary anastomosis. Surgical findings were: Case 1, an 8-cm long diverticulum at 30 cm from the ileocecal junction was found; case 2, an 8-cm in length diverticulum was observed in the ileum; in case 3, a 5 cm × 5 cm diverticulum located 45 cm from the ileocecal junction, which was resected and the video capsule was removed and in case 4, a 10-cm in length diverticulum within 53 cm of the ileocecal valve was found. The anatomopathological report revealed the presence of ulcerated ectopic gastric mucosa in the diverticulum in all the cases.

OUTCOME AND FOLLOW-UP

None had surgical or postoperative complications. The GIB disappeared after surgical treatment and they were discharged from the hospital in good conditions. Currently, none has showed recurrence of GIB.

DISCUSSION

A literature review of articles published in PubMed, Medline and Ovid databases from 2000 to date on patients with MD (confirmed by surgery) who underwent VCE was conducted. Publications describing the endoscopic characteristics of MD were selected. In addition, the demographic and clinical characteristics of patients as well as the prevalence of ectopic mucosa in the diverticulum were determined.

In total, 20 case reports[6-25] and 1 cohort study with 11 patients[26] were selected. The addition of our 4 patients gave a total of 35 patients for analysis. Of them, 30 were male (85.7%). The mean age was 28 ± 21.1 years (range: 2-80 years). Ten (28.5%) were pediatric patients (under 18 years). The majority of the patients were adults (71.5%), 68.5% were younger than 30 years old and 23% were over 50 years of age (Table 1).

The clinical manifestations of the patients were overt GIB in 26 (74.2%), anemia in 8 (23%) and abdominal pain in 5 (14.2%). Symptoms had a mean duration of 35.1 mo (range: 1-120 mo) (Table 1).

In all cases, at least one UDE and one colonoscopy were performed. In 25 patients, one or more of the following diagnostic procedures were done: CT/magnetic resonance imaging-enterography in 5 patients; plain CT scan in 2 patients; push enteroscopy in 3 patients; and, barium intestinal transit in 15 patients.

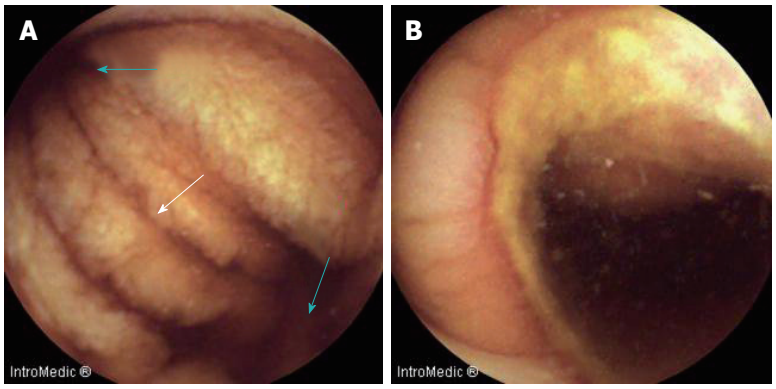

Figure 4 Image of ileum with video capsule endoscopy. A: Double lumen (blue arrows) and diaphragm (white arrow); B: Severe circumferential ulcer in one of the lumens.

All procedures were reported as negative or showing irrelevant findings.

Meckel's Scan was positive only in 2 out of 13 patients (15.3%). The 61.5% of cases having negative Meckel's Scan were pediatric patients (Table 1).

Description of the endoscopic images of MD was available in 22 cases (18 published case reports and our 4 clinical cases) (Table 2). The images could be grouped into the following categories: (1) double lumen images in 15 (68.8%) patients; among them, those showing ulcers in one lumen accounted for 9 (41%) patients (Figures 1 and 3) and those not showing ulcers accounted for 6 (27.2%) patients (Figures 2B and 4A); (2) polypoid structure (true polyp in the diverticular mucosa or diverticular eversion) in 4 (18%) patients (Figures 2A, 5A and 5B); and (3) stenotic lumen and circumferential ulcer in 3 (12.6%) patients (Figure 4B).

The capsule was retained in the small intestine in 6 (17.1%) patients. It was lodged inside the diverticulum in 4 patients. Capsule removal through laparoscopy was performed in 2 cases at 4 mo after the procedure, where unsuspected MD was found[6,24]. One patient had delayed spontaneous elimination of the capsule[8]. Finally, the capsule was removed by double balloon enteroscopy in another patient[15], and by surgery in 2 cases[10].

In 16 (88.8%) out of 18 cases, ectopic mucosa was found in the diverticulum lining, represented by 14 gastric and 2 pancreatic findings.

Some publications have reported that MD can be found in 2.9% to 16% of cases with obscure (O)GIB[26-28]. In these patients, the complete revision of the small bowel is necessary in order to identify the source of bleeding. This was not possible until 2000 when the VCE was approved by the Food and Drug Administration for clinical use. Prior to this date, push enteroscopy was the only direct method for examining the interior of the small bowel. However, the intestine was only partially reviewed, so diagnostic yield was low[29].

VCE is a noninvasive procedure that consists of a mini photographic camera that takes multiple images per second after ingestion. In accordance with the published international guidelines[30,31], VCE should be used as the first procedure for small bowel examination in the diagnostic strategy of OGIB. In recent years, the use of VCE has been extensively increased worldwide, in such a way that a greater number of physicians face the challenge of identifying endoscopic patterns of small bowel diseases. It is strange that so far, very few studies on the endoscopic characteristics of MD by VCE have been published.

Results yielded from this review

Age: Symptomatic MD is described as a predominant condition in children and adolescents and as infrequent in adults over 40-year-old[4]. The majority of patients included in our analysis were adults (71.5%). Many children with MD do not usually undergo a VCE because they are operated on, since they more frequently present complications of the disease[32]. Notwithstanding, this review seems to indicate that clinically-manifested MD is not an uncommon condition in adults.

Clinical manifestations: In this analysis, 34 of 35 patients had GIB and only 1 had abdominal pain. Hemorrhage was overt in 76.4% of cases. GIB has been described as one of the most frequent clinical manifestations of MD in children and adults. In a study with 119 adults with MD (mean age: 43 years), of whom 52 (43.6%) experienced clinical symptoms, GIB was observed only in 15% of the patients. Twenty-two percent of the whole group developed complications, which required urgent surgical intervention (inflammation, intestinal perforation, intestinal obstruction, severe abdominal pain, foreign body perforation)[33]. Another study involving 43 adults reported that patients with symptomatic MD had significant morbidity. Complications arising from surgical resection of incidental or symptomatic diverticulum were uncommon (8% to 9%), but were more frequently fatal[34].

Table 1 Clinical, demographic and pathological characteristics of 35 patients with Meckel's diverticulum confirmed by surgery

Parameter	*n* (%)
Male	30 (87.5)
Female	5 (12.5)
Age in yr, mean ± SD (range)	24 ± 21.1 (2-80)
< 18	10 (28.5)
19-39	14 (40)
40-60	7 (20)
> 60	4 (11.5)
Symptoms	
Overt GIB	26 (74.2)
Occult GIB	8 (22.8)
Abdominal pain	5 (14.2)
Duration of symptoms in mo, mean (range)	35.1 (1–120)
Imaging studies prior to VCE	
Reported studies	25 (71.4)
No reported studies	10 (28.6)
CT/MRI enterography	5
CT scan	2
Push enteroscopy	3
Barium intestinal transit	15
Meckel's Scan	
Reported studies	13
Positive Meckel's Scan	2 (15.3)
Ectopic Tissue	
Reported studies	18
Gastric/pancreatic	16 (88.8)

CT: Computed tomography; GIB: Gastrointestinal bleeding; MRI: Magnetic resonance imaging; VCE: Video capsule endoscopy.

Table 2 Endoscopic patterns by video capsule endoscopy of 22 patients with surgically-confirmed Meckel's diverticulum

Feature	*n* (%)
Double lumen	15 (68.8)
Double lumen with ulcers	9 (41)
Double lumen without ulcers	6 (27.2)
Polypoid structure (true polyp or diverticular eversion)	4 (18)
Stenotic lumen with ulcer	3 (13.6)

Duration of symptoms: The diagnosis of MD in most of the patients in this review was made late (mean time of 3 years, ranging from 1 mo to 10 years). The majority of the patients underwent multiple transfusions, repeated hospitalizations and diverse endoscopic and radiological examinations. This may indicate that the current recommendations of the international guidelines for the diagnosis of OGIB (concerning early use of VCE) are not followed in many cases.

Diagnostic procedures: Conventional imaging procedures performed before VCE, did not suggest the diagnosis of MD in any case. Some published reports show the diagnostic accuracies of intestinal transit with barium, plain CT and mesenteric angiography to be 44%, 33% and 60%, respectively[33]. The CT-enterography scan, which combines the advantages of CT with those of conventional barium enteroclysis, could improve the diagnostic performance of MD[35]. However, its diagnostic performance in MD is unknown.

Meckel's Scan: This test was positive in only 18.7% of the patients-a low figure compared to those reported in the literature. Some publications have reported sensitivity and specificity of 85% and 95% in children and of 62% and 9% in adults, respectively[36]. It is noteworthy that in this review, 61.5% of patients with negative Meckel's Scan were pediatric patients, contrary to the aforementioned results. The causes of the poor sensitivity of Meckel's Scan in both pediatric and adult patients in this review are difficult to explain. The presence of factors that produce a false negative result (*i.e.* active bleeding, poor vascular supply, previous use of barium for diagnosis of intestinal disorders, use of atropine, gastrointestinal study with barium, or small diverticulum) cannot be ruled out[37].

Endoscopic characteristics: Double lumen was the most frequent endoscopic pattern in patients with MD (69%). In some cases, ulcers in the circumference of one of the lumens were observed. Some authors have described a diaphragm image in the interluminal septum, which they called a "diaphragm sign" (Figure 4A). The double lumen image is strongly suggestive of MD and should lead to the indication of complementary imaging procedures or double balloon enteroscopy in order to establish preoperative diagnosis. In addition, other images of MD should be taken into account for diagnostic suspicion, such as a polypoid formation (which can be confounded with an intestinal tumor) and which was seen in 18% of cases in this review, or circumferential ulcers with luminal stenosis (which can evoke a nonsteroidal anti-inflammatory drug enteropathy or Crohn's disease) and which was observed in 13% of the patients. The sensitivity and specificity of VCE in the diagnosis of MD is unknown; however, in a cohort study in which surgery was used as a gold standard test, the positive predictive value of VCE was 81.8%[26].

Capsule retention is the most feared complication of VCE, but occurs in only 2% of the patients. Crohn's disease and intestinal tumor significantly increase this risk, up to 13%[30-38]. Capsule retention in this analysis was more frequent (17.1%). This places MD as a high-risk condition of capsule retention, so that use of the biodegradable Agile capsule may be considered[39,40].

Ectopic mucosa: The prevalence of ectopic mucosa in the diverticulum was higher (89%) in this analysis than that reported by other studies (43% to 48%)[4,33]. Ectopic mucosa is more frequent in symptomatic patients than in asymptomatic ones (48% *vs* 14%, respectively). The sensitivity of Meckel's Scan in the patients with ectopic mucosa of this analysis was 16%, and this figure is far lower than that published in other

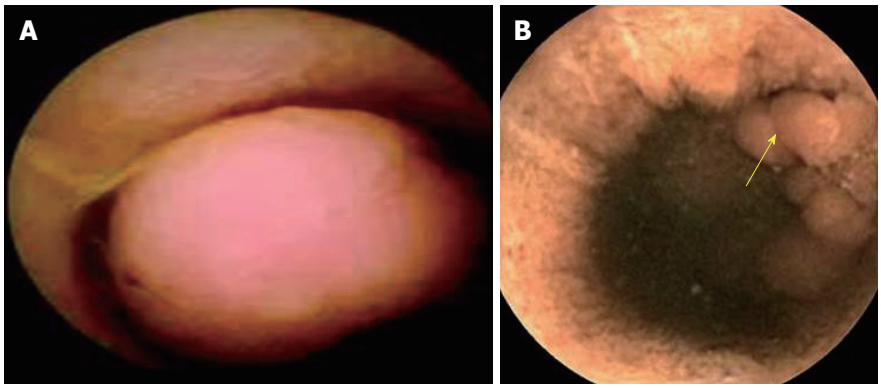

Figure 5 Image of ileum with video capsule endoscopy. A: Polypoid image given by everted Meckel's diverticulum; B: True polyps (arrow) inside the Meckel's diverticulum.

series[36].

The limitations of this analysis are the following: (1) the number of patients was low, although this issue may reflect the low frequency with which endoscopic findings of this disease are reported in the literature, even in the era of VCE; and (2) the patients that comprised this analysis were selected by the fact that they underwent a VCE, and therefore may not represent the universe of patients with MD since the asymptomatic ones and those who required emergency surgery were not included.

In conclusion, our review indicated that symptomatic MD is not infrequent in adults. As such, we suggest that this condition should always be included in the differential diagnosis of OGIB or intestinal disease in this age group. We also found that conventional imaging studies have a low diagnostic sensitivity, and Meckel's Scan may be negative, even in pediatric patients, suggesting that this test should not be taken as a reference for decision making. In addition, VCE appears to have high probability of diagnosing MD, so it should be done as early as possible. However, it is highly recommended that gastrointestinal endoscopists be trained for recognizing the different endoscopic patterns of MD. Images should be interpreted in the appropriate clinical context in order to perform complementary studies to confirm (or rule out) MD before surgery. Finally, we found the most frequently observed endoscopic pattern of MD to be the double lumen image and that MD may be considered as a high-risk condition of VCE retention, even with previous normal imaging studies.

In view of the difficulties for preoperative diagnosis of MD, the performance of multicenter studies with a large number of patients, in which the precise role of VCE in the diagnosis of MD is assessed, will be necessary.

CONCLUSION

Because of this review, we think that MD is an underdiagnosed disease in adults. Abdominal imaging procedures (CT/MR-enterography), have limited usefulness for diagnosis and Meckel's Scan may not be a diagnostic reference test. VCE and balloon enteroscopy, which allow direct examination of small bowel, increase the probabilities of preoperative diagnosis. Notwithstanding, endoscopic patterns of MD have not been defined and there are very scarce publications concerning this issue. The most frequent endoscopic pattern of MD observed in our patients and in other reported cases was "double lumen", followed by polyp formations and circumferential ulcers with luminal stenosis. In our experience with four patients reported here, diagnosis was initially missed in the first two cases because of lack of experience of endoscopist on recognition of endoscopic patterns of MD at that time. Endoscopic diagnosis was established retrospectively in them. Three patients had a long history of GI bleeding without etiologic diagnosis and VCE indication was delayed.

The improvement of preoperative diagnosis rates of MD will be possible through high suspicion of this condition and the training of gastrointestinal endoscopists on recognition of endoscopic features of MD obtained with VCE.

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CASE REPORT

Carney complex: Two case reports and review of literature

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Author contributions: Duan L and Lu L designed the report; Wang FD and Jin ZY collected the patients' clinical data; Li S wrote the paper.

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Abstract

Carney complex (CNC) is an extremely rare genetic syndrome of pigmented skin lesions, endocrine hyperfunction and myxoma. Given its diverse clinical manifestations, CNC is often misdiagnosed. Recognition of some special clinical manifestations and imaging features may help with the diagnosis. Early diagnosis of CNC would alert ongoing surveillance of tumors and complications; the prognosis of CNC may thus be improved by early treatment. Herein, we report two cases of CNC with bone lesions.

Key words: Carney complex; Osteochondromyxoma; Primary pigmented nodular adrenocortical disease; Computed tomography; Magnetic resonance imaging; Case report

Core tip: Carney complex (CNC) is a very rare disease which is often misdiagnosed because of its diverse clinical characteristics. The imaging features of bone lesions in two cases have been summarized in this paper. Recognition of some special clinical manifestations and imaging features may help with the diagnosis; the prognosis of CNC may thus be improved by early treatment.

Li S, Duan L, Wang FD, Lu L, Jin ZY. Carney complex: Two

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INTRODUCTION

Carney complex (CNC) was first described in 1985 by J Aidan Carney, and its main clinical features are spotty pigmentation, endocrine overactivity, and myxoma[1].

The mutation of the *PRKAR1A* gene on chromosome 17q22-24 and another gene called *CNC2* on chromosome 2p16 is considered to be associated with the cause of the disease[2,3]. The prevalence of CNC is unknown, and only about 750 patients have been reported worldwide with CNC by January 2008, based on reports from the National Institutes of Health and the Mayo Clinic (the United States), and the Hospital Cochin (France)[4,5]. Moreover, the diagnosis is often delayed owing to its rarity and complexity. Although some non-endocrine tumors are rare, they are highly characteristic, such as cardiac myxomas and osteochondromyxomas. Herein, we report two cases of CNC with bone lesions and review the relevant literature.

CASE REPORT

Case 1

A 27-year-old female who had suffered from recurrent fractures for 17 years, visual decline for 12 years, and a gradually rounded face for 7 years was admitted to our hospital. For 17 years, she has often suffered from various fractures (involving almost every part of the body) after mild activity. Twelve years ago, she suffered ocular proptosis, widened eye distance, and decreased binocular vision. In recent years, she has slowly developed a rounded face and her weight has increased significantly. Three years ago, she developed amenorrhea, and both adrenals were found by abdominal computed tomography (CT) to have multiple nodules. Therefore, the patient underwent bilateral adrenalectomy, and primary pigmented nodular adrenocortical disease (PPNAD) was confirmed (Figure 1A). After the surgery, she regained her normal menstrual cycles. Physical examination revealed an overweight female patient with a full moon face, thin skin, multiple purple striae on both sides of the abdomen, and numerous punctate areas of black or brown pigmentation on her lips and buccal mucosa. Detailed enquiry found a family history of "facial asymmetry", as demonstrated in Figure 2.

Laboratory tests revealed an abnormal rhythm of cortisol secretion and increased urine free cortisol. Both the low-dose and high-dose dexamethasone suppression tests were not inhibited, indicating primary hypercortisolism. Serum adrenocorticotropic hormone (ACTH) level was less than 5.00 pg/mL (normal range: 5-50 pg/mL).

Skull CT examination showed that the skull and maxillofacial bones were remarkably enlarged, with both sclerotic and lytic lesions (Figure 3A and B). Head magnetic resonance imaging (MRI) revealed diffused bone lesions in the frontal, occipital, and sphenoid bones, with low to intermediate and high signal intensity on both T1-weighted (WI) and T2WI images. Some of these retained high signal intensity on fat saturated T1WI and were markedly enhanced after the injection of gadolinium (Figure 3C-F). Spine MRI demonstrated multiple flatted vertebrae, with patchy bone lesions that were of low signal intensity on T1WI, mixed signal intensity on T2WI, and high signal intensity on fat saturated T2WI, with enhancement on gadolinium enhanced T1WI (Figure 4).

Case 2

A 26-year-old male with a gradually rounded face and increased abdominal circumference for 2 years was admitted to our hospital. For 2 years, he had noticed his face becoming rounder and redder, the abdominal circumference had increased slowly, and more and more purple lines had developed on both sides of the abdominal skin. Right adrenalectomy was performed because of bilateral adrenal nodular hyperplasia and the postoperative pathology proved to be PPNAD (Figure 1B). On physical examination, the patient had a full, sanguineous moon face and scattered spots of pigmentation on his lips and buccal mucosa, which existed at birth and were similar to his father's (Figure 5).

Laboratory tests confirmed hypercortisolism because both the low-dose and high-dose dexamethasone suppression tests were not inhibited. Serum ACTH level was less than 5.00 pg/mL (normal range: 5-50 pg/mL). An enlarged frontal bone of inhomogeneous density with scattered small lytic lesions was found on skull CT (Figure 6A). The sclerotic lesion on the left part of the frontal bone was of high density on CT and low intensity on T1WI and T2WI MRI. In contrast, the lytic lesion was of low density on CT, low intensity on T1WI, and high intensity on T2WI, and was enhanced on gadolinium enhanced T1WI (Figure 6B-D).

Genetic testing was undertaken by both patients to detect the mutation of the *PRKAR1A* gene, which was negative in the first case and positive in the second case. According to the patients' clinical findings, imaging manifestations, and gene mutation, the diagnosis of CNC was made. Both patients were regularly followed after discharge, which was uneventful.

DISCUSSION

CNC is an autosomal dominant disorder, characterized by multiple endocrine tumors and skin and heart involvement. The diagnostic criteria for CNC are: (1) at least two manifestations out of spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner

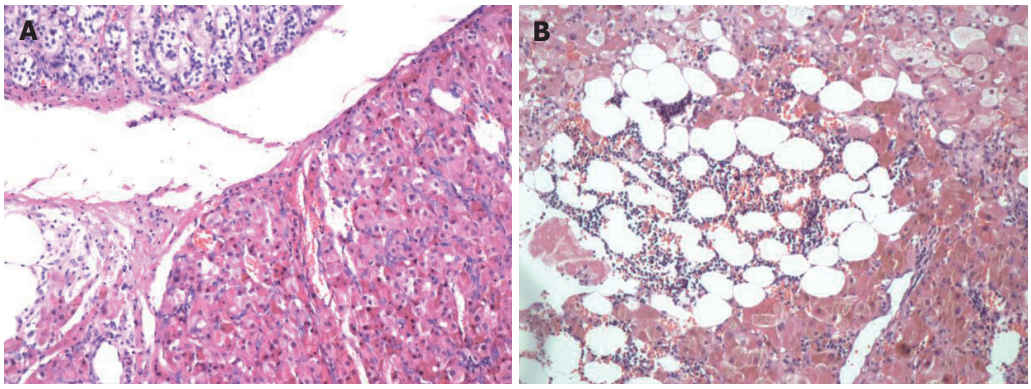

Figure 1 Histopathology (H and E staining, × 100). A: The left adrenal lesion of Patient 1 conforms to primary pigmented nodular adrenocortical disease (PPNAD); B: The right adrenal lesion of Patient 2 conforms to PPNAD with local myelolipoma like change.

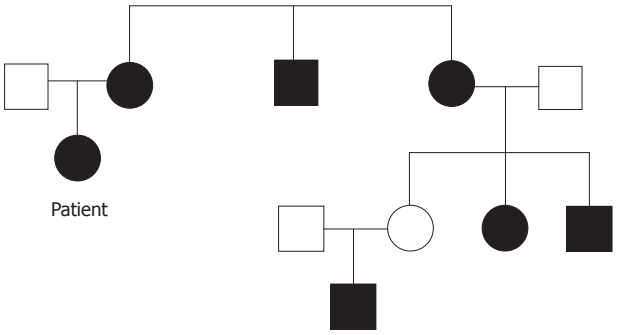

Figure 2 Pedigree chart of Patient 1. Many of the patient's family members had "facial asymmetry". Circles represent females; squares represent males. Graphics in black represent "facial asymmetry".

or outer canthi, vaginal and penile mucosa), myxoma (cutaneous and mucosal), cardiac myxoma, breast myxomatosis, PPNAD, acromegaly due to growth hormone-producing adenoma, large-cell calcifying Sertoli cell tumor, thyroid carcinoma, psammomatous melanotic schwannoma, blue nevus, breast ductal adenoma, and osteochondromyxoma; or (2) one of these manifestations plus one of the supplemental criteria (an affected first-degree relative or an inactivating mutation of the *PRKAR1A* gene)[6]. Both of the cases reported here had a positive family history, typical skin changes, and endocrine abnormalities, and one of them had *PRKAR1A* gene mutation. Thus, the diagnosis of CNC was made.

These two cases are interesting because both of them had multiple bone lesions. The most common bone lesions in CNC patients are osteochondromyxoma. Osteochondromyxoma is an extremely rare kind of bone tumor, presenting within the context of 1% of CNC cases[7], and is specific for the diagnosis. "Osteochondromyxoma" was used as a key word to search the PubMed database; only nine cases were identified after exclusion of repeated cases. All of them were CNC combined with osteochondromyxoma, three of which were in Japanese, Russian, and Italian, respectively[8-10]; only six cases are reported in English literature[11-13]. According to these limited reports, osteochondromyxoma usually presents as painless masses, which are noticed for their compression effects, such as proptosis and nasal obstruction.

Our first case was a young woman whose bone lesions involved the skull and maxillofacial bones; the second case was a young man with only the frontal bone involved. Both of our cases had a mixed pattern of osteosclerotic bone lesions combined with osteolytic lesions, with Patient 1 affected more markedly. Specifically, the cranial bone lesion in the first patient showed regions with high intensity on fat saturated T1WI and T2WI, which may be the "myxoid matrix". Furthermore, the enhanced MRI scan revealed marked enhancement of osteolytic regions, for the tumor may contain rich sinusoidal blood vessels. The first patient also has spinal lesions. Golden *et al*[14] found spinal osteochondromyxoma, presenting with increased T2WI signal intensity and enhancement on post-contrast studies[15], which is similar to our patient. But Patient 1 also had flat vertebral bodies, presumably due to osteoporosis. It was proposed by Golden *et al*[14] that although little was known about the appearance of osteochondromyxoma, it can be distinguished based on its unique site, symptoms, and radiographic appearance which are different from other bone lesions. Therefore, even though there was no bone biopsy in our two cases, osteochondromyxoma was highly suggested on the basis of the imaging features analysed above.

CNC has been previously called NAME (Nevi, Atrial Myxoma, Ephelides) and LAMB (Lentigines, Atrial myXoma, Blue nevi) syndrome. However, it is different from Carney triad, which presents with gastrointestinal stromal tumours, lung chondromas, and paragangliomas. The clinical features of CNC and some similar genetic syndromes associated with lentigines are summarized in Table 1[16-22]. Molecular genetic studies of CNC have shown that it is linked to the regulatory subunit type Ⅰ alpha of protein kinase A (*PRKAR1A*) gene located on 17q22–24, referred to as *CNC1*. *CNC1* encodes PRKAR, which plays an important role in the cAMP signaling pathway[2]. In addition, the *CNC2* gene located on 2p16 was also detected in CNC, but its role needs to be further studied[3]. The main causes of CNC

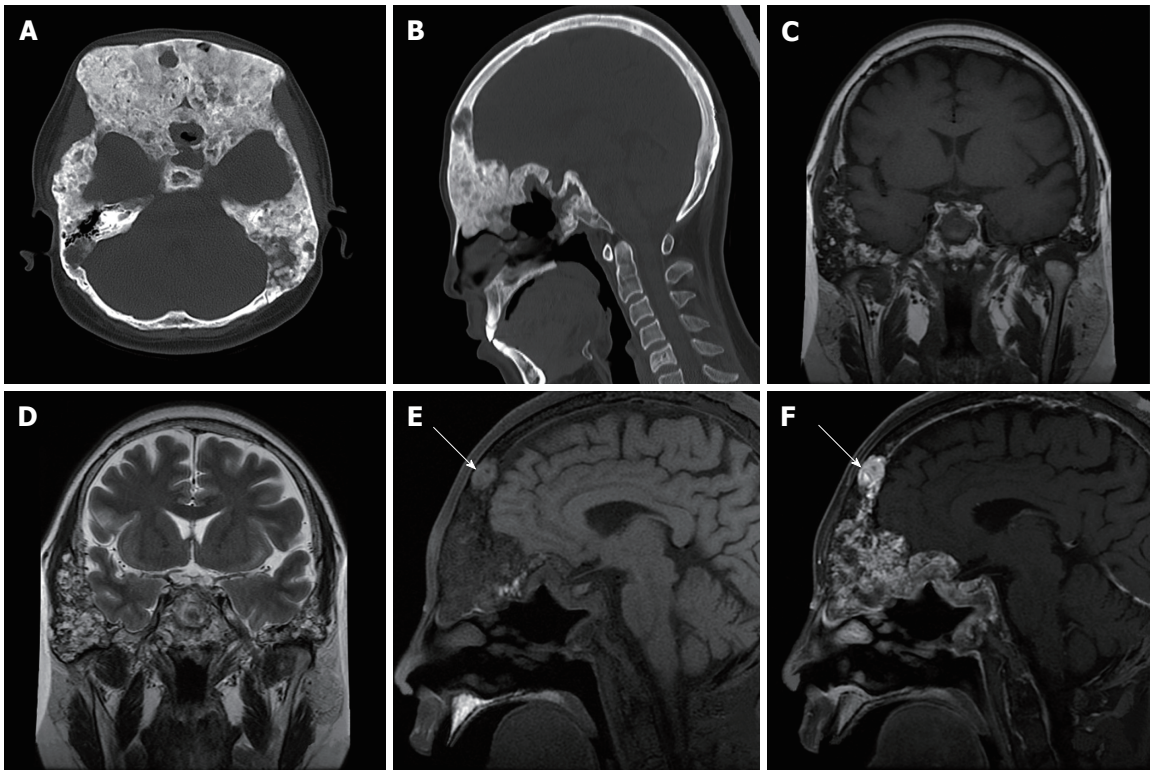

Figure 3 Computed tomography and magnetic resonance imaging images of Patient 1. A and B: Axial and sagittal skull computed tomography images showing that the skull and maxillofacial bones were remarkably enlarged with both sclerotic and lytic lesions; C-F: Coronal T1-weighted image (C) and T2-weighted image (D) showing bone lesions with heterogeneous signal intensity in the temporal and sphenoid bones; hyperintensity in the frontal bone was found on the fat saturated T1-weighted image (E, arrow), indicating mucus; the bone lesions were markedly enhanced after enhancement (F).

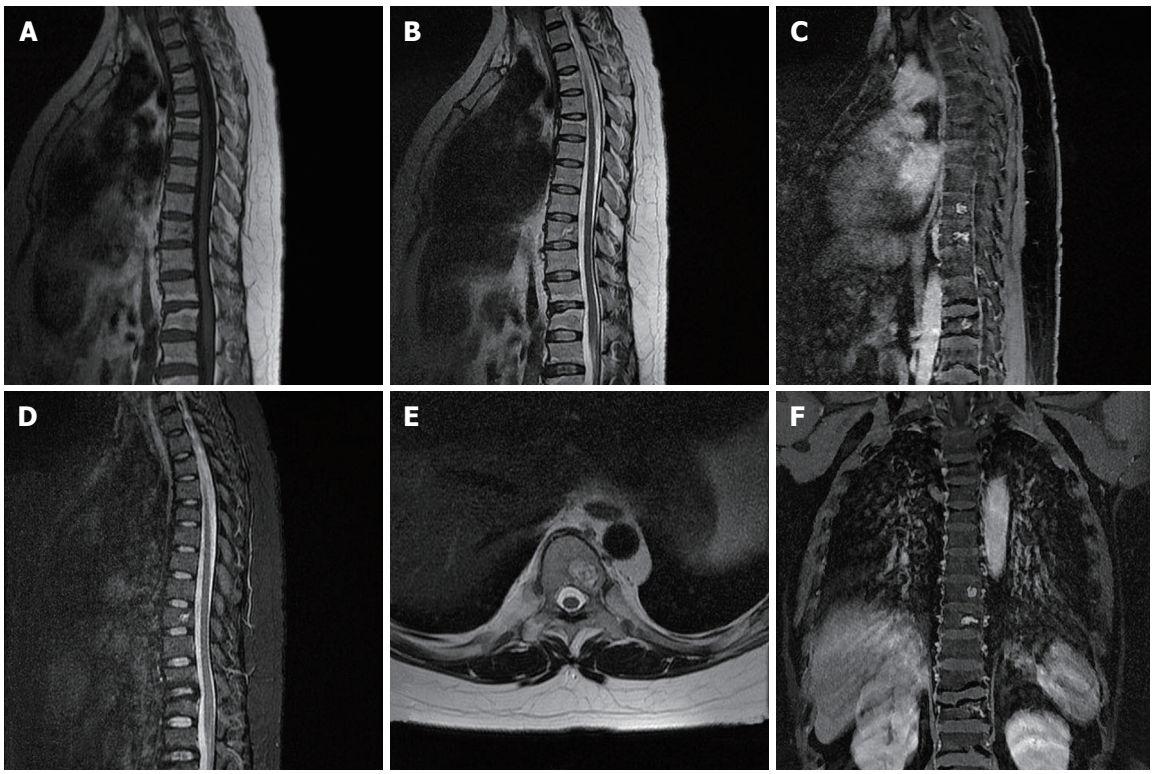

Figure 4 Spine magnetic resonance imaging of Patient 1. A-F: Patchy bone lesions that were of low signal intensity on T1WI (A), mixed signal intensity on T2WI in sagittal (B), axial (E), and coronal images (F), and high signal intensity on fat saturated T2WI (C) with enhancement on gadolinium enhanced T1WI (D).

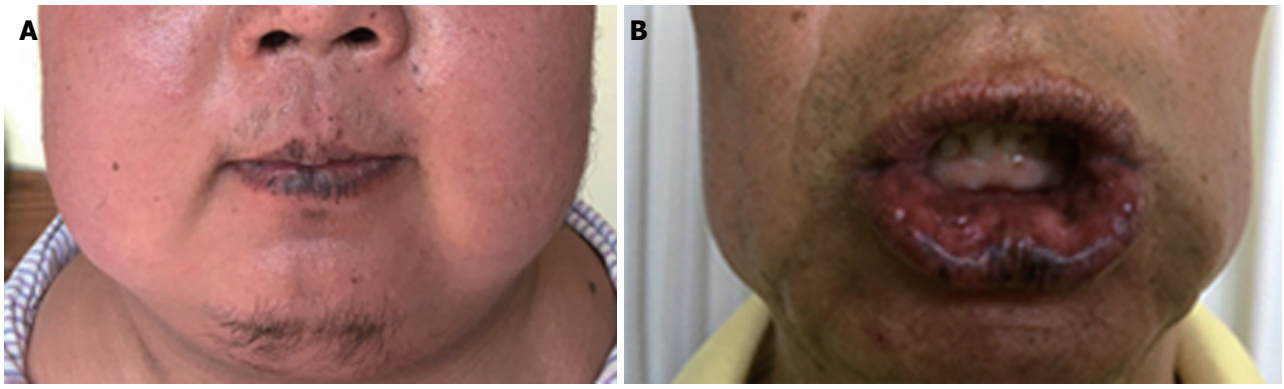

Figure 5 Pigmentation spots on the lips of patient 2 and his father. A: Patient 2 has multiple scattered pigmentation spots on the lips; B: His father has similar spots.

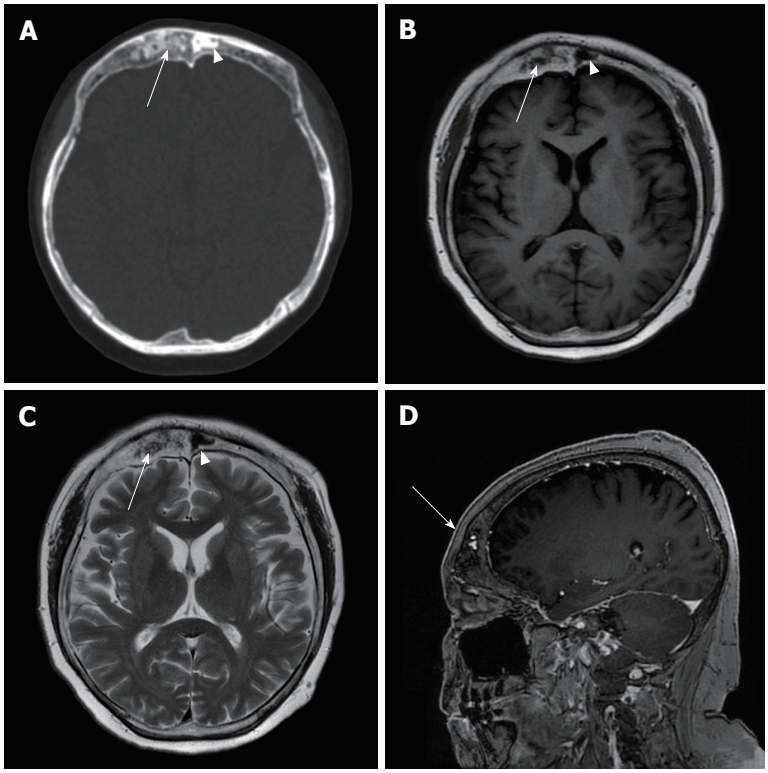

Figure 6 Computed tomography and magnetic resonance imaging images of Patient 2. A: Axial skull computed tomography image showing the thickened frontal bone with both sclerotic lesion (arrow head) and lytic lesion (arrow); B: Axial T1-weighted imaging showing that both the sclerotic lesion and the lytic lesion were hypointense; C: Axial T2-weighted imaging showing that the sclerotic lesion was hypointense and the lytic part was slightly hyperintense; D: Sagittal post-contrast T1-weighted imaging showing that the lytic lesion was remarkably enhanced on sagittal post-contrast T1-weighted imaging (arrow).

death are heart related diseases (57%), mainly cardiac myxomas and complications of operation.

CNC with osteochondromyxoma should be differentiated from McCune–Albright syndrome (MAS) clinically and radiologically. MAS is a syndrome characterized by skin pigmentation, precocious puberty, and fibrous dysplasia (FD)[23,24]. It is caused by a mutation in the guanine nucleotide-binding protein, alpha-stimulating activity polypeptide (*GNAS*) gene, which lies on chromosome 20q13 and whose mutation leads to adenylyl cyclase over-activity and abnormally increased cyclic adenosine monophosphate (cAMP) levels. Both of these diseases involve the dysregulation of the cAMP signaling pathway, which may explain their clinical and radiological similarity. However, the location of disease may help to make the differential diagnosis between FD in MAS and osteochondromyxoma in CNC from imaging findings: FD in MAS is the polyostotic FD type, which may involve almost the whole skeleton, but rarely the spine. In contrast, the spine is a common target for osteochondromyxoma. In addition, the majority of FD is surrounded by a sclerotic border that is of low signal intensity on T1WI and T2WI. However, osteochondromyxoma has no capsule and it may even

Table 1 Clinical features of Carney complex and some similar genetic syndromes

	Clinical features	Estimated incidence[7-13]
Carney complex	Lentigines	70%-80%
	Blue nevi	40%
	Cutaneous myxomas	Less than 50%
	Primary pigmented nodular adrenocortical disease	25%-45%
	Asymptomatic growth hormone hypersecretion	66%
	Large cell calcifying Sertoli cell tumors	75% of male patients
	Thyroid nodules	75%
	Cardiac myxomas	30%-72%
	Psammomatous melanotic schwannomas	18%
	Benign breast tumor	14% of female patients
	Osteochondromyxomas	< 1%
Peutz-Jeghers syndrome	Mucocutaneous pigmentation	More than 95%
	Hamartomatous polyps	Most of the patients
McCune-Albright syndrome	Peripheral precocious puberty	50% in females at 4 yr in de Sanctis C's research
	Irregular café-au-lait skin pigmentation	Almost all the patients in de Sanctis C's research
	Fibrous dysplasia of bone	50% at 8 yr of age in de Sanctis C's research

show an invasive character, thus its boundary is not very clear. Peutz–Jeghers syndrome also has hyperpigmented macules on the lips and oral mucosa, but it at the same time exhibits benign hamartomatous polyps in the gastrointestinal tract which CNC does not have. Multiple endocrine neoplasia syndromes are inherited as autosomal dominant disorders encompassing several distinct syndromes featuring tumors of endocrine glands, each with its own characteristic pattern. CNC also has a variety of endocrine tumors such as thyroid carcinoma and PPNAD, but there are other symptoms at the same time, for example, spotty skin pigmentation and cardiac myxoma.

If osteochondromyxoma can be removed completely, it is considered to be curable. Although there is a possibility of recurrence at the resection site, no distant metastasis has been reported so far. MRI, the highest resolution imaging modality for soft tissues, can identify the osteolytic lesions and indicate the pathological components through detailed analysis of the signal characteristics in various sequences. Therefore, early identification and preoperative assessment by MRI may help patients to achieve a better prognosis.

Admittedly, there is an obvious limitation of these two cases that there was no bone biopsy since both of them concerned about the invasiveness of the procedure. Nevertheless, the diagnosis of CNC is solid based on the diagnostic criteria.

In conclusion, two cases of CNC with bone lesions have been reported. Detailed analysis of the imaging manifestations of bone lesions may help in the recognition of this rare and complicated syndrome.

ARTICLE HIGHLIGHTS

Case characteristics

Carney complex (CNC) is a very rare disease with diverse clinical characteristics. Osteochondromyxoma is an extremely rare kind of bone tumor, presenting within the context of 1% of CNC cases, and is specific for the diagnosis.

Clinical diagnosis

CNC.

Differential diagnosis

Peutz-Jeghers syndrome and McCune-Albright syndrome.

Laboratory diagnosis

Hypercortisolism.

Imaging diagnosis

Osteochondromyxoma.

Pathological diagnosis

Primary pigmented nodular adrenocortical disease.

Treatment

Surgery.

Related reports

Nine cases were CNC combined with osteochondromyxoma, three of which were in Japanese, Russian and Italian, and only 6 cases are reported in English literature.

Term explanation

CNC.

Experiences and lessons

This case will contribute to improvements in our understanding of the clinical and imaging features, especially osteochondromyxoma, of CNC. In clinical practice, osteochondromyxoma should be taken into account in patients with CNC complicated with skeletal lesions. Early diagnosis will help to improve the prognosis of patients.

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CASE REPORT

Ileal bronchogenic cyst: A case report and review of literature

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Author contributions: Chen HY and Fu LY collected the patient's clinical data; Chen HY and Fu LY wrote the paper; Wang ZJ provided guidance.

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Abstract

We herein report a rare case of ileal bronchogenic cyst that was found in a 39-year-old Chinese man. He had no symptoms and the physical examination was normal. Tumor markers were within the normal range. Abdominopelvic enhanced computed tomography showed a mass in the lower abdominal cavity and the tumor had a complete capsule. Diagnostic laparoscopy was then performed, which showed that a spheroid mass with a complete capsule was located at the antimesenteric border of the distal ileum 20 cm from the ileocecal valve, measuring 6.0 cm × 6.0 cm × 5.0 cm. Considering that the malignancy of the tumor cannot be ruled out, and there is a risk of rupture during laparoscopic surgery, the patient was converted to an open surgery. Partial resection of the ileum with the tumor was performed, followed by a side-to-side anastomosis. The tumor was gray-red in color, filled with grayish yellow mucus and had no septum. The postoperative pathology revealed that the cystic wall was lined by pseudostratified ciliated columnar epithelium without cellular atypia. The wall consisted of bronchial mucous glands and smooth muscle fibers, and no abnormalities were found in adjacent ileum tissues. Thus, a diagnosis of bronchogenic cyst of the ileum was made.

Key words: Laparoscopy; Ileal neoplasms; Epithelium; Bronchogenic cyst; Abdominal cavity; Case report

Core tip: Bronchogenic cyst is related to abnormal embryonic development. The most common site of bronchogenic cyst is the mediastinum. Subdiaphragmatic bronchogenic cysts are extremely rare and bronchogenic cyst of the ileum has not been reported in the literature. This case may help us better understand where bronchogenic cysts may occur. Bronchogenic cysts should be considered in the differential diagnosis of ileal masses.

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INTRODUCTION

Bronchogenic cyst is a rare disease, which is related to the abnormal embryonic development. It has been reported that bronchogenic cysts may occur in the mediastinum[1], lung[2], heart[3], stomach[4] and retroperitoneum[5]. The diagnosis of bronchial cyst depends on pathological examination: The cystic wall is lined by pseudostratified ciliated columnar epithelium and consists of bronchial mucous glands and smooth muscle fibers. Here we report a rare case of ileal bronchogenic cyst and to the best of our knowledge, such case has not been previously reported in the literature.

CASE REPORT

A 39-year-old Chinese male was admitted for "finding an abdominal mass for 1 wk". The patient once accepted computed tomography (CT) examination because of low back pain and was diagnosed as having degenerative changes of the lumbar spine. There was no history of nausea, vomiting, hematemesis, melena, diarrhea or change of habit of discharge. Physical examination showed no obvious abnormality. Routine blood parameters and tumor markers were within the normal range. Abdominopelvic enhanced CT showed a mass of cystic density in the lower abdominal cavity with a complete capsule, which measured 5.2 cm × 4.1 cm. In the arterial phase, the CT value of the mass was 37 HU. The mass may arise from the ileum (Figure 1A). Based on these results, the preoperative diagnosis was tumor of the ileum. During a diagnostic laparoscopy, we found a spheroid mass with a complete capsule located at the antimesenteric border of the distal ileum 20 cm from the ileocecal valve, which measured 6.0 cm × 6.0 cm × 5.0 cm. Considering that the malignancy of the tumor cannot be ruled out, and there is a risk of rupture during laparoscopic surgery, the patient was converted to an open surgery. Partial resection of the ileum with the tumor was performed. The resection margin was 3 cm away from the tumor edge. Then, a side-to-side anastomosis was performed. The patient recovered successfully after the surgery. The operative time was 135 min, and the volume of blood loss was 50 mL. The unilocular cyst was gray-red in color and filled with grayish yellow mucus. The capsule was smooth and about 0.4 cm in thickness. Microscopic examination of the tumor and partial ileum together with hematoxylin and eosin staining was conducted. The postoperative pathology revealed that the cystic wall was lined by pseudostratified ciliated columnar epithelium without cellular atypia. The wall consisted of bronchial mucous glands and smooth muscle fibers, and no abnormalities were found in adjacent ileum tissues (Figure 1B and 1C). Thus, a diagnosis of bronchogenic cyst of the ileum was made based on the histological appearance. The patient was discharged 8 d after the operation.

DISCUSSION

The pathogenesis of bronchogenic cysts remains unclear. A reasonable speculation is that the disease is related to abnormal embryonic development[6]. Bronchogenic cysts are derived from the primitive foregut due to the lung bud development malformation during the third to seventh weeks of embryogenesis. The malformation occurs when the lung bud fails to attach to the trachea or esophagus and then migrates to the thoracic or abdominal cavity. The migration usually ends up in the posterior mediastinum. As the mucus in the ectopic lung bud fails to be discharged, the lung bud gets increasingly larger and eventually becomes a bronchogenic cyst. Bronchogenic cysts located in the mediastinum, lung and heart have been reported a lot, while subdiaphragmatic bronchogenic cysts such as gastric[4] or retroperitoneal bronchogenic cysts[5] are extremely rare. Among them, bronchogenic cysts in the abdominal cavity are mostly located in the left to the midline adjacent to the pancreas tail, spleen, and left adrenal gland[7]. Only two cases of bronchogenic cyst of the ileal mesentery have been reported[8,9]. However, ileal bronchogenic cysts have not been reported previously.

Most of the bronchogenic cysts were asymptomatic and found during thoracic or abdominal surgery[9]. The patients with symptomatic bronchogenic cysts often complain of abdominal pain because of secondary infection or perforation. Generally, bronchogenic cysts appear as a well circumscribed cystic lesion accompanied with or without calcification and no significant contrast uptake on CT scan[6,10,11]. On magnetic resonance images, those cysts were found to have low signal on T1WI but high signal on T2WI[12]. As for the preoperative diagnosis, endoscopic ultrasound together with fine-needle aspiration may be the most effective way[13].

Differential diagnosis of abdominal bronchogenic cysts includes gastrointestinal stromal tumor[14], teratoma[15], Meckel's diverticulum[16], enteric duplication

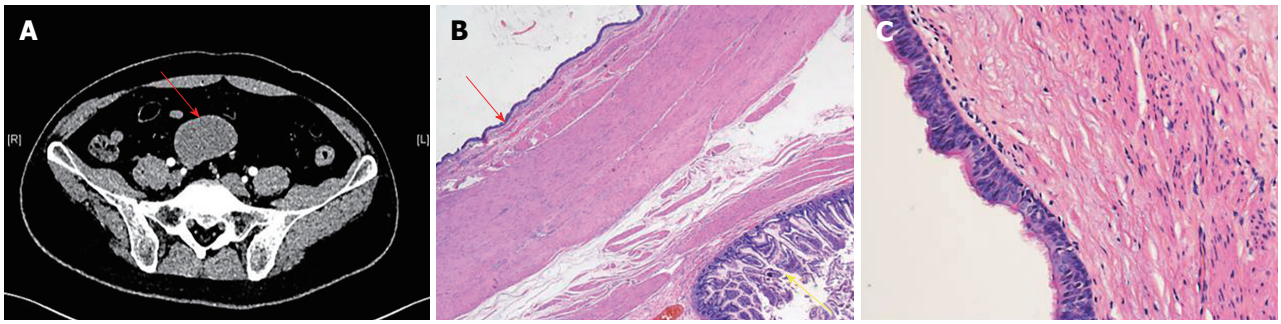

Figure 1 Imaging and pathological results. A: The abdominopelvic computed tomography scan reveals a cystic mass (red arrow); B: The microscopic findings showed the inner wall of the bronchogenic cyst (red arrow) and the ileal mucosa (yellow arrow) (HE staining; original magnification, × 20); C: Pseudostratified ciliated columnar epithelium covering the inner wall of the cystic wall (HE staining; original magnification, × 200).

cyst[17], lymphangioma[18] and echinococcosis[19]. In this case, the pseudostratified ciliated columnar epithelium of the cystic wall had no cellular atypia and there was no sign of abnormality in the neighboring ileum tissue. Therefore, there is no possibility of malignancy.

Asymptomatic bronchogenic cysts in small size are hard to diagnose. However, as bronchogenic cysts enlarge, there is a risk of secondary infection, perforation or even malignant change[5,20]. They may conceal a tumor and the malignant progression can occur both in adults and children[20]. Thus, surgical resection is the most suitable choice recommended to treat bronchogenic cysts when identified[21].

ARTICLE HIGHLIGHTS

Case characteristics

A 39-year-old man presented with an asymptomatic abdominal mass found by computed tomography (CT).

Clinical diagnosis

The diagnosis of an ileal bronchogenic cyst was made following radiological and pathological examinations.

Differential diagnosis

Differential diagnosis should include other abdominal space-occupying lesions, such as Meckel's diverticulum, gastrointestinal stromal tumor, teratoma, lymphangioma, enteric duplication cyst and echinococcosis.

Laboratory diagnosis

Serum total cholesterol and triglyceride were slightly elevated. Routine blood parameters and coagulation function indexes were in the normal range and the fecal occult blood was negative.

Imaging diagnosis

The abdominopelvic enhanced CT scan showed a cystic mass measuring 5.2 cm × 4.1 cm that was located in the lower abdominal cavity. It may originate from the ileum. The imaging diagnosis was an ileal tumor.

Pathological diagnosis

The postoperative pathology revealed that the mass was an ileal bronchogenic cyst.

Treatment

The patient received partial ileal resection and anastomosis. No drugs or chemoradiotherapy were administered after the surgery as the pathological examination confirmed that the lesion was benign.

Related reports

Bronchogenic cysts are found mostly in the mediastinum, lung and heart, and occasionally in the stomach and retroperitoneal organs. Only two cases of bronchogenic cyst of the ileal mesentery have been reported. Ileal bronchogenic cyst has never been reported before.

Term explanation

Ileal bronchogenic cyst is congenital malformation which can occur at the antimesenteric border of the ileum.

Experiences and lessons

Surgical resection should be the most suitable choice to treat bronchogenic cysts. Clinicians should take bronchogenic cysts into consideration when the radiological examination shows a cystic lesion.

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CASE REPORT

Application of ultrasound in aggressive angiomyxoma: Eight case reports and review of literature

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Abstract

Aggressive angiomyxoma (AAM) is a rare tumour that often occurs in soft tissues of the female genital tract. Eight cases of AAM are reported in this article, and the clinical features and ultrasound and magnetic resonance imaging (MRI) results of the eight cases are reviewed and summarized. The main complaints of all the patients were palpable and painless masses in the vulva or scrotum. The lesions were mainly located in the vulva, pelvis, and perineal region, with a large scope of involvement. The sonographic features of AAM were characteristic. On sonography, all of the masses were of irregular shape and showed hypoechogenicity, with a heterogeneous inner echotexture. Intratumoural and peritumoural blood flows were detected by colour Doppler imaging. On real-time ultrasonic imaging, prominent deformation of the lesions was observed by compressing the masses with the probe. Some special imaging features were also revealed, including a laminated or swirled appearance of inner echogenicity, and a finger-like or tongue-like growth pattern. On MRI imaging, the lesions showed intermediate-intensity signals and intermediate to high-intensity signals on TI-weighted and T2-weighted sequences. A rapid and uneven enhancement pattern was demonstrated. After the comparison of sonographic features with MRI

and pathological findings, we found the relevance of the ultrasonographic characteristics with MRI and histological features of AAM. Ultrasound can be a valuable imaging method for the preoperative diagnosis, evaluation of scope, and follow-up of AAM.

Key words: Aggressive angiomyxoma; Ultrasound; Soft tissue neoplasm; Case report; Gynaecological neoplasm

Core tip: Eight cases of aggressive angiomyxoma (AAM) were collected in this manuscript. The lesions of AAM appear as irregular hypoechoic masses with internal echogenicity and well-defined borders on ultrasonic imaging. Some special imaging features of AAM, such as laminated or swirled sign and finger-like growth pattern, can also be seen on ultrasound examination. The abundant intratumoral blood flows on colour Doppler ultrasound is a distinctive feature of AAM, which can be a crucial clue for the diagnosis. These ultrasonic features of AAM correlate with the findings of magnetic resonance imaging and histology. Ultrasound can be utilized in the preoperative diagnosis and follow-up of AAM.

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INTRODUCTION

Aggressive angiomyxoma (AAM), a rare neoplastic disease, was first reported by Steeper *et al*[1] in 1983. AAM usually occurs in females aged 15-60 years, and affects the female genital tract and pelvic soft tissues[2]. Cases of AAM located in the male spermatic cord and scrotum have also been reported[3]. Patients often visit hospital because of a palpable mass in the vulva or incidental imaging findings without other discomforts. Imaging options for AAM include ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), and some typical imaging features of AAM can be observed with different modalities[4,5]. Surgery is the main method for the treatment of AAM. AAM is a benign disease originating from mesenchymal tissues, with a tendency for local aggression. Therefore, a complete surgical resection of the lesion of AAM is required. The recurrence rate after surgical excision of AAM is high, and regular follow-ups through imaging methods are essential[6]. In this article, eight cases of AAM are reported. These patients were referred to Peking Union Medical College Hospital (PUMCH) from 2002 to 2016, underwent surgery in the Department of Gynecology and the Department of Urological Surgery. We review the clinical features and ultrasound and MRI results of the eight cases, and summarize the ultrasonographic characteristics of AAM. The value of ultrasound in the diagnosis of AAM is discussed based on the comparison of sonographic features with MRI and pathological findings.

CASE REPORT

Case 1

A 40-year-old woman was referred to PUMCH with a complaint of discomfort and swelling of the left buttock for 4 years, and a palpable mass in the left vulva for 1 year. Clinical examination found a massive lesion ranging from the deep pelvis to the left vulva. An irregular hypoechoic mass with well-defined margins was visualized by US. The mass was located on the left side of the perineum and extended anteriorly to the anus. The internal echogenicity was demonstrated as heterogeneous. On colour Doppler ultrasound, a blood pattern of abundant internal and external vessels was visualized. The patient received surgery for a complete removal of the lesion, which was found to be very large and extend to the left inguinal region. The lesion was finally diagnosed as an AAM mass by postoperative pathology and immunohistochemical examination.

Case 2

A 38-year-old woman was referred with a 6-year history of a gradually increasing mass on the vulva. She had undergone surgery for a vulvar mass resection 8 years previously, and the mass was identified as an AAM after pathological examination. A huge vulvar mass extending to the vagina and cervix was detected by clinical examination. US revealed a hypoechoic lesion with distinct borders, ranging from the right side of the vulva to posterior to the uterus. The size was 7.2 cm × 5.6 cm × 14.6 cm, and internal blood vessels were demonstrated on colour Doppler ultrasound. During surgery, a large mass with a diameter of 14 cm was identified and removed from the soft tissues, and was verified as an AAM by postoperative pathology.

Case 3

A 40-year-old woman complained of an egg-like mass on the left labia majora, which had obvious enlargement since it was found 2 years ago. Clinical examination found a vulvar lesion extending to the pelvis. On US, an irregular lesion anterior to the bladder, which extended to the left perineum and was approximately 17.1 cm × 10.6 cm × 8.9 cm in size, was identified. The internal texture was heterogenous, and the swirl sign was observed. Rich blood vessels were also detected. The mass presented with iso-intensity on T1 sequence and iso-hyper intensity on T2 sequence. Heterogeneous enhancement of the T1 sequence was seen after injection of a contrast agent. A complete resection of

the mass was implemented successfully. During the following microscopic examination, spindle-like cells with abnormal nuclear atypia and mitoses were found in the myxoid background. The mass was finally diagnosed as an AAM after immunohistochemical examination.

Case 4

A 35-year-old woman presented with a 10-year history of swelling of the left labia majora without any discomfort. The patient was referred to a local hospital one year ago, where a massive tumor was found by ultrasound. Clinical examination showed a soft vulvar neoplasm extending to the vagina. The US examination in our hospital demonstrated a hypoechoic mass on the left side of the uterus, measuring 16.2 cm × 6.9 cm × 7.4 cm and ending at the proximal left humerus. Internal and external blood vessels were clearly seen on colour Doppler ultrasound. MRI showed a mass with iso-intensity on T1 sequence, iso-hyper intensity on T2 sequence, and heterogeneous enhancement after injection of a contrast agent. The mass was diagnosed as an AAM by histological examination after biopsy. The patient underwent a regular gonadotropin releasing hormone agonist (GnRH-α) treatment, and received surgery after shrinking of the mass. The diagnosis of AAM was confirmed by postoperative pathology.

Case 5

A 64-year-old man was referred with a complaint of a gradual enlargement and swelling of the right scrotum for 7 mo. A large and painless tumor in the right scrotum was verified by clinical examination. A well-defined, hypoechoic, and heterogeneous mass from the top of the scrotum to the right spermatoid cord was visualized by US, with a length of approximately 10 cm. On MRI, the mass showed hyper-intensity on T1 sequence, iso-hyper intensity on T2 sequence, and heterogeneous enhancement with multiple irregular enhancement areas. Surgical treatment was recommended for the patient, and the mass was identified as an AAM by histological and immunohistochemical examinations.

Case 6

A 38-year-old woman complained of a recurrent mass of on the left vulva after resection of a left vulvar AAM 3 years ago. She planned to receive a surgery for further identification of the new mass. Clinical examination found a soft mass from the deep pelvis to the left vulva. A well-defined hypoechoic mass from the posterior wall of the vagina was observed by US examination. Uneven internal echotexture and rich blood signals were evident on US. MRI showed a mass with iso-intensity on T1 sequence and iso-hyper intensity on T2 sequence. The mass was diagnosed as a recurrent AAM tumour.

Case 7

A 45-year-old woman presented with a pelvic mass of 8 cm found by US on a regular scan, without any complaint. Clinical examination found a large and irregular tumor posterior to the uterus. US in our hospital revealed a 12.3 cm × 8.8 cm × 6.3 cm hypoechoic mass in the Douglas pouch, with a relatively distinct boundary with the rectum and uterus, extending to the left vulva. Hyperechoic bands were observed inside the mass, and blood signals could also be detected. The mass was completely resected and diagnosed as an AAM lesion by pathology.

Case 8

A 34-year-old woman presented with a palpable mass in the left vulva without any discomfort. Clinical examination found a soft mass that extended from the left vulva to the pelvis. US showed an 11 cm-long hypoechoic mass with heterogenous internal echotexture and abundant blood signals in the left posterior region of the uterus. During surgery, a grey soft mass with a length of 10 cm was seen, extending to the left back pelvis. The lesion was completely removed for histological examination, and was then identified as an AAM.

Review of the eight cases

Clinical information for the eight AAM cases is listed in Table 1. The study included 7 females and 1 male, aged from 35 to 64 (median 39) years. Three cases were recurrent AAM, and the patients were hospitalized for a second surgery. All of the patients were examined by ultrasound, and four of eight patients had an MRI examination before surgery. The main complaints of all the patients were palpable and painless masses in the vulva or scrotum. Other symptoms, such as abdominal discomfort and dysmenorrhea, were also mentioned.

According to the overall evaluation of the surgical specimens, the lesions of female patients were mainly located in the vulva, pelvis, and perineal region with a large scope of involvement. In the male patient, the mass was located in the spermatic cord and scrotum. The maximal diameters of the lesions ranged from 7 to 21 cm.

The diagnosis of AAM was affirmed on the basis of the pathologic features of the surgical specimens. Scattered spindle-formed cells were found in the myxoid and collagen background. These cells were characterized by abnormal nuclear atypia and mitoses. A variety of internal vessels were also seen in the samples after haematoxylin-eosin staining. Immunohistochemical analysis revealed positive staining for CD34, smooth muscle actin, desmin, estrogen receptors (ER), and progesterone receptors (PR) in these samples, which also supported the diagnosis of AAM (Figure 1).

Table 2 shows the sonographic features of the lesions. All of the masses were of irregular shape. Seven (87.5%) of the masses had relatively smooth well-defined margins with surrounding tissues, and a hyperechoic rim could be seen at the border of the lesion. Only one lesion from a female patient was poorly defined. All of the eight cases appeared as a hypoechoic

Table 1 Clinical information of the patients

Case No.	Gender	Age	Newly diagnosed/recurrent	Location	Maximal diameter (cm)
1	F	40	Newly diagnosed	Left side of the perineum - anterior to the anus	21
2	F	38	Newly diagnosed	Right side of the vulva - posterior to the uterus	16
3	F	40	Recurrent	Left to the perineum - anterior to the bladder	17
4	F	35	Recurrent	Proximal end of the left humerus - left side of the uterus	18
5	M	64	Newly diagnosed	Right spermatic cord - the top of the scrotum	10
6	F	38	Recurrent	Posterior wall of the vagina	7
7	F	45	Newly diagnosed	Posterior to the uterus	12
8	F	34	Newly diagnosed	Left posterior to the uterus	11

F: Female; M: Male.

Table 2 Sonographic features of the eight cases

Case No.	Overall appearance	Shape	Margin	Internal echogenicity	Blood flow in CDFI
1	Hypoechoic lesion	Irregular	Well-defined	Heterogeneous, isoechoic internal components	Positive
2	Hypoechoic lesion	Irregular	Well-defined	Heterogeneous, isoechoic internal components	Positive
3	Hypoechoic lesion	Irregular	Well-defined	Heterogeneous, isoechoic internal components	Positive
4	Hypoechoic lesion	Irregular	Poorly-defined	Heterogeneous, isoechoic internal components	Positive
5	Hypoechoic lesion	Irregular	Well-defined	Heterogeneous, isoechoic internal components	Positive
6	Hypoechoic lesion	Irregular	Well-defined	Heterogeneous, isoechoic internal components	Positive
7	Hypoechoic lesion	Irregular	Well-defined	Heterogeneous, isoechoic internal components	Positive
8	Hypoechoic lesion	Irregular	Well-defined	Heterogeneous, isoechoic internal components	Positive

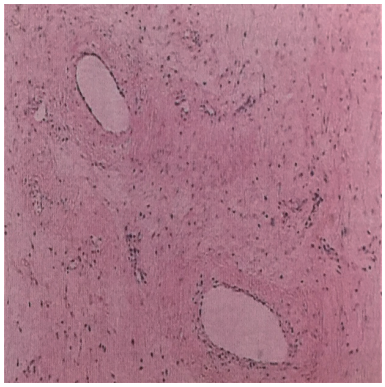

Figure 1 Pathological results after H-E staining of one case.

mass with heterogeneous inner echogenicity (Figure 2). Intratumoural and peritumoural blood flows were detected in all of the eight cases by colour Doppler ultrasound (Figure 3). On real-time ultrasonic imaging, prominent deformation of the lesions could be observed after putting pressure on the lesions, indicating the soft texture of AAMs.

Apart from the imaging results mentioned above, some special sonographic features were detected by the radiologists. The inner isoechoic to hyperechoic bands possessed a laminated or swirled appearance, stretching the lesions (Figure 4). On the edge of the lesions, a finger-like or tongue-like growth pattern was observed, as the tumors tended to infiltrate into the gaps of surrounding soft tissues (Figure 5). Small anechoic areas in the lesions were also be mentioned by two of the reports, indicating the internal cystic degeneration.

MRI results showed that the lesions possessed intermediate signal intensity and intermediate to high signal intensity on T1-weighted and T2-weighted sequences (Figure 6). Inhomogeneous MR signal intensity was demonstrated in these cases. The swirl sign was visualized on T2WI as swirled areas of low signal in a high-signal background. For the patients who had contrast-enhanced MRI examination, a rapid and heterogeneous enhancement pattern was observed (Table 3).

DISCUSSION

AAM is a kind of benign neoplastic disease that originates from mesenchymal tissues, with extensive local invasiveness and a high recurrence rate[6]. The disease presents predominantly in females in the reproductive age[7]. Most cases were reported to appear in the pelvic and perineal regions of females[4,8,9]. There were also cases occurring in the scrotum, spermatic cord, and pelvic organs of males, mainly elderly ones[10,11]. In this article, we also report a man in his 60s with AAM in the scrotum. Cases of children diagnosed with AAM have also been reported[3]. The lesions of AAMs could also occur in rare regions, including the head and neck[12,13].

Apart from gradually enlarging masses in some patients, most patients with AAM declare no evident symptoms, and some may also complain of abdominal distention, perineovulvar swelling, or urinary irritation[14]. Imaging plays an essential part in the preoperative diagnosis and management of AAMs, including US, CT, and MRI[15]. The role of the imaging modalities would be discussed in this article. The final diagnosis of AAM depends on the postoperative pathology. The surgical

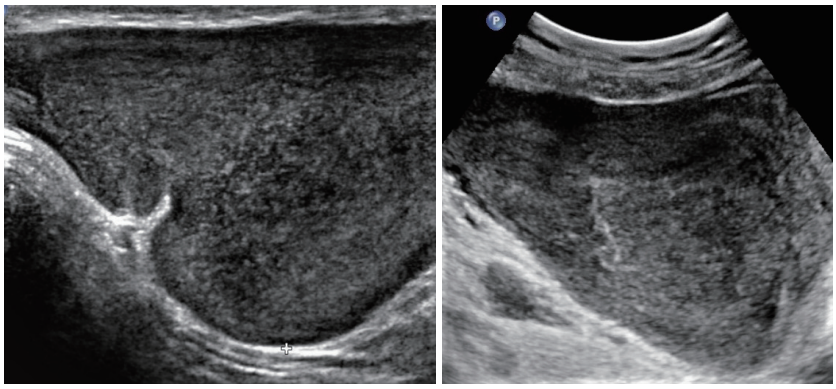

Figure 2 Gray-scale ultrasonic images showing irregular hypoechoic masses with internal echogenicity and well-defined margins.

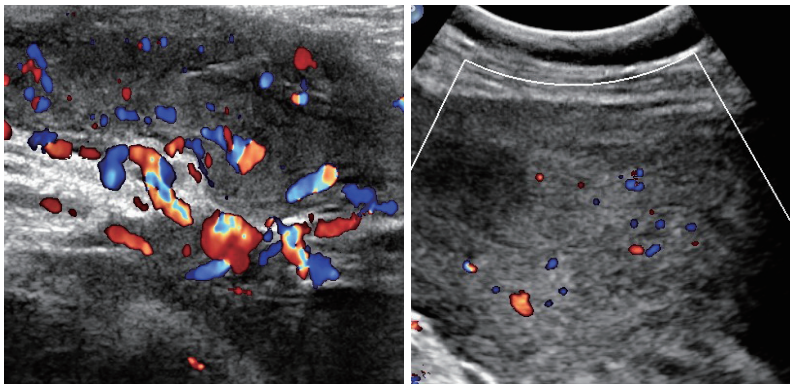

Figure 3 Internal blood flows in the mass detected by colour Doppler ultrasound.

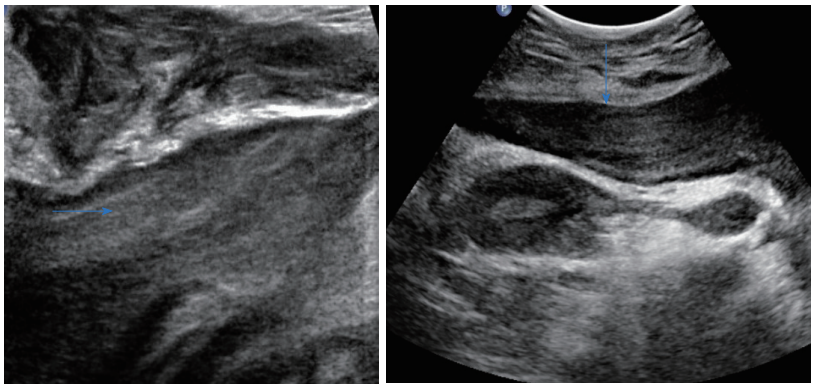

Figure 4 Laminated or swirled appearance of inner echogenicity (blue arrows).

specimen of AAM presents as a large, gray mass with gelatinous appearance and marked vascularization. Under a microscope, the lesions were found to be constituted by spindle cells scattered in a myxoid and collagen background with abundant vessels. The positive immunohistochemistry results of vimentin, desmin, SMA, CD34, ER, and PR are suggestive of the diagnosis of AAM[16-18].

Due to its aggressiveness, radical surgery is recommended for AAM, and complete excision is crucial[14,19]. GnRH-α can also be applied as an assistant drug therapy[20,21]. The postoperative recurrence rate of AAM has been estimated to be around 40%[1,22,23]. Remote metastasis of AAM was also reported[24]. As a consequence, regular follow-ups should be performed on all patients because of the high recurrence rate[14].

Ultrasound, CT, and MRI are the common imaging diagnostic methods for AAM, and MRI is the most widely used technique to identify the characteristic manifestations of AAM, including low or intermediate signal intensity on T1-weighted images and a high signal intensity on T2-weighted images, as well as the swirled configuration, which is described as swirling and laminated low-signal bands in a high-intensity

Table 3 Magnetic resonance imaging features of four cases

Case No.	TI-weighted	T2-weighted	Contrast-enhanced pattern
2	Isointensity	Iso-hyperintensity, heterogeneous	Heterogeneous enhancement
3	Isointensity	Iso-hyperintensity, heterogeneous	*
4	Hyperintensity	Iso-hyperintensity, heterogeneous	Heterogeneous enhancement with multiple irregular enhancement areas
5	Isointensity	Iso-hyperintensity, heterogeneous	Heterogeneous enhancement

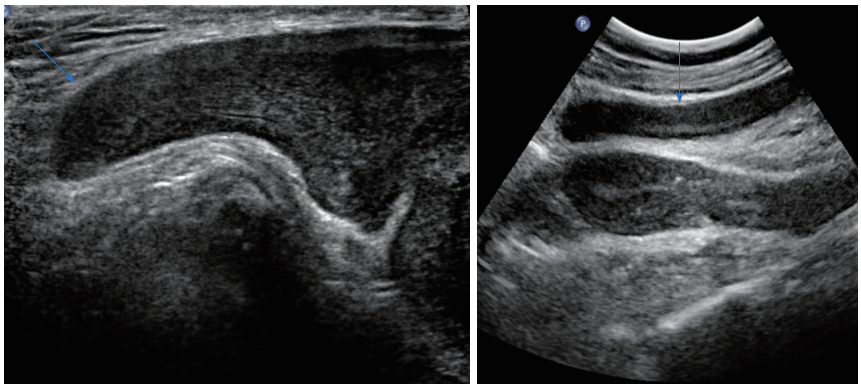

Figure 5 The finger-like growth pattern in the border of the mass could be demonstrated in both cases (blue arrows).

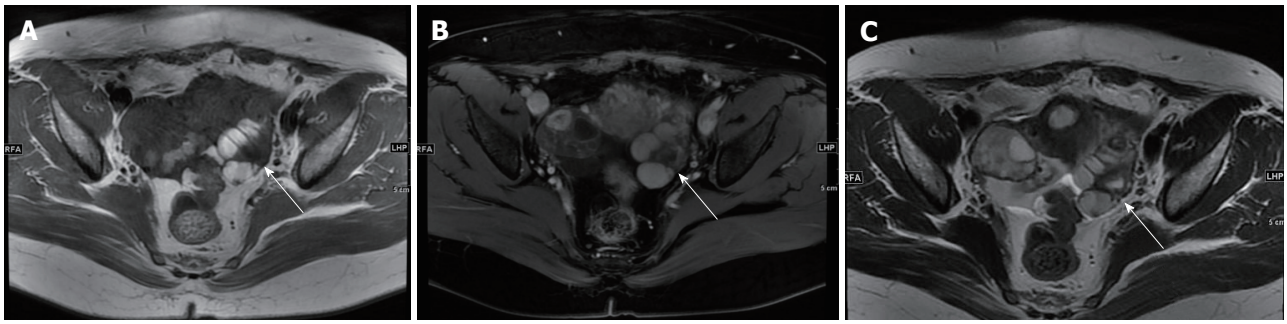

Figure 6 Magnetic resonance imaging images of case 4. A: Intermediate-intensity signals on TI-weighted sequence; B: Intermediate to high-intensity signals on T2-weighted sequence; C: Rapid and uneven enhancement pattern was shown after the injection of contrast agent.

background of water[25-27]. The behavior of AAM on the dynamic contrast enhanced (DCE) sequence can also be distinguished. A layered or swirled enhancement pattern of AAM on DCE sequence was presented by several studies[5,28]. It was also reported that AAMs demonstrated high signal intensity on diffusion-weighted imaging with high mean values in the apparent diffusion coefficient maps[5,15,29].

Ultrasound is the first choice for screening pelvic lesions before performing further imaging techniques. Based on the ultrasound results of the eight cases, characteristics of AAMs on ultrasound imaging were determined. AAM lesions were irregular and hypoechoic masses with a large scope of involvement and relatively well-defined margins. The lesions had intermediate to high echogenicity with a layered or swirled arrangement. Finger-like or tongue-like growth patterns were visible in some cases, as a result of infiltrative growth into the gaps of surrounding soft tissues. Prominent deformity of the lesions was shown on real-time ultrasonic imaging after the masses were compressed by probes, which verified the soft texture of AAMs. Moreover, abundant blood flow was detected inside and around the masses on colour Doppler ultrasound.

The ultrasonic features of AAMs observed in our study corresponded well with the recent literature. An AAM case report in 2012 described the lesion as a large hypoechoic to isoechoic mass on transvaginal ultrasound examination, with internal septa of high echogenicity, and rich blood signals scattering throughout the tumor on colour Doppler sonography[30]. Another case in 2013 also presented as a hypoechoic and heterogeneous mass with well-defined margins, abundant internal vascularity, and peripheral blood vessels[31]. The swirled sign observed on both ultrasound and MRI has also been mentioned by a recent study[26]. While in the case reports in 1990s and early 2000s, AAMs were described as hypoechoic or cystic masses without additional imaging information, which may be due to the limited resolution of ultrasound modalities in earlier years[32,33].

Comparing the findings of ultrasound, MRI, and pathologic examinations of AAMs in this study, a con-

sensus on imaging and histologic features can be reached. The overall hypoechoic patterns were due to the myxoid background and sparse tumor cells. The fibrovascular stroma presented as isoechoic to hyperechoic components or septa with swirled or laminated appearance on US because of the woven fibers stretching in the myxoid background. The finger-like growth pattern on the ultrasonic imaging indicated aggressive growth into surrounding tissues. Internal cystic degeneration could be seen as round anechoic areas. The soft texture of the lesions was delineated as deformity on real-time ultrasound after probe compression, due to the high water-content of AAMs. The affluent blood flow patterns shown on colour Doppler ultrasound illustrated the masses' collateral vessels.

AAMs can be easily confused with other common asymptomatic masses in the perineal and pelvic regions, including vulvar abscess, Bartholin's duct cyst, Gartner's duct cyst, vaginal prolapse, levator hernia[34], and other types of rare soft tissue masses in the female genital tract, such as angiomyofibroblastoma (AMFB), myxoma, myxoid sarcoma, infiltrating angiolipoma, and myxoid liposarcoma[35]. To some extent, ultrasound can be helpful in differentiating AAM from other soft tissue tumours. Ota *et al*[30] also suggested that performing preoperative ultrasound can be helpful in excluding some other possible types of perineal masses.

For instance, Batholin's gland cyst appears as a pure or complex cyst with isoechoic contents on US. In addition, no blood flow within the mass can be visualized on colour Doppler ultrasound, which is a major evidence for differentiation. Another rare mesenchymal tumor, AMFB, is difficult to be differentiated from AAM, of which the clinical and pathological characteristics overlapped with AAM. The prognosis of AMFB is better than that of AAM, with a lower recurrence rate. Therefore, it is important to clearly identify the pathological type to specify next medical plans[36]. One differential point of clinical features is that AMFB usually has smaller volume of less than 5 cm. Moreover, AMFB tends to be less invasive than AAM. Sonographically, AFMB can be a relatively homogeneous isoechoic mass, or generally an echogenic lesion with multiple hypoechoic areas. The margins of AMFB in sonography were reported to be well-defined, while AAM has rather infiltrative signs. And blood flows within the mass can also be detected by colour Doppler ultrasound[37]. Apart from postoperative histology, contrast-enhanced MRI can be helpful in differential diagnosis, when homogeneous enhancement is visualized rather than the swirled sign[38]. Other rare soft tumors, such as infiltrating angiolipoma and myxoid liposarcoma, may be delineated as a hyperechoic mass on ultrasound imaging due to the fat contents, which can differ from AAM. Superficial angiomyxoma is usually a subcutaneous multinodular mass, with small-sized, thin-walled blood vessels that lack the hypertrophic vessels and infiltrative nature of AAM[35].

To achieve complete surgical excision and minimal invasiveness, it is essential to apply an imaging method to evaluate tumor range before operation. A combination of transabdominal, transperineal, and transvaginal US scans may be helpful for proper assessment of the involved scope, and a previous case report also made the same assessment[19]. Long-term and regular follow-up plays a crucial role in promoting the patients' prognosis. Ultrasound can also be applied for follow-up of patients after surgery and pharmacological treatment, because of its cost-effectiveness and convenience.

Based on the results of eight cases of AAMs, the specific ultrasonic features of AAMs were delineated in detail in this study. Meanwhile, the role of ultrasound in the management of AAM is discussed from different aspects. We emphasized the utilization of different ultrasound probes and colour Doppler ultrasound in the management of AAM in this article. There exist several limitations of the study. First, the number of cases with complete imaging records was limited. For further establishment of the ultrasonic features of AAMs, more typical cases are warranted. Moreover, new modalities of ultrasound imaging could be added in the further study of the disease, which might be of significance in better understanding the behaviors of AAM. Three-dimensional transvaginal ultrasound was performed in a previous study, and the dimension of the lesion was fully assessed[39]. Studies about the enhancement pattern of AAM on contrast-enhanced ultrasound can assist in establishing the role of ultrasound in the management of the disease.

In conclusion, AAMs are rare benign tumours, which originate from mesenchymal tissues, and can easily be misdiagnosed as other pelvic masses. Imaging examinations, including ultrasound, CT, and MRI, are commonly used for diagnosis and follow-up. The sonographic features of AAM are relatively characteristic and helpful for differential diagnosis. Ultrasound can be of great significance for preoperative diagnosis, evaluation of tumour scope, and recurrence surveillance.

ARTICLE HIGHLIGHTS

Case characteristics

A total of eight cases of aggressive angiomyxoma (AAM) who received imaging examinations and surgical resections are reported in the article.

Clinical diagnosis

AAM.

Differential diagnosis

Bartholin's duct cyst, Gartner's duct cyst, vaginal prolapse, angiomyofibroblastoma, myxoma, and myxoid sarcoma.

Laboratory diagnosis

There is no special laboratory diagnosis for the patients.

Imaging diagnosis

Ultrasound, computed tomography, and magnetic resonance imaging (MRI) can be utilized for the evaluation of AAM. The imaging features of AAM on ultrasound and MRI are characteristic.

Pathological diagnosis
Scattered spindle cells with low mitotic activity and a myxoid and collagen matrix are the main constituents of the lesions. Immunohistochemistry can also be helpful.

Treatment
The tumour of AAM requires a complete surgical resection. Gonadotropin releasing hormone agonist is also widely used.

Related reports
Approximately 300 cases of AAMs have been reported since the first report in 1983. This article is focused on the ultrasonic features of the neoplasms.

Term explanation
Dynamic contrast enhanced (DCE) imaging: DCE imaging is acquired after a rapid intravenous injection of gadolinium-DTPA. It can delineate the vasculature of local tissues and is helpful in evaluating vascularity. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC): DWI is an important sequence of MRI; it measures the mobility of water molecules due to Brownian motion. The ADC is a quantitative measure reflecting this motion. Contrast-enhanced ultrasound (CEUS): CEUS imaging is also obtained by injection of microbubbles, for better visualization of the anatomic structures and perfusion patterns.

Experiences and lessons
The ultrasonic features of AAM are distinguished. Ultrasound as a convenient imaging method, can play an important role in the diagnosis and follow-up of the disease.

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CASE REPORT

Solitary rectal ulcer syndrome complicating sessile serrated adenoma/polyps: A case report and review of literature

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Abstract

Solitary rectal ulcer syndrome (SRUS) is a rare benign condition, which can mimic many other diseases because of their similarities in clinical, endoscopic and histological features. Sessile serrated adenoma/polyp (SSA/p) is a premalignant lesion in the colon and rectum. The misdiagnosis of SSA/p in SRUS patients has been noted, but the case of SRUS arising secondarily to SSA/p has been rarely reported. We herein report the case of a 59-year-old man who presented with an ulcerative nodular lesion in the rectum, accompanied by the symptoms of blood and mucus in the feces, diarrhea and constipation. Magnetic resonance imagining revealed thickening of the rectal mucosa-submucosa. Histologically, the lesion was characterized by the hyperplastic lamina propria and diffusely serrated crypts. Further immunohistochemical staining showed the loss of HES1 and MLH1 expression in the epithelial cells in the serrated area. The patient with SRUS had histological changes of SSA/p, suggesting a potential of tumor transformation in certain cases. SRUS uncommonly accompanied by serrated lesions should at least be considered by pathologists and clinicians.

Key words: Solitary rectal ulcer syndrome; Magnetic resonance imagining; Sessile serrated adenoma/polyp; Mucosal prolapse; *HES1*; Case report

Core tip: We report a 59-year-old man presenting with blood and mucus in the feces, diarrhea and constipation. A subsequent endoscopy of the rectum revealed a 5-cm ulcerative nodule in the anterior wall of the rectum, 5 cm from the anal verge. Abdominal magnetic resonance imagining revealed thickening of the mucosa-submucosa, raising suspicion of rectal carcinoma. The surgical resection of the rectum was performed. However, the final pathology suggested an unusual case of solitary rectal ulcer syndrome complicating sessile serrated adenoma/polyp.

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INTRODUCTION

Solitary rectal ulcer syndrome (SRUS) is an uncommon benign disease, which is characterized by chronic defecation disorder. Along with the recognition of this disease, it has become clear that SRUS may not be solitary, ulcerative or indeed confined to the rectum[1]. SRUS can resemble other conditions in clinical presentation, endoscopic appearance and histopathologic feature[1-3]. Histologically, SRUS shows characteristic fibromuscular proliferation within the lamina propria accompanied by thickening of the muscularis mucosae. In some cases, there were focal serrated glands and dilated "diamond-shaped" crypts because of embedding artifact and architectural distortion[4,5]. These distorted crypts were the common reason for misinterpretation as sessile serrated adenoma/polyp (SSA/p)[6,7]. The majority of reports on the SRUS morphology have concentrated on its hyperplastic polyp (HP)-like architecture that is distinct from true serrated lesions[7,8], so that a diagnosis of SRUS often makes the pathologists believe that this lesion with serrated changes has no neoplastic potential. We herein report a case of SRUS complicating SSA/p, highlighting the need for careful histological assessment of serrated lesions in the polypoid mucosal prolapse with serrated architecture.

CASE REPORT

Clinical history

A 59-year-old man visited a local hospital with a 3-year history of occult blood and mucus in the feces, and with a long history of intermittent episodes of diarrhea and constipation. The patient had no history of steroid use, chronic liver disease, viral hepatitis, autoimmune diseases, or neoplasm. Physical examination was unremarkable except for a lump palpable on the anterior wall of the rectum 5 cm from the anal verge. Occult blood was detected in his feces. Other laboratory studies were normal, and carcinoembryonic antigen was not elevated. A subsequent endoscopy of the rectum revealed a 5-cm ulcerative nodule in the anterior wall of the rectum, 5 cm from the anal verge (Figure 1A). Initial endoscopic biopsy was performed in the local clinic and histopathologic finding was a rectal adenoma with low-grade dysplasia. After three months, a repeated colorectal endoscopy showed an ulcerative rectal mucosa and granulation tissue with no evidence of malignancy. However, the findings of abdominal magnetic resonance imagining (MRI) revealed thickening of the mucosa-submucosa, raising suspicion of rectal carcinoma (Figure 1B). In addition, clinical symptoms persisted despite medical treatment. Therefore, surgical resection of the rectum was performed. The final pathology report was no malignancy. Thus, the patient was referred to our hospital for the pathology consultation.

Pathological findings

Grossly, a well-demarcated, superficial ulcer with polypoid mucosa involved almost the entire circumference of the rectum 5 cm from the anal dentate line. The ulcerative nodular lesion measured 5 cm × 4 cm in length and width (described in the pathological report at the local clinic).

Histological examination revealed fibromuscular obliteration in the lamina propria combined with a superficial ulcer, which is surrounded by a large amount of serrated crypts (Figure 2A). These irregular glands showed a saw-toothed pattern or a diamond-shaped architecture involving the base of crypts (Figure 2B). The epithelial cells lined in the crypts were characterized by mucin hypersecretion and slight nuclear stratification (Figure 2C), which is consistent with the pathological characteristics of SSA/p. Around the SSA/p area, microvesicular hyperplastic polyps (MVHPs) were found, showing the earliest lesions of serrated dysplasia (Figure 2D).

Immunostaining for HES1 showed loss of expression in the serrated glands, while nuclear staining was observed in the normal adjacent epithelium and interstitial inflammatory cells (Figure 3A). Similarly, there was superficial loss of MLH1 expression in the crypts with serrated architectures (Figure 3B). However, proteins encoded by other mismatch repair genes, such as MSH2, MSH6 and PMS2, were nuclear positive in all cells. The staining for β-catenin was diffusely positive along the cell membranes, and P53 showed focal nuclear positivity. Ki-67 staining increased in the crypts of SSA/p (Figure 3C), compared with the basal staining

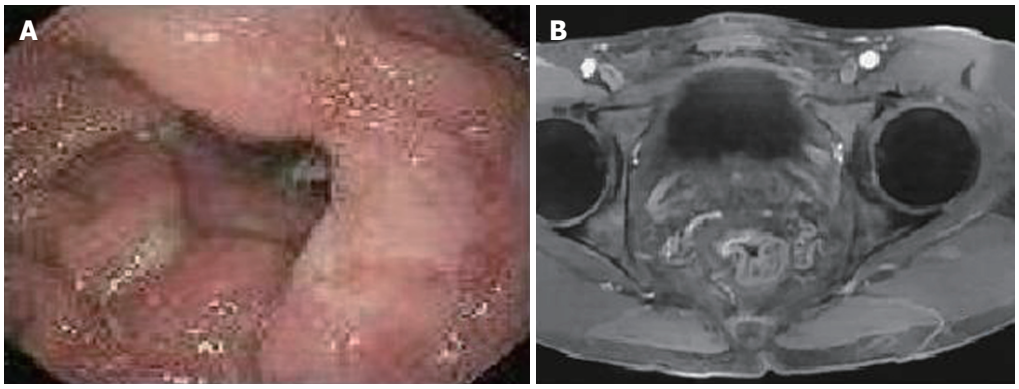

Figure 1 Endoscopic and magnetic resonance imaging of solitary rectal ulcer syndrome with sessile serrated adenomas/polyp. A: Endoscopic imaging revealed a large ulcerative nodule in the anterior wall of the rectum; B: Magnetic resonance imagining showed focal thickening of the anterior rectal wall and irregularities in the mucosal surface.

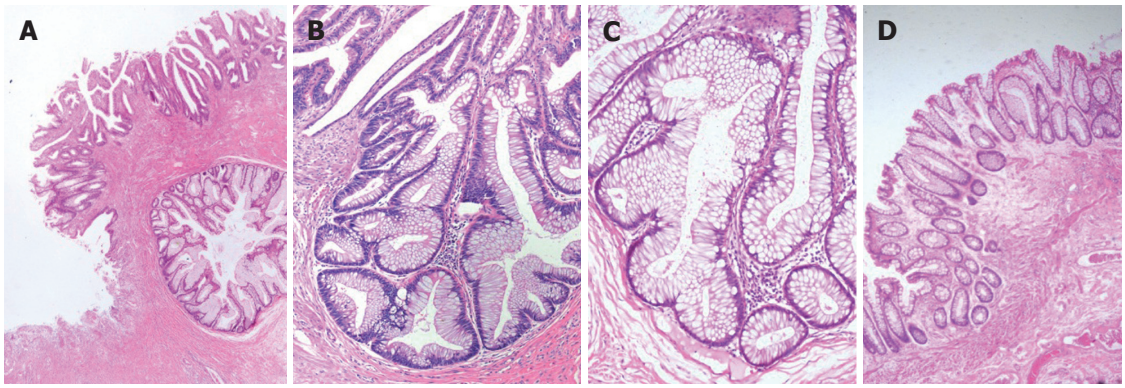

Figure 2 Histopathologic findings of solitary rectal ulcer syndrome with sessile serrated adenomas/polyp. A: A superficial ulcer and fibromuscular obliteration of the lamina propria with a few dilated and serrated crypts (H and E staining; original magnification, × 20); B: The diffuse architectural distortion with crypt dilatation and basal flattening (H and E staining; original magnification, × 100); C: Hypermucinous changes of crypt glands without epithelial dysplasia (H and E staining; original magnification, × 100); D: Microvesicular hyperplastic polyps around sessile serrated adenomas/polyp (H and E staining; original magnification, × 40).

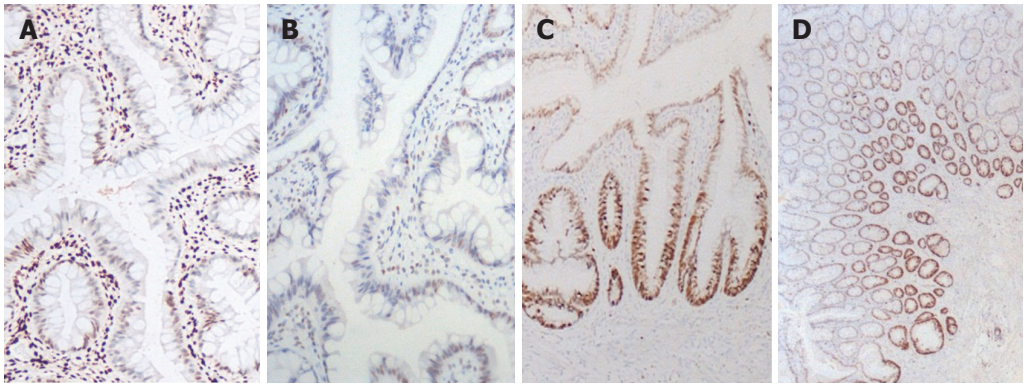

Figure 3 Immunohistochemichal staining for HES1, MLH1 and Ki67 in solitary rectal ulcer syndrome with sessile serrated adenomas/polyp. A: Loss or very weak of nuclear expression of HES1 in crypts from sessile serrated adenomas/polyp (SSA/P) (Original magnification, × 100); B: Reduced number of surface epithelial cells expressing MLH1 protein in serrated crypts (Original magnification, × 100); C: Increased strong nuclear staining of Ki67 in the surface epithelium of solitary rectal ulcer syndrome with SSA/P architecture (Original magnification, × 100); D: Basal staining of Ki67 in glands of micro-vesicular hyperplastic polyps (Original magnification, × 40).

in glands of MVHPs (Figure 3D).

DISCUSSION

SRUS is a poorly understood syndrome that was originally described in 1829 since Cruveihier reported four cases of unusual rectal ulcers[9]. The term "SRUS" was widely accepted after the initial use by Madigon and Morson[10] in the late 1960s. This syndrome usually manifests as rectal bleeding, prolonged excessive str-

aining, copious mucus passing and abdominal pain[11]. Ulcers and polyps have been the common endoscopic findings in 90% of patients[12,13]. However, some of the clinical and endoscopic presentations in SRUS patients can be completely nonspecific, and up to 26% of patients may be asymptomatic[1,14]. Hence, it is difficult to distinguish SRUS from malignancy or other diseases based on symptoms, endoscopic features or image findings[15]. Misdiagnosis of SRUS as malignancy can lead to unnecessary surgery. Herein, we present a 59-year-old man originally suspected of having rectal malignancy. An abdominoperineal resection of the rectum was performed and the final diagnosis was SRUS with SSA/p. Endoscopic examination in our case suggested a malignancy. However, MRI images showed that the lesion was not a mass but thickening of the mucosa-submucosa. This is a key point of differentiation between SRUS and cancer in imaging techniques. At present, conservative measures (diet and bulking agents) and biofeedback therapy are the first choice in SRUS treatment. Surgery usually acts as the final opinion for patients who have repeated relapse[16].

SRUS accompanied by SSA/p is extremely rare, and an accurate differential diagnosis is difficult to achieve. In our case, the histopathologic alterations of SRUS are characteristic and include the hyperplasia of the smooth muscle and thicken of the muscularis mucosae. Moreover, colonic crypts around the ulcer were no longer rounded but have diffusely serrated changes. These hypermucinous glands showed crypt dilatation and crypt flattening at the base. Surrounded by typical HPs, these serrated changes are reminiscent of a diagnosis of SSA/p. The differential diagnosis included inflammatory cloacogenic polyp with SRU, which was an inflammatory polyp of the anorectal transition zone[17]. Since previous studies have reported that the distortion and entrapment of the crypts were the common reasons for misinterpretation of SSA/p[5,8], the tumor location, diffuse HPs around the serrated changes and the striking features of SSA/p confirmed the final diagnosis of SRUS coexisting with SSA/p in our case.

Previous research illustrated that loss of HES1 expression could distinguish SSA/p from regenerative epithelia or HPs[18]. Interestingly, we found that HES1 expression was absent in the serrated glands. As the downstream target of the Notch signaling pathway, HES1 might be involved in the regulation of molecular activation and tumorigenesis in SRUS with SSA/p. Besides, some investigators showed that MLH1 deficiency was associated with the progression of sessile serrated lesions[19]. Moreover, a previous study has reported that some cases of SRUS with HP-like architectures presented focal loss of MLH1 expression, suggesting a potential of preneoplastic change in some SRUS cases[8]. Similar results were obtained in our case, which showed that the serrated crypts were negative for MLH1 staining while proteins encoded by other mismatch repair genes were normally expressed. Likewise, it has been discovered that the proliferation marker Ki67 is of value in assessing SSA/p. The Ki-67 proliferative zone tended to be distributed diffusely in the base of the SSA/p crypts, but partially in the epithelium of the normal or HP glands[20]. For our case, the basal cells within serrated crypts demonstrated diffuse staining for Ki-67, which is consistent with the features of SSA/p.

Little is known regarding the biologic characteristics and natural history of serrated lesions in SRUS. It is generally accepted that inappropriate and paradoxical contraction of the pelvic floor, which causes straining at defecation and prolapse of the rectal mucosa, further results in ulceration and polyps in SRUS patients[21-23]. Repeated trauma and repair are commonly observed in SRUS, which may be the reason of neoplastic transformation. Further studies are needed to clarify the pathogenic relationship between SRUS and tumors. Our case presented the loss of HES1 and MLH1 expression in serrated crypts, suggesting that HES1 and MLH1 may act as molecular triggers in the formation of serrated neoplasia in SRUS.

In summary, we have described an unusual case of SRUS complicating SSA/p. Loss of HES1 and MLH1 expression occurs in the serrated crypts, suggesting that alterations in molecular pathways may promote SSA/p progression in certain cases of SRUS. Pathologists and clinicians should be aware of the potential for serrated lesions to develop in SRUS.

ARTICLE HIGHLIGHTS

Case characteristics

Solitary rectal ulcer syndrome (SRUS) is an uncommon benign disease. It has been reported previously, but the case of SURS arising secondarily to sessile serrated adenomas/polyp (SSA/p) has been rarely reported.

Clinical diagnosis

Rectal ulcer.

Differential diagnosis

Rectal cancer.

Laboratory diagnosis

Blood and mucus were detected in the feces.

Imaging diagnosis

Thickening of the rectal mucosa-submucosa.

Pathological diagnosis

SRUS with SSA/P.

Treatment

Mainly medical therapy, and if not relieved, surgical management is indicated.

Related reports

A review of solitary rectal ulcer syndrome has been reported by Ala I Sharara in the *Journal of Gastrointestinal Endoscopy*.

Term explanation

SRUS: Solitary rectal ulcer syndrome; SSA/p: Sessile serrated adenomas/polyp.

Experiences and lessons

This case will contribute to improvements in our understanding of SRUS with SSA/P. This case may also serve as a reminder to gastroenterologists, surgeons and pathologists who may encounter SRUS cases in their clinical practice.

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CASE REPORT

Subdural empyema complicated with intracranial hemorrhage in a postradiotherapy nasopharyngeal carcinoma patient: A case report and review of literature

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Author contributions: Chen JC and Tan DH contributed equally to this work and should be considered as co-first authors; Chen JC and Tan DH participated in the patient treatment and wrote the manuscript; Xue ZB and Yang SY collected the clinical data and performed the literature review; Li Y and Lai RL performed the operation; Lai RL helped to design and revise the paper.

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Abstract

The prevalence of nasopharyngeal carcinoma (NPC) is higher in southern China, Hong Kong, and Taiwan than in other areas in the world. Radiotherapy is an important part of treatment for NPC patients, especially those with stage Ⅲ/Ⅳ disease. Subdural empyema is a rare but life-threatening complication in postradiotherapy NPC patients which should be paid more attention. Here, we present the case of a 64-year-old female postradiotherapy NPC patient with subdural empyema complicated with intracranial hemorrhage. She was treated by burr-hole surgery but unfortunately died because of recurrent intracranial hemorrhage. The mechanisms potentially underlying the formation of subdural empyema in postradiotherapy NPC patients and the surgical strategies that can be used in these patients are discussed in this report.

Key words: Intracranial hemorrhage; Nasopharyngeal carcinoma; Postradiotherapy; Subdural empyema; Case report

Core tip: This paper describes subdural empyema as a rare but life-threatening complication in postradiotherapy nasopharyngeal carcinoma. The opportunistic bacterial infection should be carefully considered in these immunosuppressive patients. A literature review was performed to discuss the potentially underlying mechanisms, imaging study, and comparison of two surgical strategies. It is noted that the prognosis appears to be more strongly related to the level of consciousness at the time of surgery.

Chen JC, Tan DH, Xue ZB, Yang SY, Li Y, Lai RL. Subdural empyema complicated with intracranial hemorrhage in a postradiotherapy nasopharyngeal carcinoma patient: A case report and review of literature. *World J Clin Cases* 2018; 6(14): 825-829 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/825.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.825

INTRODUCTION

The prevalence of nasopharyngeal carcinoma (NPC) is higher in southern China, Hong Kong, and Taiwan than in other areas in the world[1]. Radiotherapy is an important part of treatment for NPC patients, especially those with stage Ⅲ/Ⅳ disease. Here, we present the case of a 64-year-old female postradiotherapy NPC patient with subdural empyema complicated with spontaneous intracranial hemorrhage who was treated by burr-hole surgery. This case reveals that subdural empyema is a rare but life-threatening complication in postradiotherapy NPC patients which should be carefully considered. The mechanisms potentially underlying and surgical strategies for this condition are discussed in this report.

CASE REPORT

A 64-year-old woman was admitted after experiencing progressive headache, deteriorating consciousness, difficulty speaking, and weakness in left extremities for 2 d. Her past medical history was notable for T4N0M0 (Stage Ⅳa) NPC and hypertension. She had received a long period of radiotherapy for cancer. There was no recent history of oral anticoagulants or head trauma. A neurologic examination revealed a comatose mental state with a Glasgow coma scale (GCS) score of 7 (E1M5V1). The right pupil was fixed and dilated and not reactive to light, whereas the left pupil was normal. Additional physical examination revealed fever (38.2 ℃), left hemiparesis, and slight neck stiffness. Laboratory investigations showed leukocytosis (13.48 × 10^9/L) with neutrophilia (11.13 × 10^9/L). An elevated C-reactive protein level of 190 mg/L was also noted. A cranial CT was performed and showed a hypodense crescent-shaped accumulation of extra-axial fluid in addition to a local hyperdense lesion over the right hemisphere. There was a marked midline shift, and a tentorial herniation had formed (Figure 1A). We counseled her family and finally performed a burr-hole craniostomy with continuous closed system drainage under local anesthesia rather than a decompressive craniotomy due to her old age and poor health. A burr hole was made under CT guidance over the area of maximal lesion thickness. The dura and outer membrane were cross-incised, and we fixed an indwelling drainage catheter through the parietal burr hole under direct visualization. To our surprise, we found that the drainage of the lesion contained pus mixed with blood and was very viscous (Figure 2). An immediate postoperative cranial CT scan demonstrated that the subdural empyema had slightly decreased and that the middle structures of the brain had retracted (Figure 1B-D). In the following days, we empirically administered intravenous meropenem (0.5 g three times per day) and performed irrigation and drainage with 20 mL of saline containing gentamicin at a concentration of 0.32 mg/mL three times per day. On hospital day 4, the patient's level of consciousness had slightly improved, and her GCS score was 10 (E4M5V1). A cranial CT scan revealed that the subdural empyema had significantly decreased and that a hematoma had formed (Figure 1E). While a culture of the operative empyema grew *Corynebacterium corpse*, the blood culture was negative. However, on day 5, the patient returned to a coma state (GCS3, E1V1M1). An urgent cranial CT scan showed that a new subdural hemorrhage had formed in the middle shift, and a tentorial herniation had reappeared (Figure 1F). Although emergency treatment was given, the patient died later that day.

DISCUSSION

Subdural empyema is usually regarded as a life-threatening emergency due to its association with a synergistic cascade of rapidly accumulating pus surrounding the brain, causing increased intracranial pressure and a mass effect, severe inflammatory edema, hydrocephalus, and infarction. These events can cause death; thus, an early and precise diagnosis and emergency treatment are critical[2].

Although extensive studies of central nervous system (CNS) infection have been performed in postradiotherapy NPC patients, subdural empyema is very rare, and only one case has been previously described in detail[3-5]. This previous study demonstrated that postradiotherapy NPC patients are prone to CNS infection for the following reasons. First, advanced NPC typically destroys the skull base and breaks down the CNS barrier[4]. It is important to note that temporal lobe necrosis (TLN), a late complication of radiotherapy in NPC patients, not only leads to various degrees of coagulative necrosis of the brain parenchyma which is associated with fibrinoid changes in blood vessels, but also disrupts

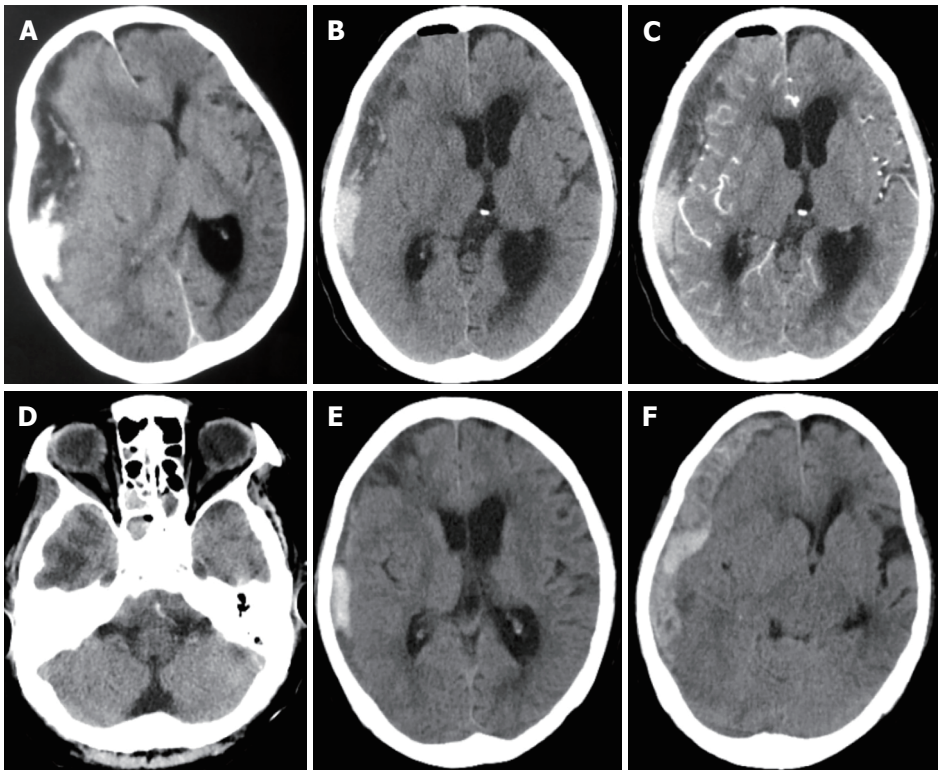

Figure 1 Radiographic images of the presenting case. A: Preoperative unenhanced CT revealed a hypodense crescent-shaped extra-axial fluid collection mixed with a local hyperdense lesion over the right hemisphere and marked midline shift of the brain; B: Immediate postoperative unenhanced CT scan demonstrated a slightly decreased subdural empyema and retraction of middle structures of the brain; C: An enhanced CT scan which is corresponding to figure B showed no enhancement of the thick rim or adjacent cerebral cortex; D: Hypointense areas (finger-like) were seen in the right lower temporal lobe; E: Unenhanced CT scan indicating significantly decreased subdural empyema at day 4; F: Unenhanced CT scan showed newly subdural hemorrhage and the middle shift of brain structures at day 5.

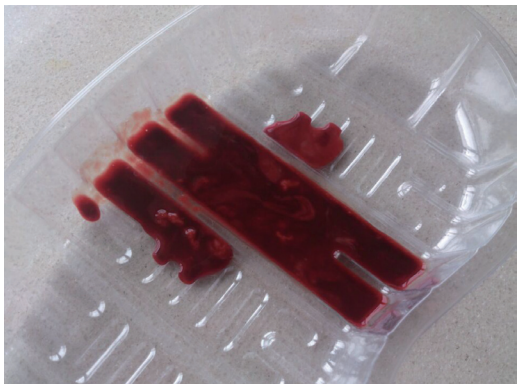

Figure 2 Drainage showed pus mixed with blood.

the blood brain barrier, which can exacerbate CNS infection[6]. Finger-like hypodense regions indicate typical reactive white matter edema in the temporal lobe, which is a characteristic feature in the diagnosis of TLN[6,7] (Figure 1D). TLN is also likely to be a mechanism that drives recurrent intracranial hemorrhage, making its diagnosis and treatment a daunting challenge. Second, nasopharyngeal tumors often block the nasal airway and Eustachian tube, causing rhinosinusitis or otitis media, which can be exacerbated by radiation[4]. Finally, performing radiotherapy in NPC patients can cause myelosuppression and immunosuppression, thereby facilitating the rise of opportunistic infections[8]. In a case series of 699 patients, Nathoo *et al*[9] had described a bacteriological spectrum for cranial subdural empyema with *Streptococcus* species being the predominant causative organism followed by anaerobes and *Staphylococcus aureus*. These three types of bacteria are consistent with the most common causative agents found in sinusitis-associated subdural empyema patients[10]. By contrast, in our case, the pathogenic bacterium was confirmed as *Corynebacterium corpse*, which was not included in the common bacteriological spectrum. *Corynebacterium* species, which are commonly found in normal skin flora and are catalase-positive Gram-positive bacilli, are increasingly being recognized as causes of opportunistic disease in immunocompromised patients[11]. Our findings support the notion that subdural empyema in postradiotherapy NPC patients is caused by hematogenous seeding of opportunistic pathogenic bacteria rather than sinusitis.

A CT scan of the head is often the first means of identification in most emergency patients because of its more widespread availability and the need for a rapid diagnosis. However, it is worth noting that subdural empyema always mimics chronic or subacute subdural hematoma because they share comparable complaints and neurological symptoms and CT scan features, as

observed in our case[3,12]. Subdural empyema commonly presents as the collection of hypodense crescent-shaped extra-axial fluid in a brain hemisphere, and it can cause a midline shift due to a mass effect. Enhancement of the adjacent cerebral cortex could be observed in many cases[13,14]. In addition to these findings, the sinuses might appear opacified, with air-fluid levels and bony erosion evident in some subdural empyema cases[15]. However, a CT scan might not show fluid collection when performed early in the evolution of the abscess, especially in abscesses in the infratentorial compartment[13,15]. Compared with a CT scan, magnetic resonance imaging (MRI) is more sensitive and superior for diagnosing subdural empyema because it has better resolution, produces fewer artifacts, and can obtain multiplanar images[13,15,16]. Subdural empyema usually appears as hypointense on T1-weighted images and hyperintense on T2-weighted images of subdual lesion[15]. Additionally, capsular enhancement is commonly noted after an intravenous gadolinium-diethylenetriamine pentaacetic acid (Gd-DPTA) injection[17]. Furthermore, compelling evidence indicates that diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) on MRI play an essential role in distinguishing subdural empyema from reactive subdural effusion. Subdural empyemas have high signal intensity on DWI and low signal intensity on ADC maps, whereas subdural effusions have low signal intensity on DWIs[15,17].

There is a great deal of controversy regarding the surgical strategies that should be used to manage subdural empyema (*i.e.*, craniotomy *vs* burr-hole surgery). A craniotomy is regarded as the best choice by some authors because it not only achieves decompression of the brain and returns cerebral blood flow but also allows the complete evacuation of purulent material, which is critical for a good prognosis[9,15,18]. Although craniotomy has many advantages, it might be rejected because of a patient's old age or poor health or because of other risk factors associated with the use of general anesthesia. Burr-hole drainage has been recommended for acute-state patients with liquid and thin collection and can be accomplished using CT or MRI guidance[16]. A clinical study conducted by De Bonis *et al*[16] compared craniotomy and burr-hole surgery and demonstrated that the outcome and morbidity observed in subdural empyema survivors were not related to the surgical method used but rather to the patient's level of consciousness at the time of surgery. However, reoperation is more frequent among patients who underwent burr-hole surgery[19], and this is an outcome that neurosurgeons are trying to improve. Eom and Kim[18] reported a case in which a favorable outcome was obtained using burr-hole surgery with continuous subdural irrigation and drainage of a subdural empyema.

Subdural empyema is a rare complication in postradiotherapy NPC patients which results from hematogenous seeding by opportunistic pathogenic bacteria rather than sinusitis. This life-threatening complication should be carefully considered and it should be noted that the prognosis of this condition appears to be more strongly related to a patient's level of consciousness at the time of surgery than to the surgical method used to treat it.

ARTICLE HIGHLIGHTS

Case characteristics

A 64-year-old woman presented with a progressive headache, deteriorating consciousness, difficulty speaking, and weakness in the left extremities for 2 d.

Clinical diagnosis

Subdural empyema complicated with intracranial hemorrhage.

Differential diagnosis

Chronic or subacute subdural hematoma.

Laboratory diagnosis

While a culture of the operative empyema grew *Corynebacterium*, blood culture was negative.

Imaging diagnosis

A cranial CT showed a hypodense crescent-shaped accumulation of extra-axial fluid in addition to a local hyperdense lesion over the right hemisphere. There was a marked midline shift, and a tentorial herniation had formed.

Treatment

A burr-hole craniostomy with continuous closed system drainage and use of antibiotics were administered to the patient.

Related reports

A patient presenting with subdural empyema after completion of concurrent chemoradiotherapy for stage IVB nasopharyngeal carcinoma (NPC) has been reported in detail by Dr. Chan from Singapore National University Hospital in 2006.

Term explanation

Burr-hole craniotomy under CT or MRI guidance is an invasive surgical approach for chronic subdural hematoma or subdural empyema. Compared with craniotomy, burr-hole drainage can be performed under local anesthesia and is a less invasive surgical choice for patients with old age or poor health condition.

Experiences and lessons

Subdural empyema is a rare but life-threatening complication in postradiotherapy NPC. It results from hematogenous seeding opportunistic pathogenic bacteria rather than sinusitis. Subdural empyema can mimic chronic or subacute subdural hematoma because of the similar clinical manifestations and imaging findings.

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CASE REPORT

Giant monostotic osteofibrous dysplasia of the ilium: A case report and review of literature

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Abstract

BACKGROUND

Osteofibrous dysplasia (OFD) is a developmental skeletal disorder, and cases with a giant affected area in the pelvis are rare.

CASE SUMMARY

In this case report, a 48-year-old man presented with a large tumor in the right iliac region that turned out to be OFD. The patient had rebound tenderness in his right hip. After radiography examination, magnetic resonance imaging examinations and some physical examination, extensive bone destruction in the right ilium was confirmed. Moreover, changes in bone mineral density and peripheral cortical bone sclerosis with surrounding soft tissue swelling were observed. Thus, this patient was considered to have giant monostotic OFD of the ilium. The tumor-related area was removed completely by surgery, and the remaining cavity was filled by artificial bones from the opposite ilium. According to the results of follow-up, the patient had normal flexion and extension activities of the right hip joint, and there was no evidence of recurrence of the tumor.

CONCLUSION

Suture of iliopsoas and gluteus medius muscle following focus curettage and bone grafting is a promising and effective method to treat giant OFD of the ilium. It is a feasible way to fill a large cavity after removing a lesion like the one is this case.

Key words: Osteofibrous dysplasia; Monostotic type; Giant tumor; Ilium; Case report

Core tip: Osteofibrous dysplasia is a developmental skeletal disorder, and cases involving the pelvis with a large affected area are rare. This report is the first case, to our knowledge, of a 48-year-old man with a huge tumor in the right iliac that turned out to be osteofibrous dysplasia. With the assistance of computed tomography and magnetic resonance imaging, the tumor was completely removed, and the left empty cavity was reasonably filled by pulling and suturing nearby muscles and using some artificial bone.

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INTRODUCTION

Osteofibrous dysplasia (OFD) is a developmental skeletal disorder and is characterized by substitution of normal bone with benign cellular fibrous connective tissue[1]. Currently, OFD can be classified as monostotic, polyostotic and McCune Albright syndrome[2]. Most cases of monostotic lesions present no significant symptoms and are often found incidentally on radiography taken for other symptoms[3]. Monostotic fibrous dysplasia mainly affects patients in their third decade of life[4]. Generally, monostotic OFD involves the ribs, the proximal femur, and craniofacial bones[5]. Cases involving the pelvis are uncommon, and cases with a large affected area are even rarer in clinics. Here, we report one patient with giant monostotic OFD of the ilium who was treated by tumor curettage and bone grafting. In the surgical procedure, we sutured the iliopsoas and gluteus medius muscle together and filled the remaining empty cavity to reduce the dead cavity volume and achieve a good outcome. We report here the diagnosis and treatment of giant OFD of the ilium.

CASE PRESENTATION

Chief complaints

A 48-year-old man who was diagnosed with a right iliac tumor more than 2 mo ago during a general physical examination.

History of present illness

The use of painkillers, like aspirin, did not alleviate his discomfort in the right hip. Radiography examination showed giant bone destruction in the right ilium (Figure 1A).

History of past illness

Past and family medical history was unremarkable.

Physical examination

On physical examination, the patient had deep tenderness in the right hip, and the flexion and extension activities of the bilateral hip joints were normal.

Laboratory testing

The results of chest radiography examination and other laboratory examinations were all normal.

Imaging examination

Subsequent computed tomography (CT) and magnetic resonance imaging (MRI) examinations indicated extensive bone destruction of the right ilium, with a size of about 10 cm × 5 cm × 5 cm. Bone mineral density was changed in this area, and peripheral cortical bone sclerosis with surrounding soft tissue swelling was noted (Figures 1 and 2).

FINAL DIAGNOSIS

Postoperative pathological examination confirmed the diagnosis of OFD (Figure 3).

TREATMENT

Intraoperative findings showed that the bone cortex in front of the focus in the right iliac bone was thin. A bone knife was used to chisel open the medial thin bone cortex, and the gray-looking tumor-like tissue was visualized. The texture was tenacious; its boundary was clear, without invasion of surrounding soft tissues. After the tumor was completely curetted, there remained a giant empty cavity. There was an even larger empty cavity after the giant empty cavity was filled with bone harvested from the opposite ilium and 20 g artificial bone. During the operation, a bone knife was used to chisel open a part of the external iliac plate in the thin bone cortex at the posterior-lateral side of the empty cavity. After the window was opened, parts of muscle bellies of the anterior iliopsoas and posterior gluteus medius muscle were pulled together and sutured to fill up the empty cavity.

OUTCOME AND FOLLOW-UP

Post-operative radiography reexamination (Figure 4) showed that the artificial bone and autogenous bone in the weight-bearing area of the acetabulum top were in place, and the coverage was satisfactory.

A follow-up at 6 mo showed that the visual analogous scale pain score was 0, and the patient had normal flexion and extension activities of the right hip joint. There was no evidence of recurrence of the tumor.

DISCUSSION

In 1966, the lesion described in this case was named

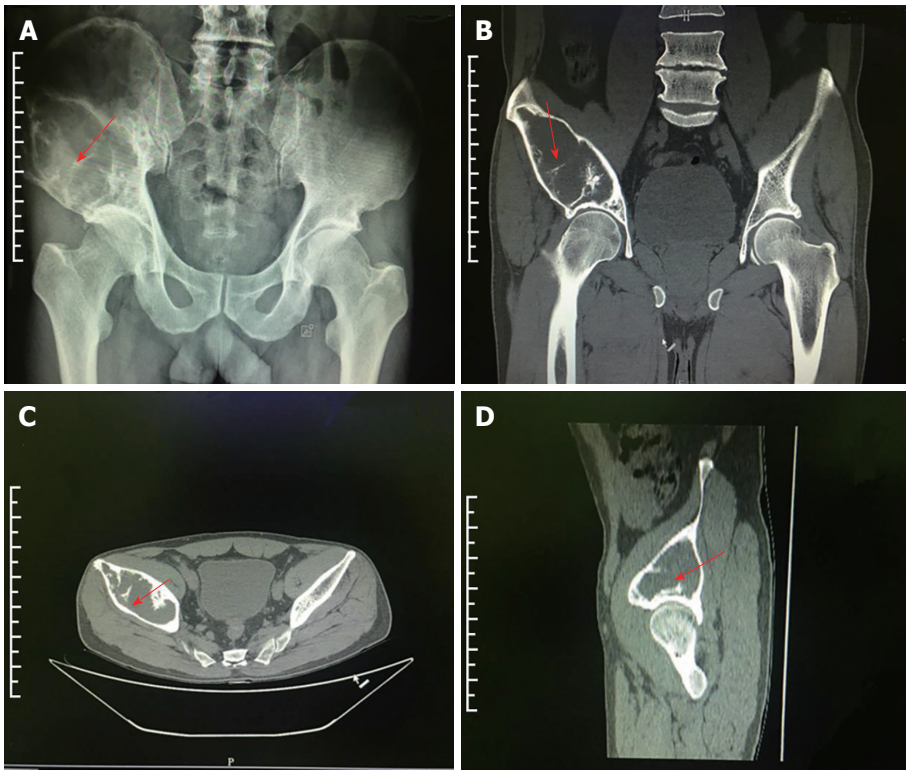

Figure 1 Radiography examination results. A: Extensive bone destruction of the right ilium on radiography examination, with a size of about 10 cm × 5 cm × 5 cm, and bone density also changed; B: Computed tomography shows osteosclerosis in the surrounding area of the ilium tumor without significant periosteal reaction in the coronary site; C: Trans-sectional site; D: Sagittal position (arrow indicates the area of lesion).

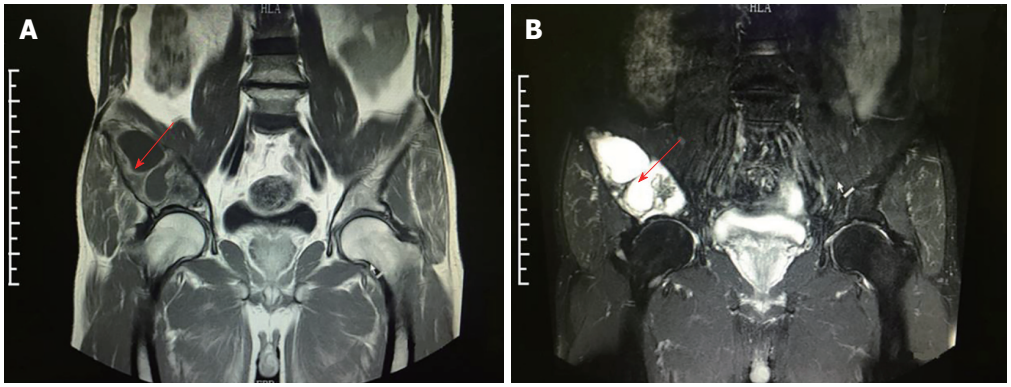

Figure 2 Magnetic resonance imaging examination results. A: Extensive bone destruction in right ilium. T1w suggests low-density change; B: T2w suggests high-density change, with surrounding soft issue swelling (arrow indicates the area of lesion).

"ossifying fibroma" by Kempson[6]. In 1976, OFD was commendably categorized by Campanacci[7]. Subsequently, Campanacci and Laus[8] reported 35 cases from their facility; and 22 additional cases were also reviewed in the literature. OFD is a kind of fibro-osseous process that is commonly found in the diaphysis of the tibia. According to a series of 80 OFD cases reported by Park *et al*[9], 77 were tibia-related and only three appeared in the fibula. Moreover, nine involved of both the tibia and fibula on the ipsilateral side. In other case reports, the ulna and the radius were also common sites of involvement.

OFD is a kind of benign deformity-inducing fibro-osseous lesion that usually occurs during childhood and often involves the mid-shaft of the tibia with or without involvement of the fibula. OFD is regarded as a common and benign skeletal disorder[10]. OFD appears generally as a localized mass, with the potential of pseudoarthrosis caused by bowed tibia, with or without pain. As the patient feels no special discomfort, misdiagnosis and occasional pathological fracture may occur[11]. The case reported here is extremely rare, not only because the large tumor was found in the right iliac of a middle-aged male but also because this tumor turned out to be OFD.

In immunohistochemical studies, single or strands

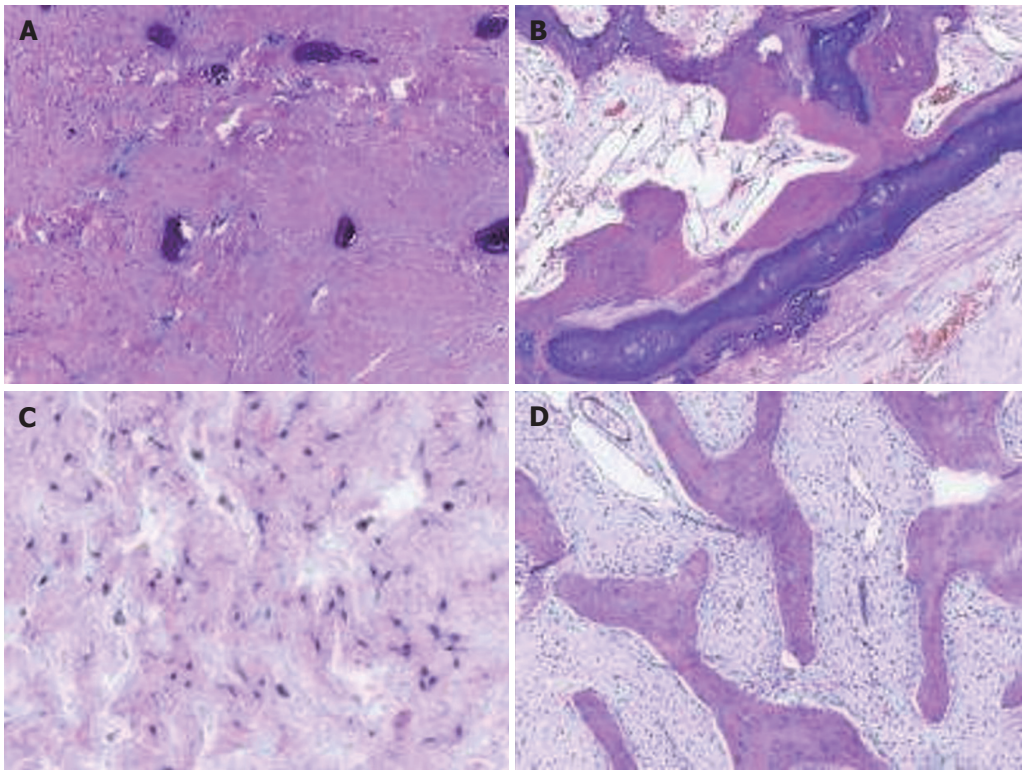

Figure 3 Pathological reports. A: Calcified woven bone can be seen (HE; 40 ×); B: No osteoblast and osteoclast hyperplasia can be seen (HE; 40 ×); C: It shows Fibroblast and Mucoid matrix (HE; 40 ×); D: It shows fibro-osseous lesions, with discontinuity of the trabecular bone and calcification (HE; 40 ×). HE: Hematoxylin-eosin.

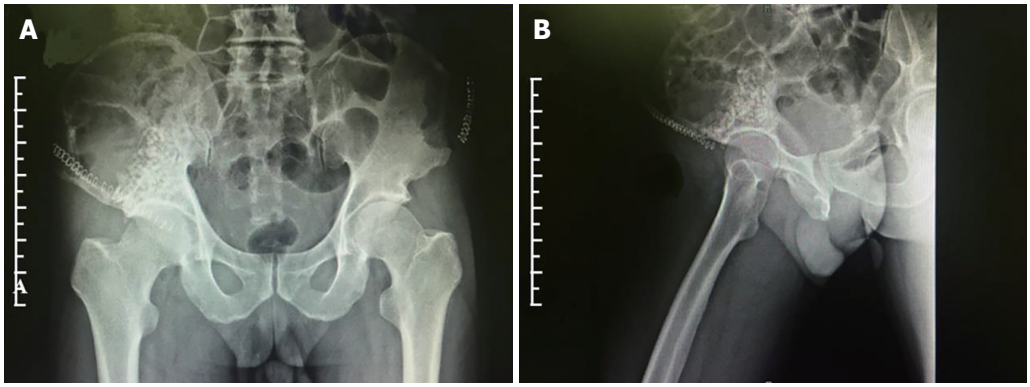

Figure 4 Postoperative radiography examinations. A and B: Artificial bone and autogenous bone in the weight-bearing zone of top acetabular were in place with satisfactory coverage.

of keratin-positive cells are found in most of cases of OFD. In a series of immunohistochemical studies, cytokeratin-positive cells were identified in 80% of 85 OFD patients[12-15]. According to a case report by Kahn[16], isolated cytokeratin-positive cells were distinguishable as mast cells and not epithelial cells in corresponding hematoxylin and eosin and Giemsa stained preparations. This discovery aided an issue concerning the histogenesis of all isolated cytokeratin-positive cells in previous studies. The OFD in long bones should not be confused with the entity gnathic ossifying fibroma with well-circumscribed mass that occurs in jaw. Additionally, the expression of cytokeratin (CK) 19 was demonstrated in OFD, whereas the expression of CK8 and CK18 was negative[15]. Similar findings, including a high incidence of CK1 positivity and a basal cell phenotype, were reported for both entities[17]. Furthermore, Bovée *et al*[18] demonstrated that epidermal and fibroblast growth factor type 2 and its receptor were expressed in OFD. In this study, related laboratory diagnosis was performed: complete blood count and electrolytes were normal, and C-reactive protein and alkaline phosphatase were slightly elevated.

OFD is often identified with radiography examination, where it is typically manifested as glass-like change. The bone cortex grows expansively to become

thinner, and the boundary is clear without periosteal reaction[19]. In clinic, radiography examination combined with CT and MRI examinations is conducive to determine the surgical procedure[20]. In this case, the imaging examination combined with the medical history of the patient indicated that there was extensive bone destruction in the right ilium, the focus had a clear boundary, and the bone cortex was extensive and thin and showed a ground glass-like change, without significant periosteal reaction. The affected area was considered to be a benign tumor-like lesion, with a high possibility of it being OFD. The involving range of tumor was large, and a part of the focus was located in the non-weight-bearing area of the acetabulum top. Thus, it was necessary to carry out bone grafting to reduce damage to the functional structures in the weight-bearing area. Complete curettage of the tumor led to a large residual cavity, which could easily form a dead cavity and increase the risk of infection. Therefore, a part of the external iliac plate in the thin cortical bone was chiseled open, and the anterior iliopsoas and posterior gluteus medius muscle were pulled together and sutured. This method not only effectively reduces the dead cavity, but it also minimizes the surgical trauma and does not affect the overall stability of the pelvic ring, making it conducive to postoperative recovery.

At present, the major treatment strategies for OFD are conservative treatment and surgical treatment[21]. Although it is a benign lesion with no symptoms, it is progressive and may lead to severe defects and lesions in bone and skin[2]. The surgical methods for OFD mainly include focus curettage and bone grafting combined with or without external fixation[22-25]. Curettage is a common treatment method for benign lesions, aggressive lesions, some cartilaginous malignant lesions and bone metastases[26]. However, the bone cavity created after curettage often needs to be filled with filling substances, such as acrylic cement or bone grafts, to guarantee its mechanical stability[27-29]. In this case, the allogeneic bone mixed with autogeneous bone was implanted in the weight-bearing area of the acetabulum. There is a large amount of cancellous substance in the ilium, and it has a good osteogenic activity. Compared to other materials, it has a faster creeping replacement. In addition, under the condition that the stability of the pelvic ring is unaffected, simple windowing in the external iliac plate and suturing between muscles can reduce the dead cavity and avoid internal fixation. Therefore, this method not only reduces the operation time and the operating difficulty but also lowers the cost for the patients.

In conclusion, the case recorded in this report was rare because most OFD occur in the mid-shaft of tibia with or without involvement of the fibula. Furthermore, the surgical methods utilized were effective without influencing the stability of pelvic ring. Moreover, the cavity generated by curettage was treated by filling up with mixture of autograft and allograft. Finally, the patient had noticeable recovery, specifically as normal flexion and extension activities of the right hip joint were observed in the patient without any evidence of tumor recurrence. Therefore, it is reasonable to believe that performing focus curettage and bone grafting with suture of iliopsoas and gluteus medius muscle will provide a promising and effective method in treating giant OFD of the ilium. This method not only reduces operation time and the operating difficulty but also lowers the cost for the patients. To our limited knowledge, it is the first case report to describe a large OFD tumor in the right iliac, its removal, and the filling of the empty cavity created after tumor removal by surrounding muscles and artificial bone. A limitation in this case is that the long-term efficacy needs further observation in the following period.

EXPERIENCES AND LESSONS

Some experiences and lessons were shared in this case, specifically: (1) combination of MRI and CT examinations to make precise diagnosis; (2) the allogeneic bone mixed with autogeneous bone was implanted in the weight-bearing area of the acetabulum to fill the hole caused by surgery; and (3) parts of muscle bellies of the anterior iliopsoas and posterior gluteus medius muscle were pulled together and sutured to fill up the empty cavity. Above-mentioned processes in this case not only reduce the operation time and the operating difficulty but also avoid the utilization of internal fixation and lower the expense.

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CASE REPORT

Postoperative redislocation of the hip in a patient with congenital insensitivity to pain with anhidrosis: A case report and review of literature

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Author contributions: Wang R and Liu Y are equally contributed to the work. Wang R, Liu Y and Yuan P designed the report; Zhou YY, Xu ZJ, Chen SY and Wang QQ collected the patient's clinical data; Wang R and Wang JY analyzed the data and wrote the paper.

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Abstract

Pelvic osteotomy is commonly used to adjust acetabula dysplasia for congenital dislocation of the hip, whereas congenital insensitivity to pain with anhidrosis (CIPA) is a rare hereditary disease that often has the characteristics of joint development deformity and easy fracture. This article reports the case involving a CIPA patient who was surgically treated by Chiari pelvic osteotomy and proximal femoral rotation osteotomy for congenital dislocation of the left hip joint and was provided long-term follow-up for redislocation and bilateral femoral head absorption.

Key words: Pelvic osteotomy; Congenital insensitivity to pain with anhidrosis; Congenital dislocation; Case report

Core tip: Reports of congenital insensitivity to pain with anhidrosis (CIPA) cases are relatively rare, and there is no standard treatment prescription. We report a case of

postoperative redislocation of the hip in a patient with CIPA in this article, and try to explore the causes of this situation and look for a solution.

Wang R, Liu Y, Zhou YY, Wang JY, Xu ZJ, Chen SY, Wang QQ, Yuan P. Postoperative redislocation of the hip in a patient with congenital insensitivity to pain with anhidrosis: A case report and review of literature. *World J Clin Cases* 2018; 6(14): 836-841 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/836.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.836

INTRODUCTION

Congenital insensitivity to pain with anhidrosis (CIPA) is a rare autosomal recessive genetic disease, mainly caused by mutations in the neurotrophic tyrosine receptor kinase 1 (*NTRK1*) gene. Patients often experience repeated fractures and joint deformations. There is no standard treatment prescription. In this article, we report a case of postoperative redislocation of the hip in a patient with CIPA.

CASE REPORT

Anamnesis

The present female patient was born in 2000 and had suffered multiple fractures in succession throughout the entire body as well as bilateral hip joint dislocation. Since she was four and a half years old, she had experienced fractures involving the left heel, left tibia, left femur, and right femur. The left tibia and right femur fractures occurred twice. She also suffered from repeated, long-term and unexplained high fevers from 2 mo old to 6 years old. Subsequently, the fevers were controlled, except during admissions when the patient reported anxiety. Although she showed a congenital insensitivity to pain, her temperature sensation was normal. When the patient was 2 years old, she began to show a self-mutilation tendency by biting the tip of her tongue twice. Moreover, when she was 10 years old, she bit an entire fingernail and approximately 1/3 of the finger. After her parents prevented her actions, no additional similar behaviors were exhibited. The patient's intelligence level was normal, and she presented a light-colored sclera, anhidrosis, tears when crying, and no obviously unusual skin thickness, elasticity or color. She was preliminarily diagnosed with CIPA, incomplete osteogenesis, and other hereditary bone-forming disorders.

Local condition

When the patient was 6 years old, she experienced an upper left femur fracture caused by a slight strike. Her parents chose conservative treatment, and the bone healed well. Subsequently, a left hip dislocation occurred when she was 7 years old (Figure 1A), and 2 mo of conservative treatment did not improve the situation (Figure 1B). Thus, she was admitted to our hospital for further treatment. The admission check showed the following: general situation, normal; left hip joint activity, slightly limited; no pain; Allis and Trendelenburg syndrome, positive; and left lower limb shortened by approximately 2 cm. A pelvic X-ray showed the following: healed deformity after fracture of the upper segment of the left femur; dislocation of the left hip; slightly flattening of the ipsilateral femoral head; left acetabular index of 28° and center-edge (CE) angle of 14°; right acetabular index of 20° and CE angle of 26°; left femoral head approximately 0.4 cm longer than the right; discontinuous left Shenton line; and Crown type Ⅱ and Tonnis Ⅱ degree of left hip dislocation.

Follow-up

The patient has been followed to the present. After the operation, it was found during the follow-up that the internal fixation position was good. The bone grew and healed well. Pelvic X-rays (Figure 1C) at 1 d after the operation showed that the acetabulum contained well; the left acetabular index was 21°, and the CE angle was 23°. The left femoral head was equal to the right in height, and the left Shenton line was continuous. One month after the operation (Figure 1D), it was found that the acetabular relationship was good, and the fracture healed well with internal fixation. Two months after the operation (Figure 1E), wear-and-tear absorption of bone was observed on the outside edge of the top portion of the left acetabulum. The left femoral head moved upward, with the acetabular index reaching up to the 33°; the left femoral head was 0.7 cm higher than the right, and the Shenton line was discontinuous. All of these findings could be described as clinical type Crown type 1 and Tonnis 2°. The patient's family requested conservative treatment. Five months after the operation (Figure 1F), it was found that the end of the osteotomy healed well, the upper margin of the left acetabulum was further absorbed, the level of the femoral head was not significantly increased, and the fracture healed well. Taking into account the patient's repeated fracture history and acetabular absorption, we told the patient to reduce weight bearing on the lower limbs. One year after the left hip surgery, she was readmitted for open reduction and internal fixation due to a right femoral intertrochanteric fracture (Figure 2A) after trauma. Fourteen months after the left hip surgery (2 mo after the right femur surgery, Figure 2B), the left pelvis and upper part of the femur were removed from the internal fixation device; then, the left femoral head was moved further upward to a position 0.9 cm higher than the right. The clinical classification was Crown type 2 and Tonnis 3°, and left acetabular wear increased. The false

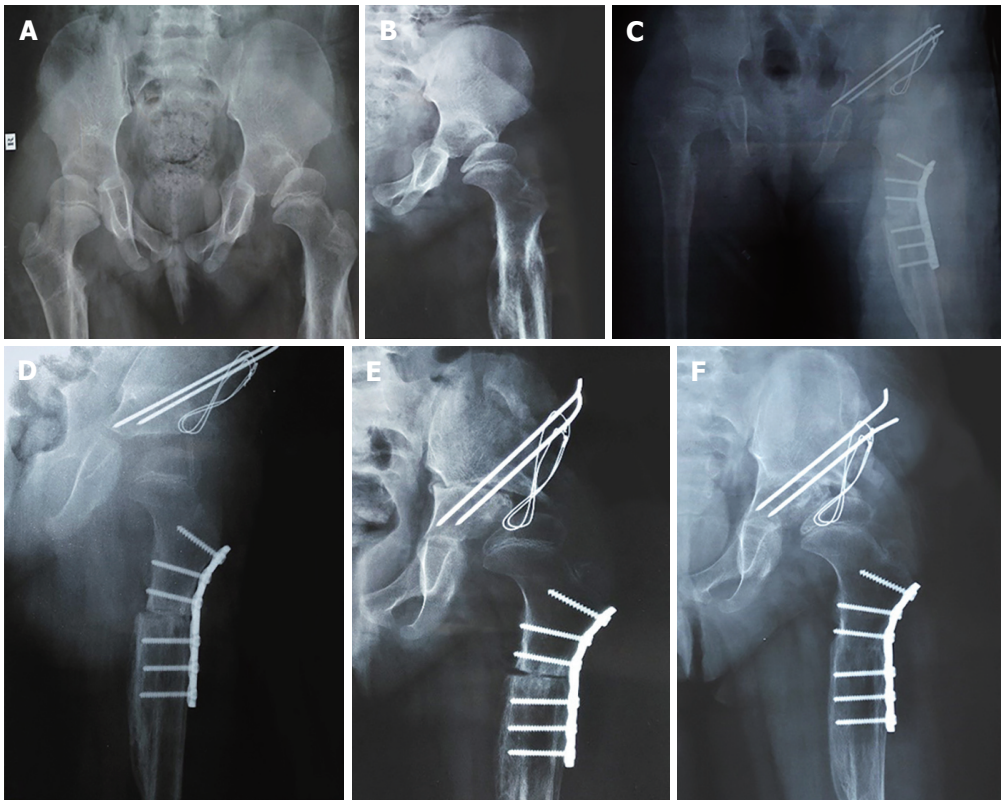

Figure 1 X-ray images of the patient. A, B: Before the operation; C: One day after the operation; D: One month after the operation; E: Two months after the operation; F: Five months after the operation.

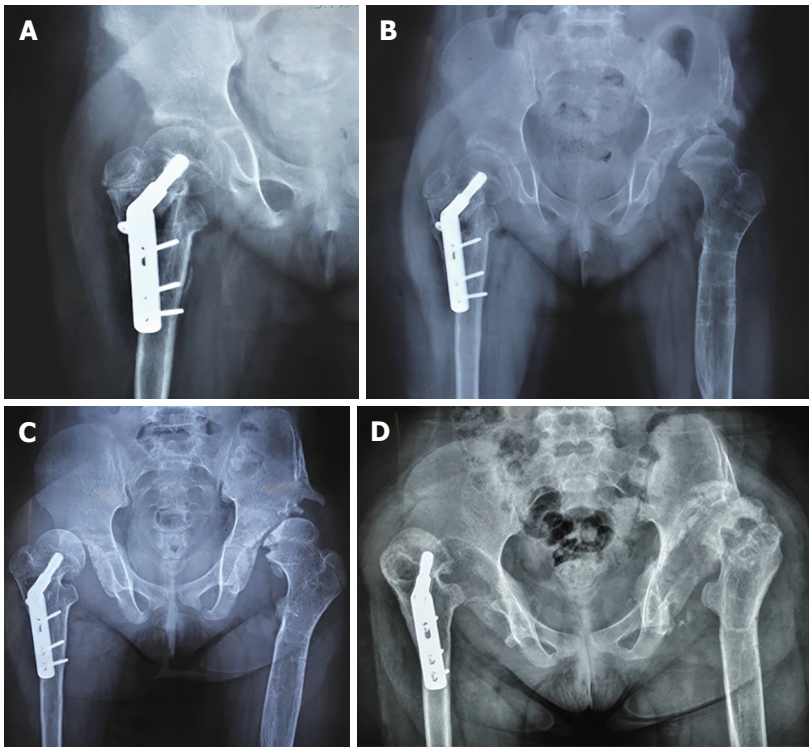

Figure 2 Postoperative X-ray images of the patient. A: Postoperative internal fixation of an intertrochanteric fracture of the right femur (1 year after left hip surgery); B: Two months after the right femur surgery (removal of the left hip internal fixation device); C: One year after the operation on the right femur; right hip dislocation; D: One year and eleven months after the right femoral intertrochanteric operation: bilateral femoral head necrosis and loss of the normal acetabular form.

Table 1 Genetic test results (possibly pathogenic genes)

Gene (Location)	Nucleic acid variation (Amino acid variation)	Heterozygosity	Disease (Genetic model)	Pathogenicity	Parent source
NTRK1 (exon 14)	NM_002529 c.A1787G (p.Asp596Gly)	Com_het	Congenital sensory neuropathy (AR)	Likely pathogenic	Maternal
NTRK1 (intron 14)	NM_002529 c.1806-2A>G	Com_het	Congenital insensitivity to pain with anhidrosis (AR)	Pathogenic	Paternal
GORAB (exon 4)	NM_002529 c.G733A (p.Ala245Thr)	Het	Senile skin with dysplasia of bone (AR)	Likely pathogenic	Maternal

joint occurred in the left acetabulum, and there was no further visible absorption. Then at 1 year after the operation (Figure 2C), the patient was found to have a right hip dislocation for the first time even after a manual joint reset, and her family members requested conservative treatment. The dislocation degree of the right hip joint was Crown type 2/Tonnis 2°, the right acetabular index was 20°, and the bilateral femoral head was not significantly changed. One year after the operation on the right femoral intertrochanteric region (Figure 2D), the double femoral head was completely absorbed, and the bilateral acetabulum lost its normal shape.

The results of a genetic test (Table 1) in January 2018 showed the following: (1) *NTRK1* (intron 14) gene mutation (mutation classification: pathogenic); (2) *NTRK1* (exon 14) genetic variation (mutation classification: likelihood of disease); and (3) *GORAB* (exon 4) gene mutation (mutation classification: probability of disease). Among these findings, the *NTRK1* gene suggested CIPA, and the *GORAB* gene mutation suggests senile skin with bone dysplasia. According to the genetic test results and clinical symptoms, the patient was considered to have CIPA.

DISCUSSION

CIPA is a rare autosomal recessive genetic disease, mainly caused by mutations in the *NTRK1* gene; NGF is a neurotrophic factor, and TrkA is an NGF receptor tyrosine kinase encoded by the *NTRK1* gene. The Ngf-Trka system supports the survival and maintenance of NGF-dependent neurons in the development process and plays a key role in pain, itching and inflammation[1]. Clinical manifestations include impaired temperature sensation and insensitivity to deep and shallow pain, but other feelings are rarely affected. They also show no sweating and exhibit different levels of mental disorders. Because there is no sweat, this condition often presents with unexplained fever; moreover, as there is no sensitivity to pain, patients display different degrees of self-injuring tendencies, often biting their tongue, lips, oral mucosa, and fingers, which often results in bruises, scars, and skin infections. In addition, patients often experience repeated fractures and joint deformations. Many have Charcot joint and fractures occur in the early years. Fractures and deformities can occur in bone joints throughout the body but are more prevalent in the lower extremities; most of the causes of fracture and dislocation are not well documented and are often due to minor injuries. Liu *et al*[2] through genetic studies showed that mutations in different locations of the *NTRK1* gene have different effects on intelligence levels; gene mutations in the core of the protein often have a greater impact on intelligence, and dislocation mutations located in the peripheral NTRK1 protein do not endanger important structural domains and tend to cause mild symptoms, usually without mental impairment. In 1996, Szöke *et al*[3] reported that CIPA patients show hip joint disease; Bar-on confirmed his data and stated that fractures often occur in the lower extremities and that patients often present age-independent joint dislocation and risk of infection[4]. In the preset case, the intelligence level was normal, there was no sweat, but there was insensitivity to pain, high fever of unknown origin, easy fracturing, joint dysplasia or other typical characteristics. The genetic testing is in line with the CIPA gene variant phenotype, and thus, with the clinical diagnosis of CIPA. This patient's intellectual development has not been affected; however, lower extremity fractures and joint symptoms were obvious.

Congenital dislocation of the hip, formerly known as primary dislocation of the hip, was later renamed "developmental dislocation of the hip" (DDH). The indicated cases include hip relaxation, acetabular dysplasia, dislocation of the hip and subluxation.

The treatment principle for DDH is early diagnosis and early treatment, as this can often mean that less invasive treatment is possible, and outcomes are significantly improved if treatment is initiated at an early stage and certainly before 6 wk of age[5]. Two to three-year-old children often undergo nonsurgical treatment, with a closed reduction after the use of frog-shaped gypsum or fixation of subbranches. Some countries such as Germany have universal screening programmes and have seen a decrease in the rates of surgical reduction in DDH[6]. Patients over 3 years old are treated by surgery. The goal of the surgical treatment in previously untreated juvenile hip displacement is to

achieve a stable and concentric reduction of the femoral head with the best range of motion and without severe complications related to avascular necrosis and stiffness of hip joint[7]. The commonly used surgical methods are: (1) Salter iliac osteotomy; (2) Chiari pelvic osteotomy; (3) Pemberton articular iliac osteotomy; and (4) multiple osteotomy of the pelvis. Femoral shortening and derotation osteotomy was classically reserved for children older than 3 years and has now been shown to be a useful and prudent procedure in younger patients[8].

In the case of this patient, the pelvic film showed outward movement from the left femoral head, but there was no obvious dislocation when she was 6 year old. At 7 years of age, there was left hip dislocation. Chiari osteotomy seemed to be the most appropriate surgical method, so Chiari pelvic osteotomy and proximal femoral rotation plus osteotomy were used to treat dislocation of the hip, postoperatively and 1 mo after surgery; the reduction effect was good and more satisfactory. However, after 2 mo of surgery, resorption of the upper margin of the acetabular bone was found, the acetabular index recovered, and the femoral head moved upward. During the subsequent review, the acetabular absorption gradually increased, and the femoral head gradually moved upward. At the age of 9 years, the right hip dislocation was found without definite inducement, and conservative treatment was adopted. After 1 year, the bilateral femoral head was completely necrotic, and the normal anatomical morphology disappeared. The patient's family described the fracture healing time as occurring before the age of 10 years old, with an average of 3 mo to achieve satisfactory results such as walking normally, after which the period of fracture healing was significantly prolonged, on average, up to 5-6 mo.

The authors conclude that, in cases with fractures after slight trauma, no sensitivity to pain and no sweat symptoms, the exact diagnosis is CIPA according to the results of a gene test. CIPA patients often have congenital and acquired joint deformities, Charcot disease, and easy-fracture characteristics. In this case, there were no obvious surgical mistakes, and after the operation, the left hip was well restored, no special drugs were administered, and the acetabular index recovered after the upper margin of the acetabulum, resulting in dislocation of the left hip after the operation. The postoperative absorption of the lateral acetabular margin may have been due to the high pressure on the top of the acetabulum caused by the femoral head; however, the characteristics of CIPA patients with dysplasia of bone and joint development should also be considered, and spontaneous dislocation of the right hip with no definite inducement was also considered. There was femoral head dislocation on both sides and necrotic absorption after 1-year period, which may be caused by defective blood transport caused by dislocation, but the patient's family reported significantly slowed fracture healing. Thus, CIPA, with a likelihood of worsening skeletal symptoms, must also be considered.

In conclusion, reports of CIPA cases are relatively rare, and there is no standard treatment prescription. Whether these patients are prone to recurrent dislocation or femoral head resorption after hip dislocation surgery requires further study. This operation did not achieve the desired therapeutic effect in the present patient; therefore, in such unique cases, the development of the operation plan should take full account of the bone characteristics, joint development and deformity, employing strictly accurate operative indications. If the surgical indication is clear, full communication with the patients and their families is essential. Drug therapy and rehabilitation therapy can be used perioperatively to improve the bone and joint condition and to develop the most appropriate comprehensive treatment plan.

ARTICLE HIGHLIGHTS

Reports of congenital insensitivity to pain with anhidrosis (CIPA) cases are few, and reports of CIPA patients with congenital dislocation of the hip are fewer. As a result, the operative risk and postoperative complications are unknown. In this article, we report a postoperative redislocation of the hip in a patient with CIPA and discuss the causes of the postoperative outcome.

Clinical diagnosis

CIPA.

Genetic diagnosis

CIPA.

Treatment

Chiari pelvic osteotomy and proximal femoral rotation osteotomy.

Experiences and lessons

This case shows possible postoperative complications of CIPA patients with congenital dislocation of the hip, which may play a guiding role in the future treatment. For such patients, we suggest that we pay more attention to the particularity of its joints and try comprehensive treatment. More research is needed to prove our conjecture.

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CASE REPORT

Open surgical treatment of choledochocele: A case report and review of literature

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Author contributions: Li YX designed the report; Yang J and Xiao GF collected the patient's clinical data and wrote the paper.

Informed consent statement: Consent was obtained from the patient's relatives for publication of this report and any accompanying images.

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Abstract

Choledochocele (also known as type Ⅲ choledochal cyst according to Todani's classification) is a cystic dilation of the distal segment of the common bile duct protruding into the duodenal lumen. Cases are rare and the etiology remains unclear. It is usually misdiagnosed as peptic ulcer, as in the patient whose case is described here. Multislice spiral computed tomography and magnetic resonance cholangiopancreatography may be comparable to endoscopic retrograde cholangiography for diagnosis of choledochocele. Both endoscopic therapy and open surgical management are safe options, and size of the cyst plays a role in the decision-making for which approach to apply. A 50-year-old woman admitted to our hospital with upper abdominal pain caused by choledochocele with large size was successfully treated by open surgical management. We present the details of her case in this case report and discuss the recent literature on such cases and their therapeutic management.

Key words: Choledochal cyst; Endoscopic retrograde cholangiopancreatography; Choledochocele; Operative surgical procedure; Case report

Core tip: Choledochocele, also known as the type III choledochal cyst according to Todani's classification, is a rare disease. We present the case of an adult female with a large-size choledochocele that was successfully treated by open surgery. We also provide a detailed discussion of the recent literature on such cases and their therapeutic management.

Yang J, Xiao GF, Li YX. Open surgical treatment of choledochocele: A case report and review of literature. *World J Clin Cases* 2018; 6(14): 842-846 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/842.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.842

INTRODUCTION

Choledochocele (also known as type Ⅲ choledochal cyst according to Todani's classification[1]), is a cystic dilation of the distal segment of the common bile duct protruding into the duodenal lumen. Considered rare, these cases comprise less than 2% of all reported cases of choledochal cyst[2]. The rarity of the disease serves to obscure its diagnosis and treatment.

The case described herein, accompanied by a review of the current literature, will help to increase our knowledge about this rare disease.

CASE REPORT

A 50-year-old woman was admitted to our department with an > 10-year history of repeated upper abdominal pain, but without vomiting, jaundice, chills and fever. During that period, she had been admitted to the gastroenterology outpatient clinic several times, where she was diagnosed with and treated for chronic nonatrophic gastritis; yet, her symptom was never alleviated.

Physical examination produced no positive findings, except a mild tenderness on the upper abdomen. Routine blood panel, liver function markers, blood amylase and tumor marker test results were normal. Abdominal ultrasound showed gallstones and nondilated intrahepatic and extrahepatic bile ducts. As such, the cause of the patient's presenting symptom remained undetermined.

Multislice spiral computed tomography showed a 3.0 cm-long, 1.5 cm-wide cystic lesion at the junction of the descending and horizontal portion of the duodenum (Figure 1). Duodenoscopy was performed and showed a huge submucosal mass connected to the major duodenal papilla; the distal segment of the common bile duct was not evident in endoscopic retrograde cholangiopancreatography (ERCP) (Figure 2). We considered these findings to indicate a choledochocele, and we decided to treat with open surgical management.

The cystic lesion became grossly visible when the descending part of the duodenum was incised longitudinally, and complete cystectomy was performed (Figure 3). Then, the orifices of the common bile duct and pancreatic duct were found and each marked with 6-Fr silicon tube. Sphincteroplasty was performed under the guidance of the silicon tube. Cholecystectomy was also carried out to address the gallstones. An abdominal cavity drainage tube and a duodenostomy tube were placed. A T-tube was also placed, to facilitate external drainage of bile. Lastly, a nasojejunal nutrition tube was placed perioperatively, and enteral nutrition support was started on the 3rd day after surgery. The operation time was 4 h and intraoperative blood loss was 120 mL. Postoperative pathological examination of the resected tissue showed duodenal mucosa with regional low-grade intraepithelial neoplasia inside the choledochocele.

At 1 wk postoperation, the nasojejunal nutrition tube was removed and the duodenostomy tube was occluded; at this time, oral feeding was initiated and tolerated without event. The postoperative period remained uneventful, and the patient was discharged at 10 d after the operation. At 45 d postoperation, the T-tube and duodenostomy tube were removed. At the 1-year follow-up, the patient had survived and was asymptomatic.

DISCUSSION

The first case of choledochocele was reported by Wheeler[3] in 1915. The report described the anomaly as a small, tense cyst occupying a position in or about the orifice of the common bile duct[3]. Since then, with the development of medical techniques like endoscopy and imaging, the number of publications on choledochocele has steadily increased.

In 1993, Masetti *et al*[4] reviewed 116 cases of choledochocele reported in the literature to date. In 2015, Lobeck *et al*[5] reviewed 71 individual case reports as well as 42 institutional reviews, totaling 254 cases of choledochocele; unfortunately, the authors did not affirm whether or not there were duplications between the included cases. A single case series of choledochocele including 28 patients was reported by Ziegler *et al*[6] in 2009, representing the largest institution-based collection of case data. In this article, we summarized 22 case report studies of adult choledochocele patients receiving treatment between 1995 and 2015 in PubMed database (Table 1).

In Japan, choledochocele has been regarded as the type Ⅲ choledochal cyst (according to Todani's classification[1]) and reportedly accounts for the lowest proportion of choledochal cyst case series[2]. However, both Ziegler *et al*[6] and Dong *et al*[7] considered that the choledochal cysts should not include the choledochocele because patients with choledochocele differ from those with choledochal cyst in age, sex, presentation, pancreatic ductal anatomy, and their management. Choledochoceles were classified as type A and type B based on the anatomic appearance by Sarris and Tsang, and the type A Choledochoceles were further divided into 3 subtypes (intraluminal with common opening for the common bile duct and pancreatic duct, intraluminal with separate openings for the common bile duct and pancreatic duct and completely intramural)[8]. Other classifications had also been proposed like Kagiyama[9] and Horaguchi[10], however none has been widely accepted.

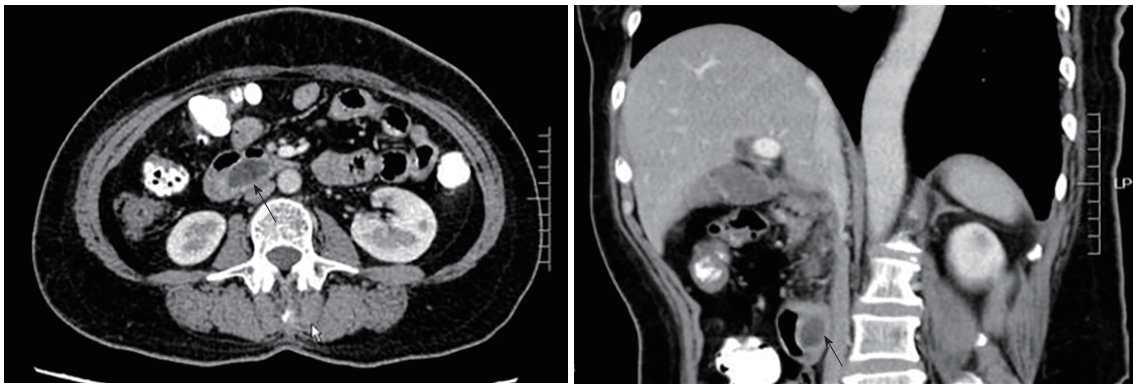

Figure 1 Multislice spiral computed tomography indicating a cystic lesion at the duodenum. Black arrows indicate the cystic lesion.

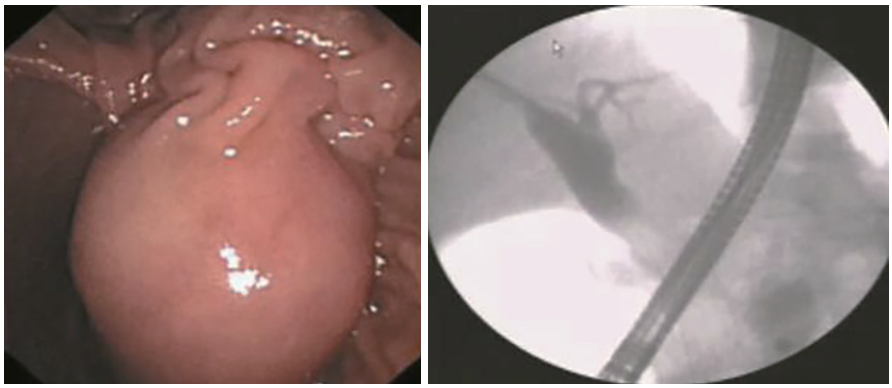

Figure 2 Duodenoscopy showing a huge submucosal mass connected to the major duodenal papilla. The distal segment of the common bile duct was not evident.

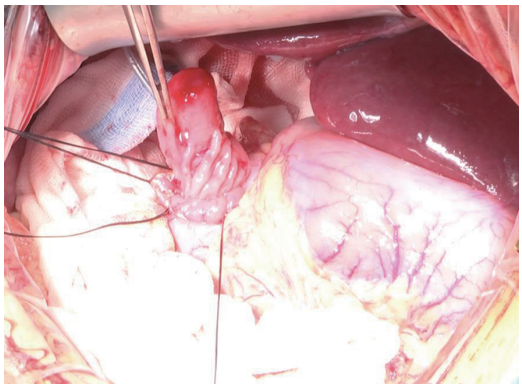

Figure 3 The cyst lesion was found to be attached to the duodenal papilla during the surgery.

The etiology of the choledochocele remains unclear. Tanaka[11] suggested that the mechanism for formation was failed regression of a bile duct during embryogenesis. However, Sterling[12] considered that some choledochocele appear to be acquired and proposed that papillary stenosis or sphincter of Oddi dysfunction may cause obstruction to bile flow, resulting in increased pressure within the distal bile duct, which could then evaginate into the duodenum. Sarris and Tsang[8], in the review of 24 patients, reported that the epithelium inside the choledochocele was duodenal mucosa in 63% of the cases and biliary tract epithelium or unclassifiable glandular epithelium in 37% of the cases.

In histopathology, the presence of intestinal mucosa creates controversy as to whether choledochocele is a type of duodenal duplication cyst or a unique entity. Congenital intraluminal duodenal diverticulum has been suggested in relation to the pathogenesis of choledochocele in young children, because most cases describe duodenal mucosa. However, unlike congenital forms, in older patients a papillary stenosis may cause dilatation of the ampulla by way of an inflammatory process induced by stasis of bile and pancreatic juice. Thus, biliary tract epithelium and undifferentiated epithelium are predominant later on[13].

Abdominal pain is the most common symptom of choledochocele, others include nausea, vomiting and jaundice. Image examination plays an important role in the diagnosis. Noninvasive B-ultrasound examination can detect cystic mass in the duodenal cavity; however, the image could be disturbed by intestinal gas. Usually, there are no specific findings, as in our case. Endoscopic ultrasound could show the wall layers of the cyst as well as the connection with the pancreaticobiliary tree, it also might guide both classification of the lesion and treatment decisions[14]. Some think the confirmation of a choledochocele appears to be best made by ERCP.

Table 1 Case report studies of adult choledochocele patients receiving treatment, 1995-2015

Author	Clinical presentation	Treatment	Malignancy	Symptom relief
Eisenman 1995	Abdominal pain	ET	Not noted	Yes
Tajiri 1996	Abdominal pain	OST	No	Yes
Tanno 1996	Jaundice, fever	ET	Not noted	Yes
Krepel 1997	Anaemia, Abdominal pain	OST	No	Yes
Iwata 1998	Abdominal pain, fever	OST	No	Not noted
Chatila 1999	Abdominal pain	ET	No	Yes
Adamek 2000	Nausea, abdominal pain	ET	Not noted	Yes
Groebli 2000	Abdominal pain	OST	Not noted	Not noted
Can 2006	Abdominal pain	OST	Not noted	Yes
Moparty 2006	Abdominal pain	OST	Not noted	Not noted
Berger 2007	Abdominal pain, nausea	ET	No	Yes
Hackert 2007	Abdominal pain	OST	No	Not noted
Izumiya 2007	Abdominal pain	ET	Not noted	Yes
Kawakami 2007	None	ET	No	-
Lakhtakia 2007	Abdominal pain, vomit	ET	No	Yes
Kaye 2008	Abdominal pain	OST	Not noted	Yes
Park 2009	Abdominal pain	ET	No	Yes
Amezaga 2010	Jaundice, anorexia	ET	Not noted	Yes
Cakmakci 2012	Abdominal pain	OST	Not noted	Yes
Darji 2012	Abdominal pain, vomit	ET	Not noted	Not noted
Zhu 2014	Abdominal pain, vomit	ET	Not noted	Yes
Villa 2015	Abdominal pain	ET	Not noted	Yes

OST: Open surgical treatment; ET: Endoscopic treatment.

In the literature, ERCP has been performed in 67% of the reported cases, and this method holds the benefit of simultaneous treatment implementation. Multislice spiral computed tomography and magnetic resonance cholangiopancreatography are considered to have comparable specificity and sensitivity, and may replace ERCP for diagnosis[15,16]. In our patient, both endoscopic and radiologic techniques were used to obtain an optimal image.

Open surgical management, like transduodenal complete cyst excision with sphincteroplasty, was performed by Wheeler on the original choledochocele case (a 65-year-old male patient) with success, and is still frequently performed. In 1974, endoscopic sphincterotomy treatment was implemented for the first time by Mane *et al*[17], on a 21-year-old female patient. Since then, endoscopy has been recognized as a feasible alternative treatment with satisfactory results. Both therapies have been applied successfully in pediatric patients[18,19].

The choice of treatment method is still uncertain, however, and size of the cyst plays a role in the clinical decision-making process. Three centimeters in diameter may be the cut-off value, above which transduodenal cyst resection should be performed[5]. However, the fundamental purpose of choledochocele treatment should be to maintain normal outflow of bile and pancreatic juice, with the additional objective of minimizing risk of malignancy. The large diameter of the cyst lesion in our patient led us to decide to perform open surgery. Almost all of the patients have relieved after treatment either by endoscopy or surgery. Malignant transformation of a choledochocele has been rarely reported[20], and wasn't happened in the case reports we reviewed in the table. However, choledochocele might be accompanied or caused by pancreaticobiliary maljunction, in such a condition, biliary tract malignancy was more frequent according to Horaguchi's report[10]. Nonetheless, sustaining follow-up could be beneficial for patients who are asymptomatic or accidentally discovered.

In conclusion, choledochocele is a rare disease and the choice of treatment method is still controversial. For choledochocele with large-size (*i.e.*, > 3 cm in diameter), we suggest treatment with open surgical management, according to our case's successful outcome.

ARTICLE HIGHLIGHTS

Case characteristics

A 50-year-old woman with upper abdominal pain lasting for more than 10 year.

Clinical diagnosis

Choledochocele.

Laboratory diagnosis

No positive laboratory test results were found.

Imaging diagnosis

A 3.0 cm-long, 1.5 cm-wide cystic lesion at the junction of the descending and horizontal portion of the duodenum.

Pathological diagnosis

Duodenal mucosa with regional low-grade intraepithelial neoplasia inside the choledochocele.

Treatment

Open surgical management involving cyst excision with sphincteroplasty.

Related reports

Choledochocele is considered a rare disease, and cases are seldom reported.

Term explanation

Choledochocele, also known as the type Ⅲ choledochal cyst according to Todani's classification, is a cystic dilation of the distal segment of the common bile duct protruding into the duodenal lumen, and accounts for < 2% of all reported cases of choledochal cyst.

Experiences and lessons

Choledochocele is a rare disease and usually misdiagnosed as peptic ulcer. For the choledochocele with large size (*i.e.*, > 3 cm in diameter), we suggest treatment with open surgical management, according to our case's successful outcome.

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CASE REPORT

Mesenteric heterotopic pancreas in a pediatric patient: A case report and review of literature

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Abstract

Heterotopic pancreas (HP) is a congenital anomaly defined as pancreatic tissue that has no contact with the orthotopic pancreas and its own duct system and vascular supply. The most common locations of HP are the upper gastrointestinal tract, specifically, the stomach, duodenum, and proximal jejunum. Involvement of the mesentery is rare. Here, we describe a rare case of mesenteric heterotopic pancreas (MHP) in a 12-year-old girl who presented with acute abdomen. The patient underwent emergency laparotomy, and the mass and adjacent small bowel were resected. Results of the postoperative histopathologic examination confirmed the diagnosis of MHP. Observation of the patient for 12 mo postoperatively showed no evidence of recurrence. Preoperative diagnosis of HP is difficult, even in a symptomatic patient. Increased awareness and understanding of the image characteristics of MHP will aid in correct preoperative diagnosis and appropriate patient management.

Key words: Heterotopic pancreas; Mesenteric; Acute abdomen; Computed tomography; Magnetic resonance imaging; Case report

Core tip: Heterotopic pancreas (HP) is a congenital anomaly defined as pancreatic tissue that has no contact with the orthotopic pancreas and its own duct system and vascular supply. The most common locations of HP are the upper gastrointestinal tract, specifically, the stomach, duodenum, and proximal jejunum. Involvement of the mesentery is rare. Here, we describe a rare case of mesenteric heterotopic pancreas (MHP) in a 12-year-old girl who presented with acute abdomen. MHP should be considered in the differential diagnosis of a mesenteric mass, especially when its morphology and enhancement are similar to those of orthotopic pancreas.

Tang XB, Liao MY, Wang WL, Bai YZ. Mesenteric heterotopic pancreas in a pediatric patient: A case report and review of literature. *World J Clin Cases* 2018; 6(14): 847-853 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/847.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.847

INTRODUCTION

Heterotopic pancreas (HP) is most commonly found in the proximal gastrointestinal tract. Although the reported incidence of HP varies, the true incidence is difficult to determine because the patients are usually asymptomatic and the condition is usually found incidentally at autopsy or during laparotomy[1,2]. Male preponderance is seen among adults, with the incidence of disease peaking during the fourth to sixth decades of life[3,4]. The most frequent location of heterotopic pancreatic tissue is the stomach (47%), followed by the jejunum (35%), duodenum (11.7%), and ileum (5.8%)[5]. Involvement of the mesentery is rare. Until now, no more than ten cases of mesenteric heterotopic pancreas (MHP) have been described in the medical literature[6-13]. Here, we describe a case of MHP in a 12-year-old female patient.

CASE REPORT

A 12-year-old girl with no significant medical history was admitted to our department with intermittent vomiting and abdominal pain for 3 d. Her growth and development were normal. On admission, she was in a good general condition. Her temperature was 36.6 ℃, heart rate was 106 beats/min, and the blood pressure was 100/69 mmHg. Her physical examination showed abdominal tenderness with peritoneal irritation. The laboratory results were unremarkable. Abdominal ultrasonography revealed a well-defined, heterogeneous, medially echoic mass located at the margin of the intestinal mesentery in the abdominal cavity that measured approximately 4.9 cm × 2.6 cm. Contrast-enhanced computed tomography (CECT) of the abdomen showed an enhanced oval, soft-tissue mass (42 mm × 25 mm) in the mesentery at the level of the umbilicus (Figure 1). The clinical diagnosis of a mesenteric mass was made. The differential diagnosis included intestinal duplication cyst, inflammated Meckel's diverticulum, and mesenteric lymphangioma.

Because of peritoneal irritation, the patient underwent emergency laparotomy 12 h after hospitalization. Laparotomy revealed a yellowish, soft-tissue mass measuring 4 cm in diameter that was located in the mesentery of the proximal jejunum and adhered to the serosal surface of the jejunum (Figure 2). The mass and the adjacent jejunum were resected, and an end-to-end anastomosis was performed.

Gross pathology demonstrated a 4 cm × 3 cm mass in the jejunal mesentery that was adhered to the serosa of the jejunum. Postoperative histopathologic examination of the resected specimen revealed ectopic pancreatic tissue consisting of acini, islet cells, and pancreatic ducts, adjacent to the jejunal serosa (Figure 3). There was no evidence of malignant change in the ectopic pancreatic tissue. The pathologic diagnosis was MHP.

The patient's postoperative course was uneventful, and she was discharged on postoperative day 8. Follow-up of the patient by abdominal ultrasonography for 12 mo postoperatively showed no evidence of relapse.

DISCUSSION

HP was first described by Jean Schultz in 1727, which is a congenital anomaly defined as pancreatic tissue that is anatomically separate from the main gland, without vascular or ductal continuity. No more than ten cases of MHP have been described in the medical literature[6-12]. Including our case, only four cases of pediatric MHP have been reported in the medical literature[6,7,9], with patients ranging in age from 12 to 15 years.

The embryologic basis of HP is controversial, but the most widely held theory is the misplacement theory (Figure 4), according to which, deposits of pancreatic tissue are "dropped" into the developing gastrointestinal system, in anatomic isolation from the main body of the pancreas[11,13]. This theory accounts for the fact that heterotopic pancreatic tissue was mostly located in the upper gastrointestinal tract near the pancreas (derivatives of the primitive foregut).

HP is well differentiated and cannot be distinguished histologically from orthotopic pancreas[1]. Gross specimens always show a firm intramural mass that has a lobular shape and a well-defined interface with surrounding tissues[14]. Most lesions (80%) are solitary and smaller than 3 cm, but they can range in size from 0.2 cm to 5.0 cm[14,15]. The first and most common histological type of heterotopic pancreatic tissue is composed of all the elements of the normal pancreas,

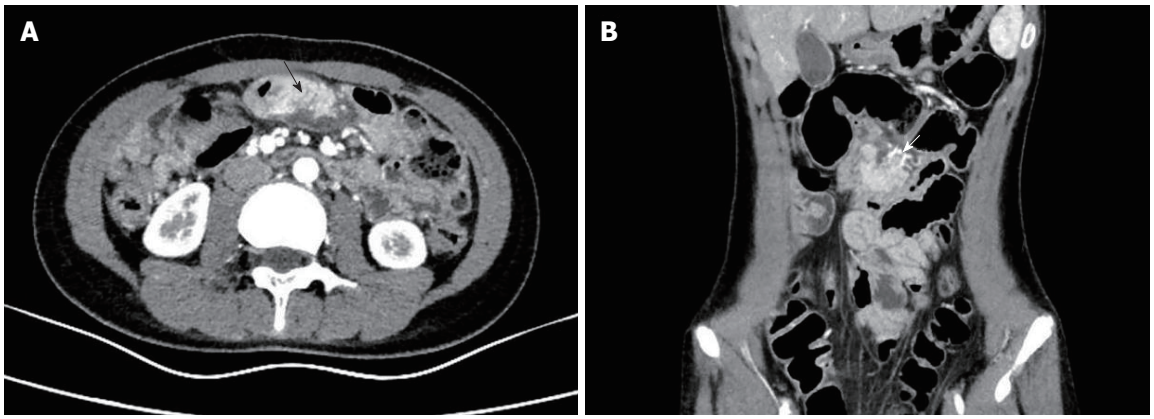

Figure 1 Contrast-enhanced computed tomography images of the abdomen. A: Axial contrast-enhanced computed tomography (CECT) image of the abdomen showing an enhanced oval, soft-tissue mass in the jejunal mesentery at the level of the umbilicus (black arrow); B: Coronal CECT image showing that the mass had its own blood supply (white arrow).

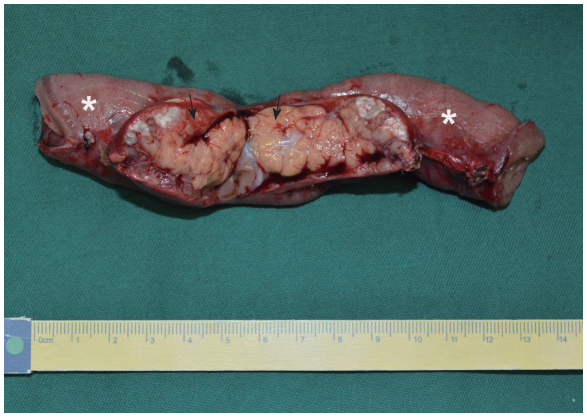

Figure 2 Photograph of the resected mass and the adjacent small bowel. Photograph of the gross specimen demonstrates a 4 cm × 3 cm, yellowish, soft-tissue mass (black arrows) located in the jejunal mesentery and adhered to the serosal surface of the jejunum (white asterisks).

including the acini, ducts, and islet cells[16]. However, not all three of these components were identified in a single case. The morphologic feature of MHP closely resembles that of the orthotopic pancreas and manifests as a homogeneous, well-enhanced, and elongated mass with pancreas-like clefts or lobulations[17].

Uncomplicated HP is typically asymptomatic, which is always discovered incidentally during surgery, imaging examination, or autopsy. Any complication that can occur in the orthotopic pancreas can also occur in HP. Associated complications include pancreatitis, pseudocyst formation, abnormal hormone secretion, bowel obstruction, common bile duct obstruction, gastrointestinal bleeding, intussusception, and malignant degeneration[3,4,18-20]. Depending on its location and size, and involvement of the overlying mucosa, HP can cause symptoms. The most common findings were abdominal pain, abdominal distension, nausea and vomiting, malaise, anorexia, anemia, body weight loss, jaundice, and upper gastrointestinal bleeding according to the study by Zhang *et al*[1].

Because of its rarity and nonspecific clinical manifestation, accurate preoperative diagnosis of HP remains difficult[5,21]. The definitive diagnosis has been always achieved after postoperative pathology. CECT and magnetic resonance imaging (MRI) may demonstrate the lesion that enhances similarly to the orthotopic pancreas[22-26]. The most common CT manifestation of HP is a small intramural and endoluminal mass with microlobulated margins[22]. On an MRI scan, HP is isointense to the orthotopic pancreas, with characteristic T1-weighted high signal intensity and early avid enhancement after the administration of intravenous contrast material[17,22], which is particularly helpful for differentiating HP from other lesions. Heterotopic pancreatic tissue has a rudimentary ductal system. The existence of a central duct along the long axis of the mass is another key finding for the diagnosis of HP[8,17,22]. Sometimes the duct can be confirmed as draining into the fourth portion of the duodenum by magnetic resonance cholangiopancreatography[8]. Knowledge of the characteristic imaging appearance of MHP is key to confirming the diagnosis preoperatively. First, as with HP in other locations, MHP has morphologic and enhancement characteristics similar to the orthotopic pancreas, named "another pancreas in the mesentery"[17,22]. Second, the mean long axis diameter/short axis diameter ratio of MHP was much greater than that of gastric HP (3.0 *vs* 1.4-1.5)[17]. Third, a duct-like structure paralleling the long axis of MHP is seen more frequently than HP in other locations[17].

MHP should be considered in the differential diagnosis. A gastrointestinal stromal tumor, carcinoid tumor, lymphoma, and metastasis can manifest as a homogeneous and well-enhanced soft tissue mass located in the mesentery, and the enhancement pattern is unreliable to differentiate from MHP on an enhanced CT scan[17]. Because of the potential serious complications and malignant change, local excision of MHP is the

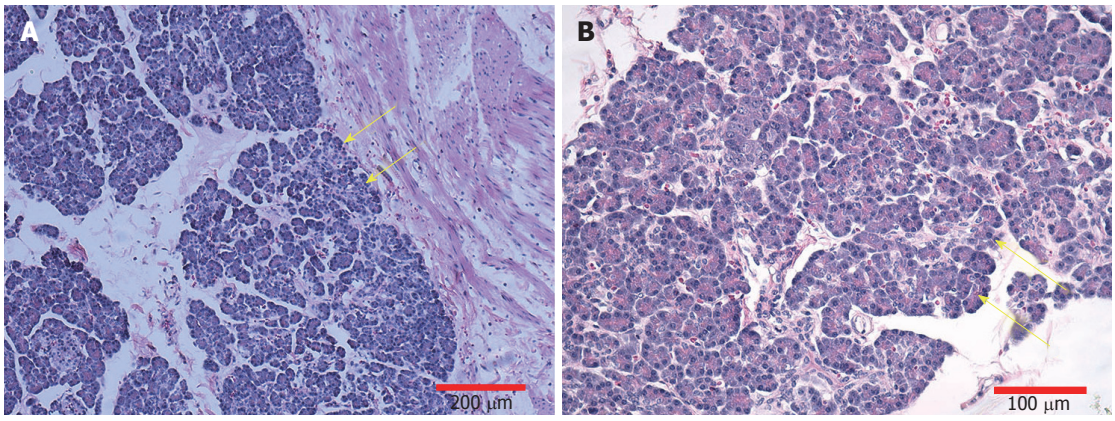

Figure 3 Histopathologic examination of the resected specimen. Microscopic appearance showing that the lesion consisted of heterotopic pancreatic tissue (yellow arrows), including acini, islet cells, and pancreatic ducts, extending to the jejunal serosa (H and E staining; A: Magnification, × 100, scale bar = 200 μm; B: Magnification, × 200, scale bar = 100 μm).

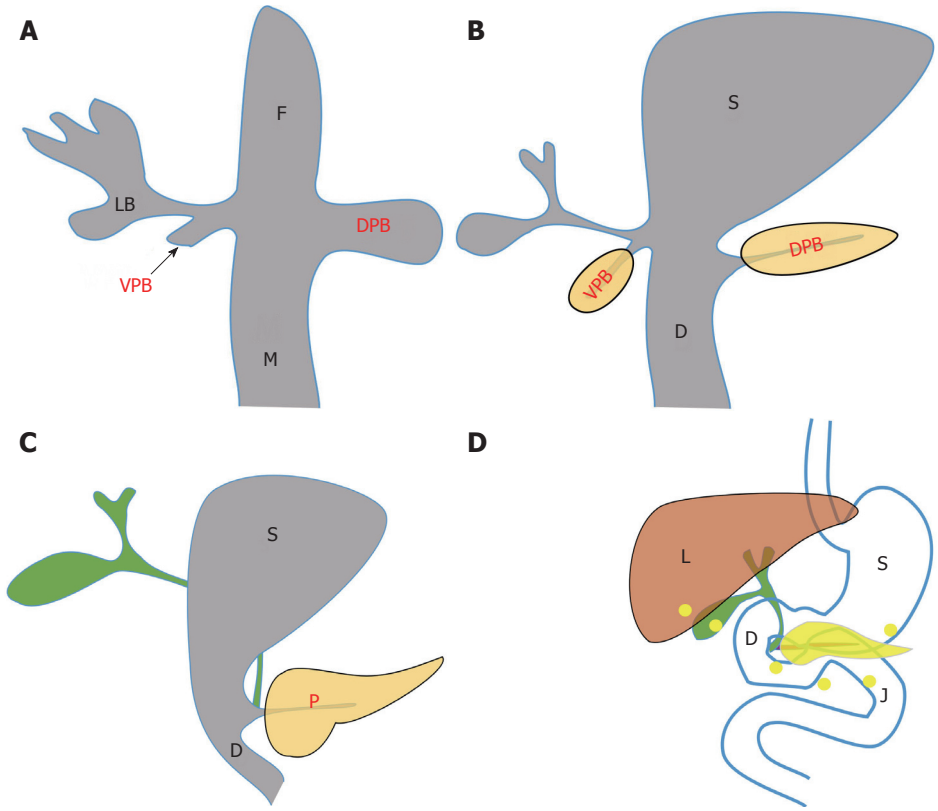

Figure 4 Schematic diagram of the "misplacement theory". A, B: The pancreas develops from the ventral and dorsal pancreatic buds, which develop at the junction of the foregut and midgut during the 4th week of gestation; C: As the foregut elongates, the developing ventral pancreas, gallbladder, and bile duct rotate clockwise posterior to the duodenum and join the dorsal pancreas in the retroperitoneum. The ventral pancreatic bud rotates clockwise and fuses with the dorsal bud at the 7th week of gestation; D: According to the misplacement theory, deposits of pancreatic tissue are "dropped" into the developing gastrointestinal system during rotation of the foregut when fragments of pancreas become separated and develop into mature elements. Yellow points in D indicate possible locations of heterotopic pancreas. F: Foregut; M: Midgut; VPB: Ventral pancreatic bud; DPB: Dorsal pancreatic bud; LB: Liver bud; S: Stomach; D: Duodenum; P: Pancreas; L: Liver; J: Jejunum.

optimal treatment[2,26].

We list the cases of MHP in medical literature (Table 1) and found some characteristics of MHP. First, MHP was not seen in children younger than 10 years old. Of the eight cases of MHP, 50% (4/8) were teenagers aged from 12 to 15 years old, 50% (4/8) were adults aged from 38 to 75 years old. Second, there is a female preponderance (75%, 6/8) of MHP, which is opposite to the male preponderance of HP. Third, the majority of MHP (75%, 6/8) were located in jejunal mesentery. Fourth, CECT and MRCP were the most useful diagnostic method for MHP. These characteristics can be applied in

Table 1 List of cases of mesenteric heterotopic pancreas in medical literature

Ref.	Age (yr)	Sex	Clinical manifestation	Location	Imaging features	Operation
[6]	15	F	Right upper quadrant pain; Diffuse abdominal tenderness, most pronounced in the right upper quadrant and nonspecific guarding	Jejunal mesentery	CECT: A 3.3 cm × 2.3 cm soft tissue mass in the mesentery, with morphology and homogeneous enhancement characteristics similar to the pancreas	A 3 cm mass in the jejunal mesentery, adjacent to the transverse colon and omentum The mass and the adjacent small bowel were resected
[7]	12	M	Periumbilical abdominal pain, nausea and vomiting; Temperature of 100 °F A rigid abdomen with absence of bowel sounds	Jejunal mesentery	No imaging examination	A purulent node (1.5 cm × 1 cm × 0.7 cm) with fibrinous exudate at the base of the midjejunal mesentary This node was excised
[8]	57	F	Pain in the right side of the back, nausea, a similar episode of pain approximately 1 mo before Mild, generalized abdominal tenderness and nonspecific guarding	Small bowel mesentery	CECT: A 3.7 cm × 1.7 cm soft tissue mass in the mesentery, enhancement similar to the pancreas MRCP: A duct within the mesenteric mass, draining into the fourth portion of the duodenum	Treated conservatively
[9]	15	F	Abdominal pain of recent onset and abdominal distention of several years of duration A large tumor filling the left hypochondrium	Mesocolon	CT: A hypodense, intraperitoneal, circumscribed mass dislocating the spleen and left kidney	A spherical, encapsulated tumor mass (210 mm in the largest diameter) in the mesocolon Resection of the mass with a segment of transverse colon
[10]	75	F	Acute periumbilical pain, nausea and vomiting Acute abdomen with peritoneal irritation findings	Jejunal mesentery	US: Cholelithiasis and gallbladder wall thickening US before the surgery: An abdominal tumoral mass, pseudokidney image, originating from the intestine or mesentery	An inflammatory mass in the mesentery, 15 cm × 8 cm × 5 cm A great portion of the inflammatory mass was excised, and cholecystectomy
[11]	38	M	One episode of syncope, 2-d history of melena The heart rate was 96 beats/min; no abdominal tenderness	Jejunal mesentery	CECT: An elongated soft tissue mass in the jejunal mesentery, attenuation similar to orthotopic pancreas and extended to the periduodenal fat plane	A soft-tissue mass 20 cm in diameter in the jejunal mesentery, infiltrating the adjacent jejunal wall The lesion was excised with part of the adjacent jejunum
[12]	67	F	Postprandial epigastric stabbing pain, nausea and vomiting. Similar episodes had recurred over the past 30 yr Past medical history: A laparoscopic cholecystectomy; Tenderness of epigastrium	Jejunal mesentery	CECT: A mass in the mesentery. A small ductal structure in the mass, communicating with the adjacent jejunal loop MRCP: A mass in the mesentery isointense to the native pancreas, with a small duct draining into a proximal jejunal loop	A mass (6.5 cm × 2.5 cm × 1.6 cm indurated teardrop-shaped) mass in the jejunal mesentery The mass with the overlying adherent jejunum was resected
This study	12	F	Intermittent vomiting and abdominal pain Abdominal tenderness with peritoneal irritation	Jejunal mesentery	US: A well-defined, heterogeneous, medially echoic, 4.9 cm × 2.6 cm mass at the margin of the mesentery CECT: An enhanced oval, soft tissue mass (42 cm × 25 mm) in the mesentery	A yellowish, soft-tissue mass 4 cm in diameter in the mesentery, adhered to the serosa of the jejunum The mass and the adjacent small bowel were resected

CECT: Contrast-enhanced computed tomography; CT: Computed tomography; MRCP: Magnetic resonance cholangiopancreatography; US: Ultrasonography.

clinical diagnosis of MHP.

In conclusion, MHP is very rare and an unusual cause of acute abdomen in patients older than 12 years. Preoperative diagnosis of MHP is difficult, even in a symptomatic patient. When a mesenteric mass has morphology and enhancement similar to the orthotopic pancreas, MHP should be considered in the differential

diagnosis. Increased awareness and understanding of the imaging characteristics of MHP will aid in correct preoperative diagnosis and appropriate patient management.

ARTICLE HIGHLIGHTS

Case characteristic

A 12-year-old girl with intermittent vomiting and abdominal pain for 3 d.

Clinical diagnosis

Mesenteric mass.

Differential diagnosis

Intestinal duplication cyst, inflammated Meckel's diverticulum, and mesenteric lymphangioma were considered.

Laboratory diagnosis

The laboratory results were unremarkable.

Imaging diagnosis

Contrast-enhanced computed tomography (CECT) of the abdomen showed an enhanced oval, soft-tissue mass (42 mm × 25 mm) in the mesentery at the level of the umbilicus.

Pathological diagnosis

Mesenteric heterotopic pancreas (MHP).

Treatment

Resection of the mass and adjacent small bowel.

Related reports

Two cases of pediatric MHP have been reported in the medical literature from the University of Chicago Medical Center and Boston City Hospital.

Term explanation

Heterotopic pancreas of the mesentery.

Experiences and lessons

This case will contribute to increasing clinicians' awareness and understanding of the imaging features of MHP in order to help in making correct preoperative diagnosis and giving appropriate treatment.

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CASE REPORT

Intralesional and topical glucocorticoids for pretibial myxedema: A case report and review of literature

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Author contributions: All the authors materially participated in this work, read and approved the final manuscript; Zhang F is the first author for this study; Yu XH is the corresponding author supervising this work; Zhang F and Lin XY managed the case and drafted the manuscript; Zhang F, Lin XY, Chen J and Peng SQ performed data analysis and interpretation based on literature review; Yu XH, Shan ZY and Teng WP reviewed the manuscript; Lin XY and Chen J prepared histopathological results; All authors participated sufficiently in the work and take public responsibility for its content.

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Abstract

Pretibial myxedema (PTM), an uncommon manifestation of Graves' disease (GD), is a local autoimmune reaction in the cutaneous tissue. The treatment of PTM is a clinical challenge. We herein report on a patient with PTM who achieved complete remission by multipoint subcutaneous injections of a long-acting glucocorticoid and topical glucocorticoid ointment application for a self-controlled study. A 53-year-old male presented with a history of GD for 3.5 years and a history of PTM for 1.5 years. Physical examination revealed slight exophthalmos, a diffusely enlarged thyroid gland, and PTM of both lower extremities. One milliliter of triamcinolone acetonide (40 mg) was mixed well with 9 mL of 2% lidocaine in a 10 mL syringe. Multipoint intralesional injections into the skin lesions of the right lower extremity were conducted with 0.5 mL of the premixed solution. A halometasone ointment was used once daily for PTM of the left lower extremity until the PTM had remitted completely. The patient's PTM achieved complete remission in both legs after

an approximately 5-mo period of therpy that included triamcinolone injections once a week for 8 wk and then once a month for 2 mo for the right lower extremity and halometasone ointment application once daily for 8 wk and then once 3-5 d for 2 mo for the left lower extremity. The total dosage of triamcinolone acetonide for the right leg was 200 mg. Our experience with this patient suggests that multipoint subcutaneous injections of a long-acting glucocorticoid and topical glucocorticoid ointment application are safe, effective, and convenient treatments. However, the topical application of a glucocorticoid ointment is a more convenient treatment for patients with PTM.

Key words: Intralesional injection; Pretibial myxedema; Glucocorticoid; Halometasone; Triamcinolone acetonide; Case report

Core tip: Pretibial myxedema (PTM) is an extrathyroidal, dermatological manifestation of Graves' disease. And PTM may be associated with autoimmunity. Local glucocorticoid therapy is the most common and effective option for PTM. However, any difference in efficacy between the external use of a glucocorticoid ointment and intralesional glucocorticoid is unclarified. Our experience with this patient suggests that multipoint subcutaneous injections of a long-acting glucocorticoid and topical glucocorticoid ointment application are safe, effective, and convenient treatments. However, the topical application of a glucocorticoid ointment is a more convenient treatment for patients with PTM.

Zhang F, Lin XY, Chen J, Peng SQ, Shan ZY, Teng WP, Yu XH. Intralesional and topical glucocorticoids for pretibial myxedema: A case report and review of literature. *World J Clin Cases* 2018; 6(14): 854-861 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/854.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.854

INTRODUCTION

Pretibial myxedema (PTM) is an extrathyroidal, dermatological manifestation of Graves' disease (GD). Recent research on the pathogenesis of PTM has shown that PTM may be associated with autoimmunity. The presence of thyroid-stimulating hormone (TSH) receptors in fibroblasts of the skin may play a major role in the pathogenesis of PTM. In general, PTM is self-limited and asymptomatic; however, advanced cases may cause cosmetic or functional problems. Local glucocorticoid therapy is the most common and effective option for PTM. However, any difference in efficacy between the external use of a glucocorticoid ointment and intralesional glucocorticoid is unclarified. Therefore, we report on a patient with PTM who underwent multipoint subcutaneous injections of a long-acting glucocorticoid (triamcinolone) and topical application of a glucocorticoid ointment for the two legs.

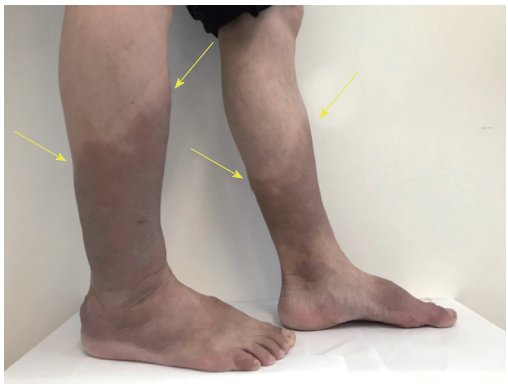

Figure 1 The patient's lower extremities presented pretibial myxedema before therapy. The bilateral pretibial and ankle skin was thickened with a hard texture, uneven surface, and non-pitting edema (yellow arrow).

CASE REPORT

Medical history

A 53-year-old man visited our clinic for fatigue, irritability, and weight loss for 3.5 years and PTM for 1.5 years. Three and a half years before, he had felt weak and had excessive sweating, palpitations, and a weight loss of 10 kg. One month later, he saw a doctor at a local hospital. His thyroid function showed a decreased TSH level and an elevated free triiodothyronine (FT3) level. His serum thyrotropin receptor antibody (TRAb) level was more than 40 IU/L (reference interval for TRAb: 0-1.75 IU/L). He was diagnosed with hyperthyroidism and prescribed methimazole 15 mg once daily. However, the patient did not take the drug regularly. One and a half years ago, swollen red areas with a diameter of about 5 cm and clear boundaries and a slightly tougher texture - but without itching - were found above both ankles. He was diagnosed at the local hospital as having PTM and prescribed halometasone 1 g twice a day and oral tripterygium. One week later, the myxedema had improved. He continued treatment for 2 wk but after discontinuing the halometasone ointment, the myxedema relapsed and was accompanied by occasional acupuncture-like pain. Later, he gave up treatment for 16 mo until he came to our hospital.

Physical examination

The patient presented with eyelid edema, slight exophthalmos, and a diffusely enlarged thyroid gland (grade Ⅱ-Ⅲ). The bilateral pretibial and ankle skin was thickened with a hard texture, uneven surface, and non-pitting edema (Figure 1).

Laboratory examination and diagnosis

The results of thyroid function showed a decreased TSH level (0.0014 mIU/L; reference interval: 0.35-4.94

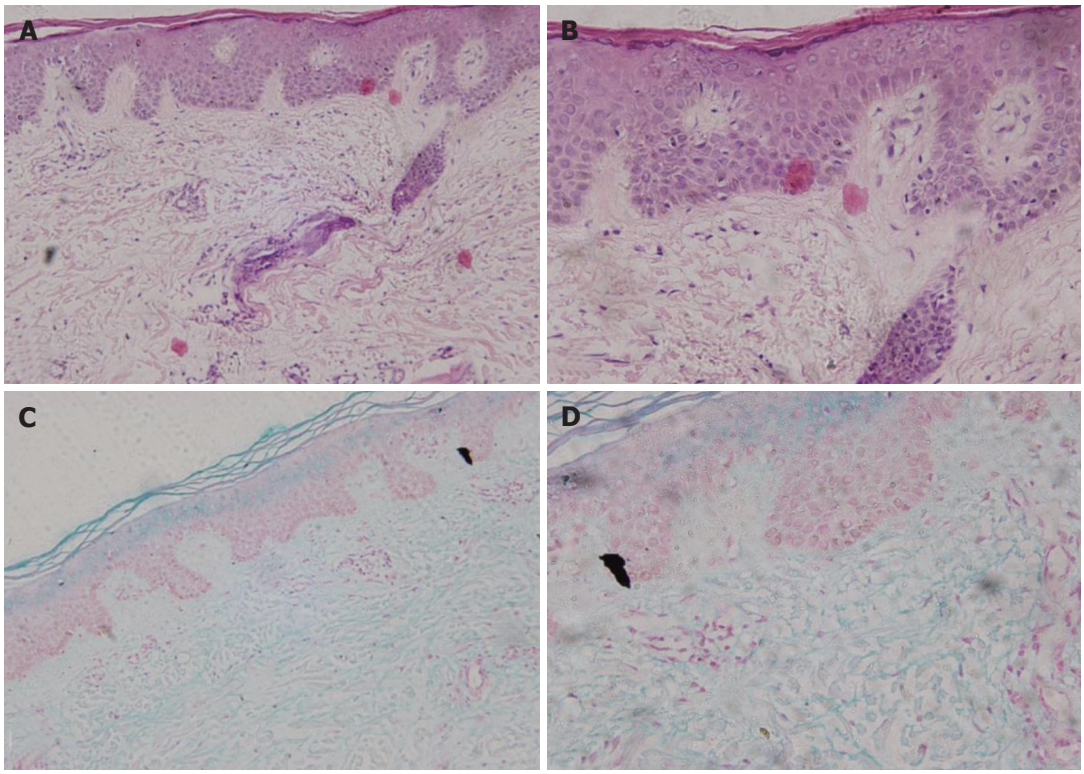

Figure 2 Pathology of pretibial skin. A and B: The biopsy specimens showed hyperkeratosis of squamous epithelium and perivascular inflammatory cell infiltration under hematoxylin and eosin staining; C and D: Alcian blue staining showing mucin-like substances deposited between collagens and the widened gaps of the collagenous fibers (A: HE staining, × 20; B: HE staining, × 40; C: alcian blue staining, × 20; D: alcian blue staining, × 40).

mIU/L), an increased FT3 level (7.27 pmol/L; reference interval: 2.63-5.7 pmol/L), and a normal free thyroxine (FT4) level (13.46 pmol/L; reference interval: 9.01-19.05 pmol/L). The titers of thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb), and TRAb were 1.73 IU/mL (reference interval: 0-4.11 IU/mL), 164.33 IU/mL (reference interval: 0-5.61 IU/mL) and > 40 IU/L (reference interval: 0-1.75 IU/L), respectively. A biopsy of the pretibial skin showed a large amount of deposited mucin-like substances between the collagen and the gaps among the collagenous fibers were widened. Moreover, hyperkeratosis of squamous epithelium and perivascular inflammatory cell infiltration were found (Figure 2). All of these findings supported the diagnosis of PTM.

An X-ray scan indicated a periosteal reaction in the phalangeal bone of the index finger of the left hand (Figure 3A). Finally, the patient was diagnosed as GD, exophthalmos, PTM, and hypertrophic osteoarthropathy (EMO) syndrome.

A computed tomography scan of the eye socket showed that the bilateral extraocular muscles were slightly thickened and both eyeballs were slightly extruded (Figure 3B).

Treatment

Intradermal injections of triamcinolone acetonide were used for PTM of the right lower extremity. The injections were once a week for 8 wk and then once a month for 2 mo. For each treatment, 2% lidocaine was used to dilute triamcinolone acetonide. The concentration of triamcinolone acetonide was 4 mg/mL. Ten injection points were used along the upper border of the skin lesions and 0.5 mL of diluted triamcinolone was injected at each point using a 1-mL syringe. A halometasone ointment was used once a day for PTM of the left lower extremity. After the first injection series, the range of the lesions of the right leg narrowed by about 1.5–2 cm; no significant change occurred on the left leg. After the second injection series, the scope and thickness of the swelling shrunk markedly in both legs. After the third injection series, the fringe skin of the lesions became soft and thin, similar to the normal skin. With treatment, the thickness of the lesions of both lower extremities was significantly reduced and eventually returned to the same thickness as that of normal skin. The color of the skin gradually lightened. Eight weeks after the injection therapy, scabs occurred around the border of the lesion on the right leg and then fell off on their own. The new skin showed a pink color, which was not obvious on the left leg. Five months later, the swelling of both lower extremities had disappeared and the thickness of the skin had returned to normal. However, little pigmentation was present. The total dose of triamcinolone acetonide used for the right leg was 200 mg. Complete remission of PTM was achieved in both lower extremities. No side effects from the glucocorticoid were found in this patient.

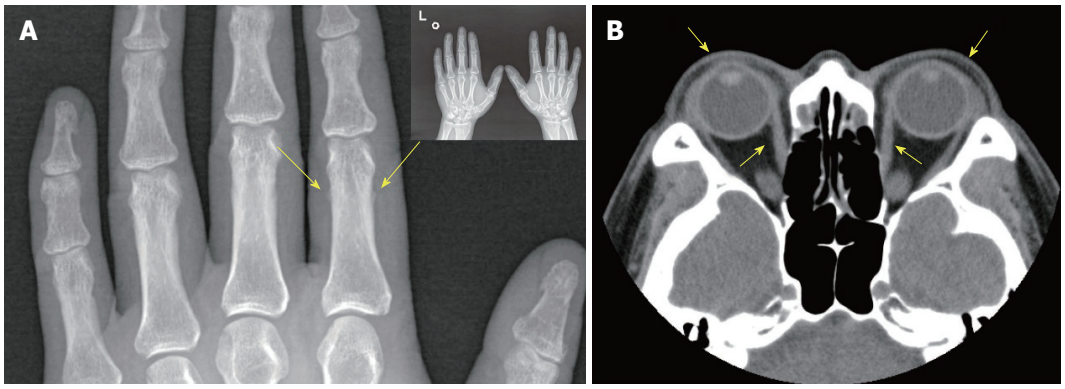

Figure 3 Imaging results of hands and eye socket. A: X-ray scan showing the periosteal reaction in the phalangeal bone of the index finger of the left hand; B: Computed tomography scan of the eye socket showing that the bilateral extraocular muscles were slightly thickened and that both eyeballs extruded slightly.

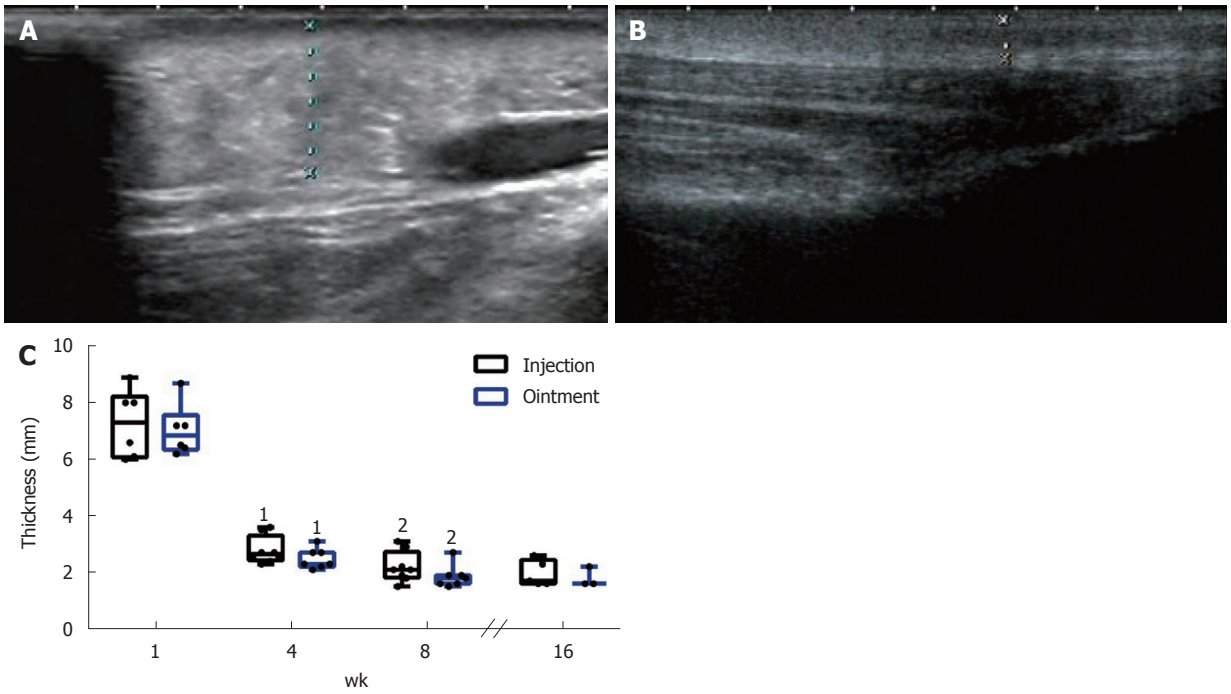

Figure 4 Ultrasound assessment of the pretibial skin area in pretibial myxedema. A: The pretibial skin of the patient; B: The pretibial skin of the patient at 4 mo after the first injection. The pretibial skin of the patient at baseline (A) was obviously thicker than that at 4 mo after the first injection (B); C: The comparison of skin lesion thickness. [1]Compared with baseline in the same leg; [2]Compared with 4 wk after treatment in the same leg.

Results

Ultrasound can be a good option for assessing PTM lesion thickness[1]. The thickened skin of this patient before the specific treatment was 7.27 ± 1.20 mm (right) and 7.03 ± 0.92 mm (left) (Figure 4A). The thickened skin of the lesions after treatment was 1.96 ± 0.46 mm (right) and 1.80 ± 0.35 mm (left) (Figure 4B). We found that compared to before treatment, the thickness of the skin lesions was significantly different after 4 wk of treatment. Significant differences were also observed in the skin thickness in both legs between 4 wk and 8 wk after treatment (Figure 4C).

The patient had been prescribed methimazole 30 mg daily for hyperthyroidism at the beginning of the treatment for PTM. The changes in thyroid function are interesting (Figure 5). During the first month of treatment, the levels of FT3, FT4, TPOAb, and TgAb were increased and TSH was decreased. Thereafter, FT3, FT4, TPOAb, and TgAb declined while TSH levels rose gradually. However, TRAb was always greater than 40 IU/L.

Seven months after the end of treatment, we followed the patient and found that pretibial skin of both legs was not swelling and lighter in color. No recurrence of PTM was observed.

Conclusion

Our experience with this patient has shown that multiple subcutaneous injections of a long-acting glucocorticoid and topical glucocorticoid ointment application had

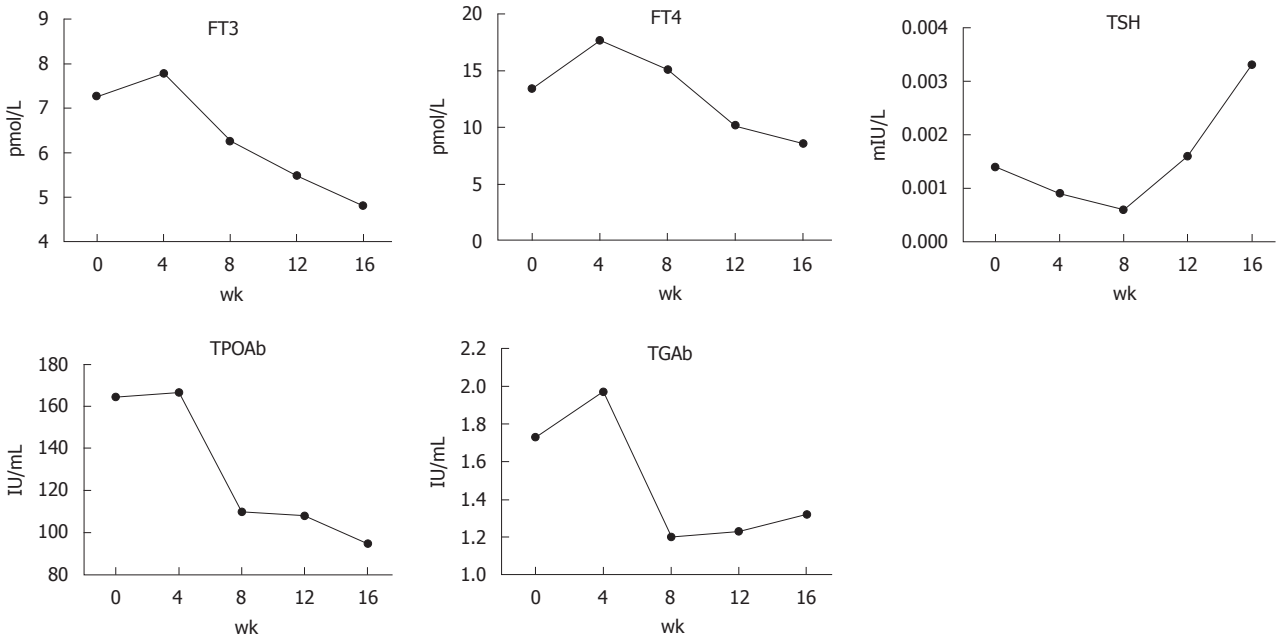

Figure 5 Increase in the levels of FT3, FT4, TPOAb, and TgAb and decrease in TSH during the first month after treatment. Thereafter, FT3, FT4, TPOAb, and TgAb declined and TSH levels rose gradually.

similar efficacy for skin lesions in PTM patients with diffuse swelling and a medical history of no more than 2 years. However, the application of a glucocorticosteroid ointment was more convenient, and the patient had no obvious discomfort. These made the patient have better compliance. The patient can apply the treatment at home according to the doctor's advice and avoid frequent entry into the hospital. Therefore, the topical application of a glucocorticoid ointment is safe and effective, and is a convenient treatment for patients with PTM.

DISCUSSION

PTM is an important autoimmune manifestation of GD. Although it is usually located in the pretibial area, it can involve the arms, back, and even the face. Therefore, it should be called localized myxedema or thyroid dermopathy. The prevalence of PTM is 1.6% in thyroid disease, 0.5%–4% in GD, and 15% in severe Graves' ophthalmopathy (GO). However, 97% of PTM patients are associated with GO[2] and 20% are associated with acropachy[3]. Myxedema can occur as a component of the triad of exophthalmos, myxedema, and osteoarthrosis (EMO syndrome), which is a rare disease and whose prevalence is < 1% in autoimmune thyroid disease[4]. The symptoms of EMO tend to occur in chronological order with the onset of eye disease followed by myxedema and then eventually osteoarthrosis or clubbing on long-term duration[5-7]. Clinically, myxedema presents as non-punctate, nodular, or plaque-like edema. In severe cases, skin disease may develop into elephantiasis. Histologically, the tissue shows extensive space between collagen bundles under hematoxylin and eosin staining and accumulation of polysaccharide acid between collagen bundles in the dermis layer under alcian blue staining. The pathogenesis of PTM is unclear but there appears to be interactions of immunologic, cellular, and mechanical processes. TSH receptors in fibroblasts can be attacked by TRAbs, inducing immune activation that is mediated by T lymphocytes[8].

Treatments for PTM include managing the risk factors and thyroid dysfunction and using specific therapy for local dermopathy. Local glucocorticoid application to PTM has been the most effective therapeutic option. Lan *et al*[9] have treated PTM using an intralesional glucocorticoid - triamcinolone acetonide acetate - at a concentration of 50 mg/5 mL and the total dose was no more than 100 mg at each session in a patient. Intralesional injection was once every 3 d (regimen 1) or once every 7 d (regimen 2) in PTM patients. Seven injection sessions were considered as a therapy course. Two-thirds of the patients in each regimen remitted completely at the 3.5-year follow-up. However, patients following regimen 1 presented with more adverse effects. The conclusions of this article indicate that early treatment of PTM with glucocorticoids is necessary to achieve a complete response. Dosage and frequency of the intralesional steroid injections and the lesion variants influence the efficacy of PTM. Once every seven days is a better regimen. Lan *et al*[10] also performed a retrospective study. An intralesional glucocorticoid was used and the dosage of triamcinolone acetonide acetate was 50 mg/5 mL. In protocol 1, glucocorticoid was used once a week and treatment was administered until the swollen lesions had disappeared. In protocol 2, glucocorticoid was used once a week for 8 wk and

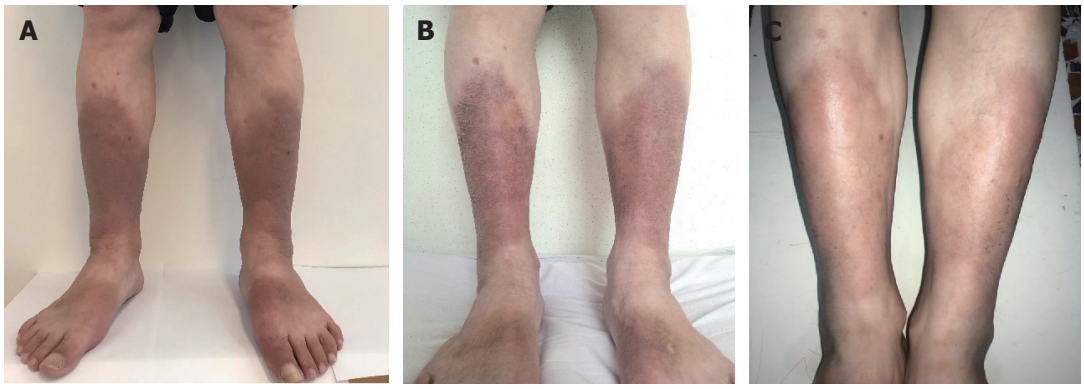

Figure 6 The contrast in the presentation of pretibial myxedema before and after glucocorticoid therapy. A: Pretibial myxedema at baseline; B: Four months after the initiation of local glucocorticoid treatment; C: Seven months after the end of treatment. Compared with baseline (A), pretibial myxedema remitted completely 4 mo after the initiation of local glucocorticoid treatment (B). Seven months after the end of treatment, no recurrence of pretibial myxedema was observed (C).

then once a month for 6 mo. Protocol 1 was used for patients with nodular, plaque, and diffusely swollen variants; all patients had a complete response. Protocol 2 was used for patients with an elephantiasis variant; 26.7% of the patients had a complete response and 73.3% had a partial response. The two protocols were both effective. Sendhil Kumaran *et al*[11] reported local glucocorticoid application for PTM with different routes of administration. In his research, a topical clobetasol propionate (0.05%) was applied twice daily under occlusion for 18 patients with plaque-type PTM and a disease duration greater than 3 years. An initial improvement in the form of reduced plaque thickness was observed in 14 patients by 6 mo. Takasu *et al*[12] applied a topical steroid ointment with sealing cover for PTM patients. He found that this option was effective in patients with several months of the appearance of PTM and ineffective in patients with 5-10 years of the appearance of PTM. The results from several other studies seemingly indicate that intralesional glucocorticoid is a better option. Schwartz *et al*[13] reported that topical subcutaneous injections were more effective than glucocorticoid-oppressive dressings. The response rate to local injections was 27.3%, which was higher than that of topical glucocorticoid daubing or compression dressings. Deng *et al*[14] reported that the use of intralesional corticoids had positive results with a shorter treatment time. Vannucchi *et al*[15] reported that treatment of PTM with dexamethazone injected subcutaneously with mesotherapy needles. One month after treatment, all patients showed improvement of PTM at clinical assessment and reduction of the thickness of the lesions at ultrasound, involving mostly the dermis. Ren *et al*[16] researched that whether a premixed corticosteroid, compound betamethasone, could enhance remission rate and decrease recurrence rate in patients with PTM. They considered that compound betamethasone with multipoint intralesional injection is a feasible, effective, and secure novel strategy in the treatment of PTM. However, we cannot evaluate the precise difference in the effects of local glucocorticoids among the different administration routes because of different clinical phenotypes, doses, and frequencies of glucocorticoid in the articles related to treatment for PTM[8-11,14,15,17].

As we know, higher-dose glucocorticoids can cause obvious side effects, such as hyperglycemia, hypertension, and Cushing syndrome. Therefore, we should choose a safe, minimal dose that can achieve therapeutic goals in patients. In this study, we treated the PTM patient by multipoint subcutaneous injections of triamcinolone at a low dose and by topical application of a glucocorticoid ointment in order to compare the effects of the two therapies.

One and a half years ago, the patient had applied a halometasone ointment to treat the PTM in both his legs. The lesions improved within two weeks. However, it relapsed one week after discontinuing the halometasone. The skin of the lesions then thickened diffusely and gradually turned dark brown. After the application of multipoint subcutaneous injections of triamcinolone to the right lower extremity and the topical application of a glucocorticoid ointment for the left lower extremity, the thickness of the skin lesions diminished gradually. The changes in the thickness of the skin were similar between the two legs. In addition, the color of both lower extremities became lighter. Before treatment, the skin lesions were dark brown. During the course of treatment, the color gradually turned red and eventually yellow, similar to the normal color of the skin (Figure 6). The color of the right lower extremity with the intralesional glucocorticoid changed faster than that of the left lower extremity with halometasone ointment. After treatment, the side with the injections was preferred to peeling, and the new skin was not different from normal skin. The numbness in the patient's legs and the acupuncture-like sensation improved during the course of treatment and completely remitted after the treatment. There were no obvious differences in the changes between the two legs except the color.

In terms of dose, we controlled the dose of the intralesional triamcinolone precisely and calculated

the equivalent dose for the halometasone ointment. Therefore, we believe that the bilateral lower extremities received consistent doses of glucocorticoid. Judging from the current treatment results, it is not difficult to find that the effect of the intralesional glucocorticoid was equivalent to the application of glucocorticoid ointment. However, the use of intralesional corticoids has recently been demonstrated to have positive results with shorter treatment times[14]. This is different from our results and we speculate that intralesional glucocorticoids have a higher absorption rate and may enter the capillaries after the injection, which could lead to systemic reactions. Thus, the local injections of a glucocorticoid in the unilateral leg could have interfered with the other side. Therefore, randomized controlled trials are needed to evaluate the differences in the efficacy between intralesional glucocorticoids and glucocorticoid ointments for the treatment of PTM.

The change in thyroid function in this patient is interesting. Before PTM treatment, the TSH levels and FT3 levels were always abnormal. However, after PTM treatment, FT3 levels decreased gradually and were normal by the end of PTM treatment, although TSH was still at a low level with a slightly increasing trend. This may be explained by the following two possible causes. First, enough dosage of methimazole (30 mg daily) and regular administration may promote the improvement of thyroid function. Second, the immunosuppressive effects of glucocorticoids may inhibit TRAb and indirectly improve thyroid function. However, due to the limitation in the TRAb detection limit, we could not assess specific changes in TRAb titers; therefore, we could not confirm our speculation.

Limitations

This article has the following limitations. First, due to the limitation in the detection limit of TRAb, we were unable to detect its precise change process. Second, a prolonged follow-up period is needed to evaluate the subsequent effects of PTM treatment. Third, this study was a self-controlled trial with a single individual. The bilateral treatment of both legs may have interfered with each other. Therefore, a large randomized controlled trial should be conducted to explore in detail the exact therapeutic effects of the two options for PTM treatment.

ARTICLE HIGHLIGHTS

Case characteristics

A 53-year-old man was diagnosed with hyperthyroidism. Swollen red areas with a diameter of about 5 cm and clear boundaries and a slightly tougher texture - but without itching - were found above both ankles.

Clinical diagnosis

It was clearly diagnosed as pretibial myxedema (PTM).

Laboratory diagnosis

The patient underwent blood tests at our hospital, which indicated Graves' disease (GD).

Imaging diagnosis

The patient underwent an imaging examination at our hospital, which indicated exophthalmos and hypertrophic osteoarthropathy.

Pathological diagnosis

The pathological examination confirmed the diagnosis of PTM.

Treatment

Intradermal injections of triamcinolone acetonide was used for PTM of the right lower extremity. A halometasone ointment was used once a day for PTM of the left lower extremity.

Related reports

The skin lesions treated using radiation therapy were reported in 2014. The lesions remitting 30 d after intralesional infiltration therapy was reported in 2015. One hundred and eleven cases of PTM treated by multipoint subcutaneous injections were reported in 2016. Sendhil Kumaran *et al* reported the treatment of 30 cases of PTM with a glucocorticoid in 2015.

Experiences and lessons

Multipoint subcutaneous injections of a long-acting glucocorticoid and the topical application of a glucocorticoid ointment are both safe and effective, with the latter being a more convenient treatment for PTM in patients with GD.

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CASE REPORT

Octreotide reverses shock due to vasoactive intestinal peptide-secreting adrenal pheochromocytoma: A case report and review of literature

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Abstract

Vasoactive intestinal peptide-producing tumors (VIPoma) usually originate in the pancreas and are characterized by diarrhea, hypokalemia, and achlorhydria (WDHA syndrome). In adults, nonpancreatic VIPoma is very rare. Herein, we report an unusual case of VIP-producing pheochromocytoma marked by persistent shock, flushing, and watery diarrhea and high sensitivity to octreotide. A 53-year-old woman was hospitalized for sudden-onset hypertension with convulsions, which then rapidly evolved to persistent shock, flushing, and watery diarrhea. Abdominal computed tomography indicated a left adrenal mass, accompanied by bleeding; and marked elevations of both plasma catecholamine and VIP concentrations were documented *via* laboratory testing. Surprisingly, all clinical symptoms responded swiftly to octreotide treatment. Once surgically treated, hormonal levels normalized in this patient, and the clinical symptoms dissipated. Postoperative pathological and immunohistopathological studies confirmed a VIP-secreting pheochromocytoma with strong, diffuse positivity for somatostatin receptor type 2. During a 6-mo follow-up period, she seemed in good health and

was symptom-free.

Key words: Pheochromocytoma; Vasoactive intestinal peptide; Octreotide; Shock; Flushing; Diarrhea; Case report

Core tip: Vasoactive intestinal peptide-producing tumors (VIPoma) usually originate in the pancreas. VIP-secreting pheochromocytoma is very rare and most of the related cases reported are characterized by diarrhea, hypokalemia, and gastric acid deficiency (WDHA syndrome). To our knowledge, this is the first reported instance of VIP-secreting pheochromocytoma marked by persistent shock flushing and diarrhea and high sensitivity to octreotide. This case helps to improve the understanding of the pathogenesis, biology, and behavior of VIPoma and pheochromocytoma.

Hu X, Cao W, Zhao M. Octreotide reverses shock due to vasoactive intestinal peptide-secreting adrenal pheochromocytoma: A case report and review of literature. *World J Clin Cases* 2018; 6(14): 862-868 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i14/862.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i14.862

INTRODUCTION

Vasoactive intestinal peptide-producing tumor (VIPoma) is an unusual neuroendocrine tumor that autonomously secretes VIP. In adult, almost all VIPomas (90%) originate from pancreatic tissues whereas the remaining 10% originate from extra-pancreatic tissues, such as the bronchus, colon, liver, and pheochromocytoma[1]. VIP-secreting pheochromocytoma is extremely rare and most of the related cases reported are characterized by diarrhea, hypokalemia, and gastric acid deficiency (WDHA syndrome)[2-4]. In this case, the patient harbored an exceedingly rare adrenal pheochromocytoma, which ultimately ruptured and bled. Its principal manifestations included persistent shock, flushing, and watery diarrhea in the aftermath of sudden-onset hypertension with convulsions. Laboratory diagnostics and immunohistochemical attributes indicated that this pheochromocytoma secreted both catecholamines (CATs) and VIP.

CASE REPORT

A 53-year-old woman was admitted to the local hospital after 1 d of convulsions leading to loss of consciousness. After the attack (approximately 20 min), the patient eventually became conscious. Six months prior, she reported having paroxysmal palpitation attacks (5-20 min each), which spontaneously subsided, and had suffered occasional headaches, without sweating or chest pain. Consequently, medical attention was never sought.

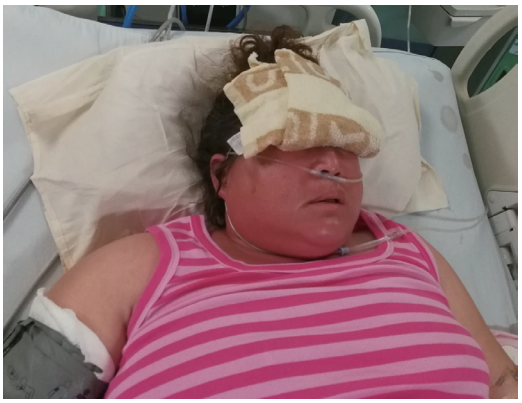

Figure 1 Flushing in the face and neck of the patient.

Computed tomography (CT) of the head showed no abnormalities; but this historically normotensive patient produced a blood pressure (BP) reading of 230/100 mmHg. Nicardipine hydrochloride (3 μg/kg per min; Astellas Pharma Tech Co, Ltd, Tokyo, Japan) was administered for BP control, which was achieved approximately 8 h later (160/90 mmHg), and the convulsions disappeared. However, treatment was withdrawn without rebound effect following a sudden drop in BP (nadir: 53/35 mmHg). She was then transferred to our facility.

At the time of admission, the patient was somnolent but could be aroused and appeared dispirited, evoking a Glasgow coma score of 9 (E, 2; M, 4; V, 3). She presented with watery diarrhea > 10 times/d (total volume, 800-1200 mL/24 h). At a height of 162 cm and a body weight of 82 kg, her baseline vital signs were as follows: BP, 68/44 mmHg; heart rate, 92 bpm; respiratory rate, 18 bpm; and temperature, 36.8 ℃. There was flushing of the face and neck (Figure 1) and sensitivity to percussion in the region of the left kidney. Thyromegaly, rales (neither lung by auscultation), cardiac murmurs, abdominal tenderness, and palpable lumps were not observed.

Laboratory tests showed that hematocrit and hemoglobin were within standard reference ranges and did not deviate significantly in several repeat attempts. Other results were as follows: glucose, 17.2 mmol/L (3.9-6.1); creatinine, 289.9 μmol/L (45-84); troponin I (TnI), 0.14 ng/mL (0.010-0.023); creatine kinase (CK), 230 ng/L (45-145); and CK-MB, 15 ng/L (2.0-7.2). A battery of biochemical tests, including liver function studies, blood gas analysis, blood coagulation indices, and electrolyte (K, Na, Cl, Ca, P, and Mg) levels, returned essentially normal results. The electrocardiogram showed T-wave inversion and slight ST-segment depression (0.1-0.2 mv) in leads V1-V6, Ⅱ, Ⅲ, and AVF. Coronary arteriography confirmed no coronary artery obstruction. By ultrasonic

Table 1 Catecholamines and vasoactive intestinal peptide levels in plasma and urine

	Day 2	Day 5	Post-operation	Reference range
Plasma				
Epinephrine (pg/mL)	547	624	35	< 130
Norepinephrine (pg/mL)	1683	1662	376	150–520
Dopamine (pg/mL)	214982	345	14	< 30
Vasoactive intestinal peptide (pg/mL)	377	126	< 10	< 100
Urine				
Metanephrine (mg/24 h)	2.4	2.3	0.12	0.04–0.19
Normetanephrine (mg/24 h)	3.2	3.4	0.21	0.09–0.37
Vanillylmandelic acid (mg/24 h)	53.8	47.5	2.80	1.4–6.5

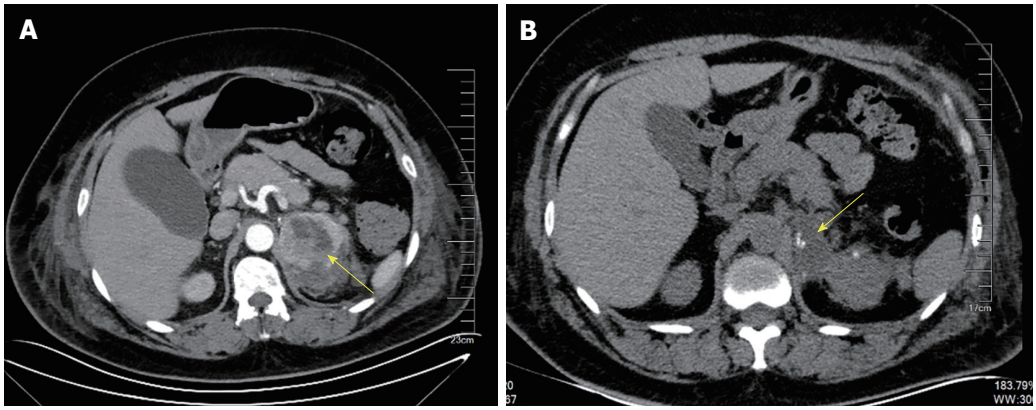

Figure 2 Abdominal computed tomography. A: The arrow indicates a heterogeneous left adrenal mass; B: After operation, the left adrenal mass was removed (arrow) and a small amount of encapsulated effusion remained.

cardiography (UCG), the following parameters were determined: interventricular septal thickness, 10-12 mm; width of posterior left ventricular wall, 10 mm; left ventricular end-diastolic (156 mL) and end-systolic (69 mL) volumes; stroke volume, 87 mL; and ejection fraction, 56%. CT studies of the patient's head and chest were not abnormal, but on the enhanced abdominal CT, a solitary mass of the left adrenal gland was identified, with signs of bleeding (Figure 2). In addition, blood and urinary CAT concentrations and urinary vanillylmandelic acid were significantly elevated (Table 1).

Treatment included copious intravenous fluid replacement (0.9% NaCl, 4000 mL/24 h), with potassium supplementation (KCl, 3-6 g/24 h), and an intravenous dopamine drip (12 μg/kg per min; Shanghai Fenge Pharmaceutical Co, Ltd, Shanghai, China) was initiated. The patient's BP increased slightly in response, with systolic pressures still fluctuating from 80-100 mmHg. There was no mental improvement or resolution of facial and neck flushing, and despite complete solid/liquid fasting, the diarrhea persisted. Besides, we administered the patient with continuous intravenous insulin to keep the blood glucose around 10 mmol/L. We rechecked CK, CK-MB, TnI, and electrocardiogram every 6 h. The patient's myocardial enzymes and TnI levels gradually returned to normal, and the ischemic manifestations on electrocardiogram were also significantly improved. This symptomology was not typical of pheochromocytoma. Given the array of hormones implicated in neuroendocrine tumors, significant elevation of plasma VIP (Table 1) was subsequently verified through additional diagnostics, whereas other substances [plasma pancreatic polypeptide, adrenocorticotropic hormone, somatostatin (SST), thyroid hormones, parathyroid hormone, calcitonin, adrenomedullin, and urine 5-hydroxy indoleacetic acid] remained normal.

To control diarrhea and facial flushing, the patient received intramuscular injections of octreotide (0.1 mg/8 h; Novartis International AG, Basel, Switzerland) on day 3 after admission, followed by a surprisingly rapid rise in BP. After 24 h, the dopamine drip was discontinued, and her BP had reached 123/75 mmHg. The patient's mental state also cleared significantly, and she was more alert; the facial and neck flushing was relieved; and diarrhea was less frequent. On day 5 after admission, she was completely conscious, her facial and neck skin had returned to normal, and the diarrhea had stopped. At this point, she developed paroxysmal hypertension (peak BP: 190/100 mmHg), for which oral terazosin hydrochloride (2 mg/d; Abbott Laboratories, Chicago, IL, United States) was given.

After 20 d, left laparoscopic adrenalectomy was performed. The mass of the left upper kidney and an encapsulated, posteriorly placed hematoma (due to

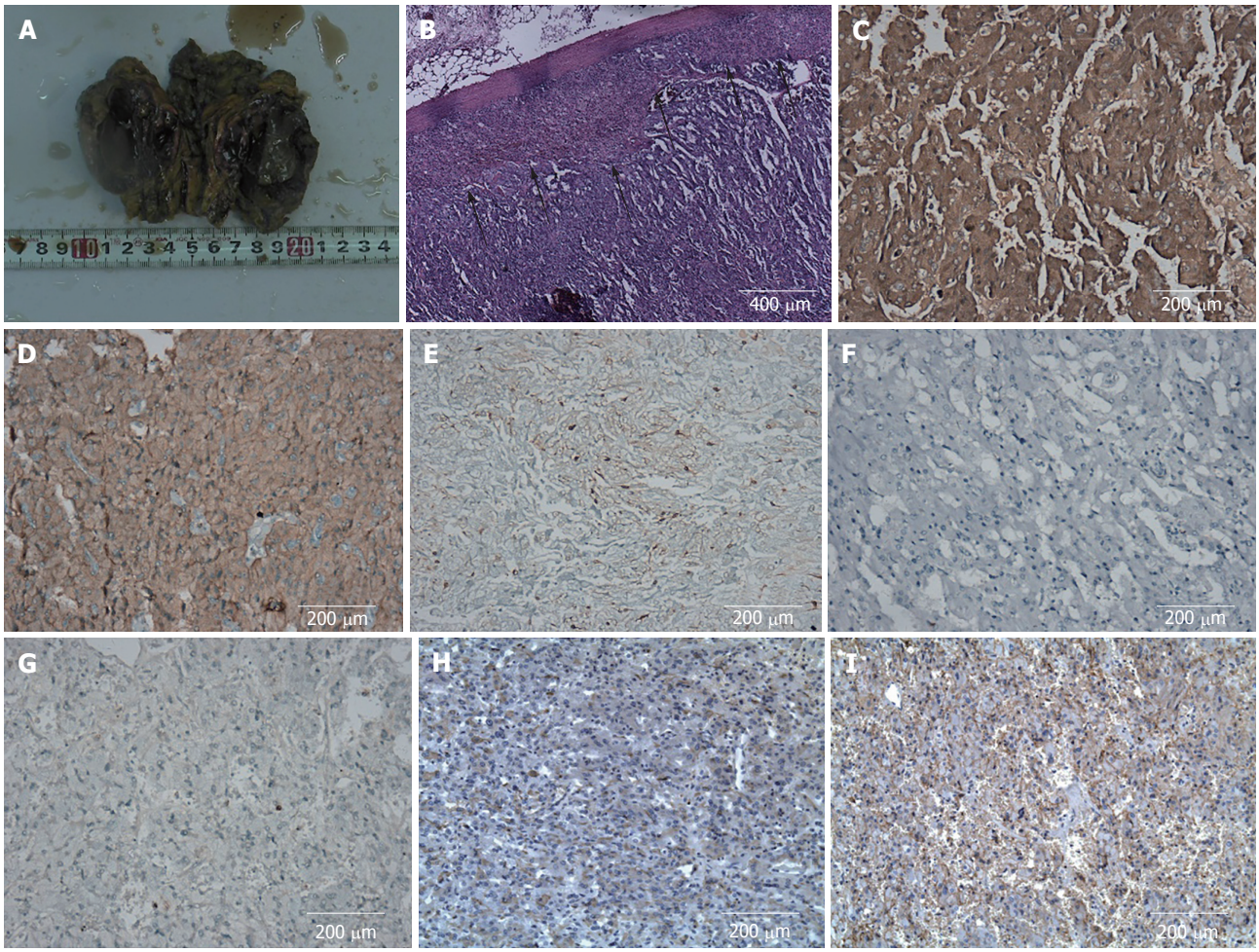

Figure 3 Histopathological and immunohistochemical staining. A: A gross pathological finding of the resected adrenal tumor; B: Hematoxylin-eosin staining of tumor tissue, black arrows indicate the juncture of normal adrenal cortex and tumor tissue; C-I: Immunohistochemical staining for synaptophysin (C), chromogranin A (D), S-100 (E), creatine kinase (F), KI67 (G), vasoactive intestinal peptide (H), and somatostatin receptor 2 (I).

rupture) were located. When dissecting this mass, the patient's BP again climbed to 240/130 mmHg. No other abdominal tumors were discovered, and the right adrenal gland was morphologically normal. The resected mass measured 7 cm × 4.5 cm. On cut section, it was soft and yellow-brown, demonstrating two subcapsular clefts of 2-4 cm (Figure 3A). In histological sections, the tumor cells were nested or arranged in trabecular pattern, with variably sized, pleomorphic nuclei. Their cytoplasm was abundant, showing basophilic or amphophilic stippling. A compressed rim of normal adrenal cortex was retained at the tumor's edge, and there was no obvious intervening septum (Figure 3B).

Immunohistochemical staining properties were as follows: Syn (+), CgA (+), S-100 (+), CK (-), and KI67 (< 5% +) (Figure 3C-G). On this basis, the histopathological diagnosis was adrenal pheochromocytoma. We then pursued immunohistochemical staining for VIP and SST receptor 2 (SSTR2), confirming 60%-70% cytoplasmic VIP positivity of pheochromocytoma cells. No positively stained ganglioneuroma component was evident (Figure 3H). Nearly all tumor cell membranes demonstrated SSTR2 positivity (Figure 3I).

After surgery, the patient discontinued octreotide and terazosin hydrochloride and recovered uneventfully from surgery. Her BP and heart rate returned to normal levels, as did various hormonal concentrations; and symptoms such as headache, palpitation, chest pain, facial flushing, and diarrhea were no longer problematic. During a 6-mo follow-up period, she seemed in good health and was symptom-free.

DISCUSSION

VIPoma syndrome of watery diarrhea, hypokalemia and achlorhydria was first described by Verner *et al*[5] in 1958, and has been considered to be due to excessive secretion of VIP. In adults, this syndrome is most commonly associated with pancreatic islet cell tumors, but is rarely caused by non-pancreatic tumors, such as bronchogenic carcinoma, medullary thyroid carcinoma, retroperitoneal histiocytoma, and adrenal pheochromocytoma[6]. In an investigation of 62 VIPoma patients, 52 (84%) had pancreatic tumors and 10

(16%) had ganglioneuroblastomas. Of the 10 patients with ganglioneuroblastomas, seven were children[7]. The first description of a nonpancreatic tumor producing VIP was a retroperitoneal ganglioneuroma reported by Fausa *et al*[8] in 1973. Loehry *et al*[9] first reported an WDHA syndrome caused by a pheochromocytoma in 1975. VIP is a 28-amino acid peptide that may stimulate the production of intestinal cyclic adenosine monophosphate, leading to massive intestinal secretion of water and electrolytes[6,7]. VIP also inhibits gastric acid secretion, promotes hepatic glycogenolysis and dilates peripheral systemic blood vessels. Clinical presentations of VIPoma commonly include secretory diarrhea, hypokalemia, hypochlorhydria, flushing, hyperglycemia, and metabolic acidosis[8]. Although this patient had obvious diarrhea, there was no apparent hypokalemia, which may be related to the relatively short onset time and electrolyte supplementation. Most patients with WDHA syndrome have suffered several months or years before seeking medical treatment, so their conditions are dire. Accordingly, we suspected that VIP was produced but only a small amount was secreted, as reported in the literature[9]. Rupture and bleeding may in fact have initiated a massive release of VIP into the circulation, igniting the patient's progression of symptoms.

As we mentioned above, VIP is also a superactive vasodilatory substance capable of producing a generalized peripheral vascular effect[10,11]. Although published reports have yet to link hypotension or shock with VIP-producing pheochromocytomas, most of the affected patients show no hypertensive manifestations[12-14], implying that VIP may effectively antagonize vasoconstrictive CAT activity due to strong action of vasodilation. In this case, octreotide treatment not only significantly improved diarrhea and flushing symptoms, but also corrected situation of shock synchronously. However, octreotide had little impact on plasma CAT concentration, corroborating previous reports[15,16], which indicate that excessive VIP release may be the most important reason causing shock. On the other hand, the cardiotoxic effects of CATs are chronicled in a number of publications, having linked CAT excess with acute myocarditis and cardiogenic shock[17,18]. This is the most common cause of shock due to pheochromocytoma. In this case, however, UCG showed that left ventricular contractility was within normal range, which is different from most of patients with pheochromocytoma-induced shock. Although single echocardiography cannot completely exclude the possibility of cardiogenic shock, this result still indicates that cardiotoxic effects of CATs may not be the main cause of shock. Unfortunately, the patient refused invasive hemodynamic so that we cannot prove our presuming.

Octreotide is a synthetic long-acting SST analogue that effectively inhibits release of VIP from tumors and is approved by the FDA for treatment of WDHA[19]. Its biologic effects are exerted largely through binding with SSTRs on target cell membranes. SSTRs are G protein-coupled receptors of five subtypes (SSTR1-5). SSTR2 is expressed in > 80% of neuroendocrine tumors and is the subtype with the strongest affinity for octreotide[20]. Although some VIP-secreting pheochromocytomas are poorly responsive to octreotide due to lack of SSTR expression[4,12], this patient was promptly restored to near-normal VIP levels through such treatment, with substantial abatement of diarrhea and flushing. Immunohistochemistry later confirmed strong, diffuse SSTR2 positivity (Figure 3I) of tumor cells and this may be the reason why octreotide plays a magical role in the present case. Despite the significant efficacy of octreotide, the definitive treatment for VIPoma is surgery[21-25]. In the cases in which complete surgical resection is either unsuccessful or not feasible, octreotide is an important pharmacotherapeutic approach to controlling symptoms in VIPoma patients[26,27]. However, the long-term administration of octreotide may result in the development of resistance, sometimes extremely high doses of octreotide is necessary for continuous effects[28,29]. In patients with poor efficacy of somatostatin, interferon-α can be combined with octreotide to improve clinical symptoms and promote tumor regression[30,31].

In summary, we report an extremely rare case of VIP-secreting pheochromocytoma marked by persistent shock, flushing, and diarrhea and high sensitivity to octreotide. This case reminds us that the diversity of hormones secreted by neuroendocrine tumor gives rise to clinically complex patient scenarios and a sudden overdose of hormonal substances, when the tumor ruptures, may be fatal to the patient. Therefore, comprehensive hormone testing may be useful for early diagnosis and effective treatment, especially when the patient is in crisis due to unknown reasons.

ARTICLE HIGHLIGHTS

Case characteristics

In adults, vasoactive intestinal peptide-producing tumors (VIPoma) is most commonly originates from pancreatic islet cell tumors, but is rarely caused by pheochromocytoma. We report a VIP-secreting pheochromocytoma case marked by persistent shock, flushing, and diarrhea and high sensitivity to octreotide.

Clinical diagnosis

VIP-secreting pheochromocytoma.

Differential diagnosis

Acute myocardial infarction and cardiogenic shock induced by pheochromocytoma.

Laboratory diagnosis

Pheochromocytoma and VIPoma.

Imaging diagnosis

Left adrenal pheochromocytoma.

Pathological diagnosis
VIP-secreting pheochromocytoma.

Treatment
Surgery after octreotide improved clinical symptoms.

Related reports
It is the first reported instance of VIP-secreting pheochromocytoma marked by persistent shock flushing and diarrhea and high sensitivity to octreotide.

Experiences and lessons
This case reminds us that the diversity of hormones secreted by neuroendocrine tumor gives rise to clinically complex patient scenarios, and a sudden overdose of hormonal substances, when the tumor ruptures, may be fatal to the patient. Comprehensive hormone testing may be useful for early diagnosis and effective treatment, especially when the patient is in crisis due to unknown reasons.

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