Peritoneal inclusion cyst in a patient with glycogen storage disease type Ib and Crohn's like disease

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Research

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Abstract

Background

Glycogen storage disease type Ib (GSD Ib) due to biallelic mutations in *SLC37A4* is often associated with inflammatory bowel disease. Peritoneal inclusion cysts (PICs) are variable sized, fluid-filled, mesothelial-lined cysts that usually occur in premenopausal woman. Risk factors for the development of PICS comprise prior abdominal surgeries and inflammatory diseases.

Results

We herein report on a female patient with GSD Ib and Crohn's like disease who underwent recurrent abdominal surgery due to suspected intraabdominal abscesses. At the age of 36, abdominal pain and an increase in the abdominal girth was observed. MRI revealed a large PIC. Due to multiple previous complications conservative management was chosen, and the cyst remained stable in size during a 1-year follow-up.

Conclusions

PIC should be included in the differential diagnosis of abdominal cystic masses especially in premenopausal women with either IBD or previous abdominal surgery. Radiologist, gynecologist, and gastroenterologist should be aware of this rare condition to prevent inappropriate and aggressive treatments.

Background

Glycogen storage disease type Ib (GSD Ib, OMIM #232220) is caused by biallelic mutations in *SLC37A4* resulting in deficiency of the glucose-6-phosphate transporter in the endoplasmatic reticulum. The estimated prevalence of GSD Ib is about 1: 500,000 (Bali et al. 1993).

The disorder is clinically characterized by severe recurrent fasting hypoglycemia, hepatomegaly, failure to thrive, growth retardation and delayed puberty, truncal obesity, doll-like facies, and bleeding tendency due to thrombocyte dysfunction. Laboratory features comprise hyperuricemia, hyperlipidemia, and elevated lactate levels (Bali et al. 1993; Chen, Margaret A. and Weinstein, David A. 2016). Additionally, GSD Ib is complicated by neutropenia and neutrophil dysfunction that may result in recurrent infections, abscesses, oral and anogenital lesions, and in many patients chronic inflammatory bowel disease (IBD). IBD in GSD Ib is usually described as Crohn's like disease (CLD).

Peritoneal inclusion cysts (PIC) are defined as aggregate masses of variable sized, fluid-filled, mesothelial-lined cysts in the abdomino-pelvic cavity (Vallerie et al. 2009). They are usually found in women in reproductive age in the third and fourth decade of life with a history of abdominal or pelvic

surgeries or inflammation (Vallerie et al. 2009). To date, less than 200 cases have been documented worldwide (Chand et al. 2020). The etiology of PICs is still not well understood. It is hypothesized that the cysts arise secondary to intra-abdominal inflammation and subsequent cyst formation, with serous fluid derived from the ovarian stroma or inflamed serosa (Vallerie et al. 2009). Management options include observation, hormonal management, aspiration of the fluid content, sclerotherapy, laser ablation, chemotherapy and surgical excision (Vallerie et al. 2009). The overall nature of this disease is benign, and treatment has to be individually tailored.

We herein report a 36-year-old GSD Ib patient with CLD who developed a large peritoneal inclusion cyst after multiple abdominal operations.

Results

Case presentation

The patient is a 36-year-old woman who was diagnosed with GSD Ib at the age of 10 months. Details on the clinical course of the patient have been published previously (Grünert et al. 2020). Dietary treatment with a calculated carbohydrate intake and nocturnal continuous feeds was started in infancy, and the patient has always remained in good metabolic control. Since the age of 9 years the patient has received granulocyte colony stimulating factor (G-CSF) treatment for neutropenia and recurrent infections. Since the age of 10 she has suffered from inflammatory bowel disease. The clinical course was further complicated by recurrent abdominal abscesses. At age 25, subtotal colectomy was performed due to long-distance stenosis of the transverse colon with an abscess in the right upper abdomen. Postoperative wound healing was impaired and required surgical wound revision and closure. Severe hepatosplenomegaly with secondary thrombocytopenia was also noted. At age 33, the patient presented with bloody stools and acute abdominal pain in the lower abdomen. MRI was suggestive of a pelvic abscess, enlarged pelvic retroperitoneal and mesenteric lymph nodes as well as inflammatory alterations of the intestine (Fig. 1).

Antibiotic therapy with meropenem, ampicillin and metronidazole was started. Explorative laparotomy with extensive resection of the small bowel was performed. The postoperative course was complicated by abdominal bleeding requiring four further laparotomies within 3 weeks as well as regular thrombocyte and erythrocyte transfusions. Following this acute period, the patient developed a large wound dehiscence (maximum diameter 29 × 18 cm) due to impaired wound healing in GSD Ib. Neither surgical revision of the abdominal wall defect nor supplementation with protein powder, arginine and glutamine to promote wound healing was of permanent success. A colonoscopy was performed and revealed mild to moderate inflammatory activity.

At the age of 35 years empagliflozin treatment was started as reported (Grünert et al. 2020). Empagliflozin is an SGLT2 inhibitor which improves neutropenia and neutrophil dysfunction in GSD-Ib. This treatment is a new approach to reduce inflammatory activity in GSD 1 b and to stop s.c. GCSF

supplementation. The Crohn's Disease Activity Index (CDAI) before start of treatment was 398. This index is a good tool for quantifying patients' symptoms and a useful parameter to assess the clinical course of Crohn's disease (Best et al. 1976). A CDAI score < 150 is defined as remission of Crohn's disease, while a value of greater than 450 is defined as severe disease. The CLD was treated with budesonide 3 mg/day, 5-aminosalicylic acid 3 × 1 g/day, vitamin E 800 mg/day and loperamide 2 mg. Stool calprotectin was within the normal range (42 mg/kg, normal < 50 mg/kg), CRP was normal (0.7 mg/dl, normal < 1 mg/dl), and the blood sedimentation rate was 25 within the 1st hour before start of treatment with empagliflozin (normal < 20 mm). Thrombocyte count was severely reduced with 42 G/L, whereas the hemoglobin level was normal at 11.6 g/dL. The patient responded very well to empagliflozin treatment with neutrophil counts remaining within the normal range, even after termination of GCSF treatment on day 41 on empagliflozin. However, 1 month after the start of empagliflozin the patient reported increasing pain in the lower abdomen. Abdominal ultrasound was suggestive of massive ascites. Diagnostic paracentesis revealed a bloody fluid with a hemoglobin level of 3.7 g/dL. Abdominal MRI on the same day showed a pelvic multilobular cystic mass that was highly suggestive of a peritoneal inclusion cyst (Fig. 2A and 2B). Different intensities of the lobules of the cyst in T1 flare sequences are compatible with bleeding into the cyst (Fig. 3).

Cytological examination was not indicative of a malignant process. Within the following days the haemoglobin concentration in blood remained stable, and the clinical symptoms did not aggravate. In view of the size of the cyst, numerous previous abdominal operations and the bleeding tendency caused by both thrombocytopenia and GSD-associated thrombocyte dysfunction, a surgical approach was considered high risk. Therefore, a conservative approach was chosen. A follow-up MRI was performed after 12 months and showed an only minimal increase in cyst size (Fig. 2C and 2D). The clinical condition remained stable, and the abdominal pain almost subsided.

Discussion

We herein report the first case of PIC in a patient with GSD Ib and CLD. The etiology of PICs is still not fully understood and different controversial hypotheses can be found in the literature. Most authors consider PICs as a collection of fluid which is physiologically produced by an active ovary, whose walls are formed by peritoneal adhesions (Mazziotti et al. 2016). Konincks et al. analysed peritoneal fluid in more than 300 women and found higher concentrations of ovarian steroid hormones in the peritoneal fluid of premenopausal women compared to plasma concentrations (Koninckx et al. 1980). This supports the theory that peritoneal fluid is predominantly an ovarian exudate (Koninckx et al. 1980). However, rare cases of PICs have also been reported in male individuals, postmenopausal women and in the upper abdomen, distant from the ovaries (Weiss and Tavassoli 1988; O'Neil et al. 1989; Ross et al. 1989). Veldhuis et al. have therefore hypothesized that active fluid secretion may also arise from inflamed peritoneal serosa (Veldhuis et al. 2013). While in healthy subjects this fluid is normally cleared by the mesothelial sheet, it may accumulate in presence of a mechanical or inflammatory injury of the peritoneum within peritoneal adhesions forming PICs (Mazziotti et al. 2016).

Typical risk factors for the development of PICs comprise abdominal or pelvic surgeries and inflammation. Association of PICs with Crohn's disease has been described in few cases (Urbanski et al. 1991; Veldhuis et al. 2013; Mazziotti et al. 2016; Sanges et al. 2019). The majority of cases in the literature are reported in women after abdominal surgery. Our patient had a combination of several risk factors including IBD, recurrent abdominal surgeries and an underlying metabolic defect which is associated with a risk of inflammation due to neutropenia and neutrophil dysfunction.

Ten percent of PICs are incidental findings on routine exam, imaging for unrelated complaints, or surgical exploration for an unrelated indication (Vallerie et al. 2009). If patients with PICs become symptomatic, the predominant presenting symptom is progressive abdominal or pelvic pain (Mazziotti et al. 2016), as was the case in our patient. In case of large PICs patients may also note a visible growth of their abdominal girth. Less common symptoms comprise back pain, dyspareunia, hernia, early satiety, constipation, tenesmus, urinary frequency, urinary incontinence, anorexia, dysfunctional uterine bleeding, infertility, postmenopausal bleeding, and pulmonary embolism secondary to compression and venous stasis (Vallerie et al. 2009). Imaging appearances of PICs are variable and range from loculated, simple fluid collections to complex, multi-septated lesions (Veldhuis et al. 2013) causing a long list of differential diagnoses, which includes lymphangioma, mesenteric or omental cysts, ovarian or tubal pathology, pseudomyxoma peritonei, endometriosis, malignant mesothelioma, and adenomatoid tumors (Vallerie et al. 2009; Mazziotti et al. 2016). As knowledge on peritoneal inclusion cysts is still limited, misdiagnoses are rather common (Mazziotti et al. 2016). When critically re-evaluating the first MRI results in our patient, it can be suggested that the findings that triggered the multiple operations at the age of 33 are well compatible with a PIC that was misdiagnosed at that stage (Fig. 1).

The nature of PICs is generally benign and PICs are associated with minimal mortality but high morbidity (Vallerie et al. 2009). To our knowledge, transformation of a previously histologically diagnosed PIC to a malignant mesothelioma in a conservatively managed patient has been described in only one case (González-Moreno et al. 2002; Sethna et al. 2003). Due to the lack of knowledge of underlying pathogenesis, long-term outcomes, and complications rates, there is no clear standard of treatment (Vallerie et al. 2009). Many different therapeutic approaches have been reported ranging from pure observation to hormonal management, aspiration of the fluid content, sclerotherapy, laser ablation, chemotherapy and surgical excision (Vallerie et al. 2009). Surgical excision is considered the only curative approach, however, patients have a 50% risk of recurrence (Vallerie et al. 2009). Since PICs often occur in patients with previous abdominal surgeries the risks and benefits of different therapeutic options must be carefully weighed against each other in an individual setting. In our patient with thrombocytopenia, bleeding tendency, impaired wound healing and neutrophil dysfunction the risk of surgery was considered too high. As the clinical symptoms were bearable, we decided for an observational approach, and MRI after 12 months showed no progress of the disease.

Conclusions

This case demonstrates that PIC should be included in the differential diagnosis of abdominal cystic masses especially in premenopausal women with either IBD or previous abdominal surgery. Radiologist, gynecologist, and gastroenterologist should be aware of this rare condition and the possibility of a conservative treatment approach to prevent the patient from inappropriate or aggressive treatments (Mazziotti et al. 2016). Apart from the large size of the cyst and the risk due to numerous previous abdominal operations, the underlying condition of GSD 1b associated with neutropenia, neutrophil dysfunction and bleeding tendency has in addition urged us to restrain surgical interventions in our patient.

Abbreviations

CDAI Crohn's Disease Activity Index

CLD Crohn's like disease

G-CSF granulocyte colony stimulating factor

GSD glycogen storage disease

IBD inflammatory bowel disease

MRI magnetic resonance imaging

PIC peritoneal inclusion cyst

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

The patient gave her written informed consent for publication.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Author contributions

SCG was responsible for the clinical management of the patient and drafted the manuscript. SB was responsible for the radiologic diagnostics and follow-up of the patient and drafted the figures. UT-S, AS, JG and US were involved in the diagnostic process and therapeutic management and critically read and revised the manuscript. All authors edited and proofread the manuscript prior to submission. The article processing charge was funded by the Baden-Wuerttemberg Ministry of Science, Research and Art and the University of Freiburg in the funding programme Open Access Publishing.

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Figures

Figure 1

T2 weighted axial MRI of the abdomen at age 33. Ovaries are marked with an asterisk, the peritoneal inclusion cyst is labelled with an arrow.

Figure 2

Abdominal MRI at age 35 (A and B, first diagnosis of the peritoneal inclusion cyst) and 36 (C and D, follow-up 12 months after the diagnosis), showing no progressive growth of the cyst over a period of 12 months. A and C: Axial T2-weighted images. Ovaries are marked with an asterix, the peritoneal inclusion cyst is labelled with arrows. B and D: Coronar T2-weighted images.

Figure 3

T1 flare axial abdominal MRI showing different intensities of the multilobular cyst compatible with intraluminal bleeding. The inclusion cyst is labelled with arrows.