Double Rarity: Malignant Masquerade Biliary Stricture in a Situs Inversus Totalis Patient. A Case Report

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Case report

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Double rarity: malignant masquerade biliary stricture in a situs inversus totalis patient. A case report

Running title: Coexistence of situs inversus totalis with malignant masquerade biliary stricture

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Abstract

Background. Situs inversus totalis is a rare anatomical variation of both the thoracic and the abdominal organs. Common bile duct strictures can be caused by malignant and benign diseases as well. 7-18% of the latter ones are 'malignant masquerade' cases, as pre-operative differentiation is difficult.

Case presentation. We present the case of a 68y male patient with known situs inversus totalis and a recent onset of obstructive jaundice caused by a malignant behaving common bile duct stricture. Technically difficult endoscopic retrograde cholangiopancreatography, brush cytology, magnetic resonance cholangiopancreatography, endoscopic ultrasound, and percutaneous transhepatic drainage with stent implantation were performed for proper diagnosis. Cholecystectomy, common bile duct resection with hilar lymphadenectomy and a hepatico-jejunostomy has been performed following multidisciplinary consultation. The final histology report did not confirm any clear malignancy, the patient is doing well.

Conclusion. In situs inversus patients, both diagnostic and therapeutic procedures can lead to various difficulties. Benign biliary strictures are frequently misdiagnosed preoperatively as cholangiocellular carcinoma. The surgery is usually unavoidable, involving a significant risk of complications.

The co-existence of these two difficult diagnostic and therapeutic features made our case challenging.

Keywords

Situs inversus; common bile duct; obstructive jaundice, perihilar cholangiocarcinoma; Klatskin tumor,

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Introduction

Situs inversus totalis (SIT) is a rare congenital abnormality characterized by a mirror-image transposition of both the abdominal and the thoracic organs. Its incidence accounts for 1/8000 to 1/25000 of the normal population [1]. This condition might cause difficulties during diagnostic and also therapeutic procedures [2]. Because of its rarity, surgeons usually do not have much surgical experience with these patients. Stricture or stenosis of the extrahepatic biliary structures can be caused by malignant and benign diseases as well. Pre-operative differentiation of the benign strictures and the malignant tumours of the biliary structures are difficult because of the lack of non-invasive diagnostic procedures, and also benign lesions can be clinically present as malignant [3]. Still, nowadays, about 50% of patients with suspected perihilar cholangiocarcinoma go under resection without a histologically proven diagnosis [4].

Case presentation

A 68-year-old male patient was referred to our institute having obstructive jaundice, pruritus and subcutaneous haematomas for two months. At the age of 10, chest X-ray revealed the situs inversus totalis (Figure 1) for the first time. He was on warfarin due to chronic atrial fibrillation. Eventually, liver enzymes, bilirubin and alkaline phosphatase levels were elevated. Current computer tomography (CT) (Figure 2) confirmed a normal size liver located on the left side; the intra- and extrahepatic bile ducts and the common bile duct (CBD) were dilated. Vascular abnormalities were also detected; the venous drainage from the liver was ensured by an independent vein, connecting straight to the right atrium of the heart. The venous drainage from the lower part of the body and the abdominal organs were ensured by the inferior caval vein located on the right side of the aorta. The first attempt at endoscopic retrograde cholangiopancreatography (ERCP) was not successful due to the different anatomical situation. Magnetic resonance cholangiopancreatography (MRCP) confirmed the dilatation of the extra- and intrahepatic bile ducts. Endoscopic ultrasound (EUS) did not find any clear sign of malignancy neither in the biliary tree, nor in the pancreas. The second attempt of the ERCP verified a duplex stenosis of the CBD affecting both its intrapancreatic and hilar section. Biliary stent placement was unsuccessful. Brush cytology sampling was performed: from the intrapancreatic section of the CBD, malignancy could not be proved, and the sample from the hilar part was uninterpretable. Percutaneous transhepatic drainage (PTD) was introduced to one of dilated bile ducts of the 'right' lobe on the left side of the liver, and biliary stent placement was successful this time, the bilirubin level of the patient started to decrease (Figure 3). Surgical consultation and a multidisciplinary oncology team assumed a Bismuth-Corlette stage II

Klatskin tumour (cholangiocarcinoma) and suggested surgery. Distal resection of the common bile duct, cholecystectomy and hilar lymphadenectomy has been performed (Figures 5 and 6) at our institution. We performed hepatico-jejunostomy to restore the biliary tract (Figure 7). Intraoperative frozen section initially showed tumour cells from the distal part of the CBD. Then, at the second attempt, after re-resecting 2 more millimeters from the CBD, it came back tumour-free. The resection was R0 – no cancer cells seen microscopically. The final histological analysis of the specimen did not confirm our diagnosis: it did not prove clear malignancy, but some epithelial dysplasia was discoverable with haematoxylin and eosin (H&E) staining (Figure 8). With enhancer of zeste homologue 2 (EZH2) immunohistochemical demonstration, some intensive positivity was seen in the biliary structures (Figure 9).

After the surgery, the patient had minor wound infection treated by bedside wound opening (Clavien-Dindo classification stage I), he did not have any other surgical complications, and was discharged after 21 days. A multidisciplinary oncology team discussed the case again after the procedure, and no oncological treatment was considered necessary. After 3 months of the surgery, the control CT-scan was completely tumour-free.

Discussion

Situs inversus totalis is an asymptomatic rare congenital anomaly. During embryonic development, the embryonic midgut normally rotates counter-clockwise at 270°, but in case of SIT, it does this rotation clockwise [5]. In situs inversus patients, both diagnostic and therapeutic procedures can cause various difficulties. Most of the time, the situs inversus itself is asymptomatic, it is revealed by chance. The inverse location of the organs might lead to misdiagnosis as a result of the false projection of the pain to the opposite side of the body, and sometimes it requires technical changes in the diagnostic procedures. In endoscopic and minimally invasive surgical procedures, 'mirror image technique' can be used; they place the patient and the equipment on the opposite side and the procedure itself is performed inversely, the operating surgeon stands on the left side of the patient [6]. In laparoscopic procedures, the careful consideration of the trocar positioning is necessary [7]. However, for right-handed surgeons, it can cause some difficulties: handling the instruments with their left hand or the pedals with their left foot can be uncomfortable [8]. Therefore, the most important factor is the careful exploration of the anatomical variations - especially the vascular anomalies that often occur - by using preoperative imaging techniques.

In the condition of situs inversus, surgery can be challenging as a result of the different anatomical situation. Although situs inversus totalis itself is not a serious hazard to normal

health and long-term survival, the early diagnosis of this condition is crucial, especially when the patient's condition requires surgical intervention [9].

In our case, the right-handed operating surgeon was standing in his standard position: on the right side of the patient. Because of its rarity and special nature, surgical patients with situs inversus may require more flexibility and creativity from the surgical team; however, many cases that have been reported in the literature - including our case as well- could have been treated successfully [5].

Patients with situs inversus may have a higher risk for cancer. In the pathogenesis of SIT, intracellular motorproteins such as KIF3 play important roles. In case of non-functional KIF3, cell-adhesion factors N-cadherin and β -catenin are not transported to the cell surface. These proteins are involved in the development and progression of cancer [10,11].

Perihilar cholangiocarcinoma (also known as Klatskin's tumour) is a rare gastrointestinal malignancy (representing 3% from all type of gastrointestinal tumours), originating from the intra- or extrahepatic bile duct epithelium [12]. Still, this is the most frequent cause of common bile duct stricture. It is usually classified according to the ductal involvement of the tumour. This classification was described by Bismuth et al. in 1988 [13], and this is the standard for decision making on resectability. There are very few cases documented of cholangiocellular carcinoma presented in situs inversus patients in the literature; only 6 cases have been reported [14].

The rate of benign strictures misdiagnosed preoperatively as cholangiocellular carcinoma is high, variant data can be found in the literature: about 7-18%, even up to 50% [4, 15, 16]. The term 'malignant masquerade' was first used in 1985 by Hadjis et al., they described the malignant-behaving, but histologically proven benign bile duct strictures with this expression, the lesions of which cannot be distinguished by clinical or imaging features [17]. Although major hepatobiliary resections have become safer in the past decades, and these patients are now referred to tertiary referral centers, morbidity (30-50%) and mortality (5%) rates of such of operations are still high [18]. Non-malignant causes of biliary obstructions are mostly due to inflammation, further defined as fibroinflammatory processes [19]. Lymphoplasmacytic sclerosing pancreatitis and cholangitis frequently involves the head of the pancreas and the distal common bile duct, and can form masses that can resemble malignancies. Diffuse fibroinflammatory lymphoplasmacytic infiltrates can be seen during histological examination. When lymphoplasmacytic sclerosing pancreatitis and cholangitis occurs, the best diagnostic and discriminating test is to test the serum for IgG4 level; it is significantly elevated in this

condition. In our case, the histological picture was not specific to this disease at all, the IgG4 level of the patient was normal, so we discarded this diagnosis.

For middle and distal common bile duct carcinomas, pancreato-duodenectomy was the gold standard procedure, but nowadays, bile duct segment resection with lymphnode dissection is also established [20]. Complete resection of the tumour with histologically proven negative resection margins ensures the best long-time postoperative survival [21]. The status of the final resected ductal margin is strongly associated with the prognosis of the patients: in case of positive surgical margin, poor long-term survival can be expected [22].

In our case, intraoperative frozen section proved malignant cells in the samples, but the final histological report came back without any clear malignancy. During the procedure of the frozen sectioning, the nuclei of the epithelium cells could be injured: in such a case, it is difficult to discriminate the epithelium for dysplasia or carcinoma in situ [23]. On the other hand; the traditional haematoxylin eosin (H&E) stained sections often cannot provide enough information to establish the appropriate diagnosis, neither to make a proper therapeutic decision. The enhancer of zeste homologue 2 (EZH2) is a recently used marker for hepatocellular carcinomas, but can also be used in the treatment of cholangiocellular carcinomas, because it is able to differentiate between neoplastic or benign (or reactive) biliary proliferation [24].

Conclusion

This case was rare and challenging in every aspect: the malignancy mimicking biliary stenosis in a situs inversus patient required both diagnostic and therapeutic considerations, performing major surgery in an unusual anatomic situation. At 6 months follow up, the patient is doing well, control CT scan did not prove recurrence or any other complications.

Declarations**Ethics approval and consent to participate**

Not applicable.

Consent for publication

Written informed consent for publication has been obtained.

Availability of data and materials

Medical records of the patient are registered in the official medical data system of the Semmelweis University.

Competing interests

The authors declare no conflict of interest.

Funding

Not applicable.

Authors' contributions

Each author equally participated in diagnosing and treating the patient, writing parts of the paper, reading and approving the final version.

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Figure legends

Figure 1: Chest X-ray of the patient with dextrocardia

Figure 2: Preoperative CT scan: The liver is located on the left side, the intra- and extrahepatic bile ducts are dilated.

Figure 3: Percutaneous transhepatic drainage was placed (PTD) to the anatomically right side of the liver, in this case it was located on the left side of the patient.

Figure 4: PTD-cholangiogram: Bismuth-Corlette stage II. Klatskin tumour is shown.

Figure 5: Intraabdominal situation. The liver is situated on the left, the stomach is on the right side.

Figure 6: Intraoperative situation. Hepatic artery (red) and portal vein (blue).

Figure 7: After the reconstruction: hepaticojejunostomy is mirrored.

Figure 8: Histology. Haematoxylin-eosin stain.

Figure 9: Histology with EZH-2 immunohistochemistry. Most of the proliferating bile ducts are EZH-2-negative, mild positivity is shown some places (dysplastic cells).

Figures

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