CASE REPORT

Immunoglobulin G4–associated sclerosing cholangitis mimicking cholangiocarcinoma

Daniel TM Chung 鍾達明
CN Tang 鄧宗毅
Eric CH Lai 賴俊雄
George PC Yang 楊丕祥
Michael KW Li 李家驊

Immunoglobulin G4–related lymphoplasmacytic sclerosing disease is an emerging disease. Recently, it has been shown to be responsible for autoimmune pancreatitis-induced strictures of the bile duct mimicking cholangiocarcinoma. Making a diagnosis of immunoglobulin G4–associated sclerosing cholangitis requires a high index of suspicion. The differential diagnoses include primary sclerosing cholangitis, cholangiocarcinoma, and pancreatic cancer. The preoperative diagnosis is likely to be missed due to the lack of specific symptoms; a clinical presentation that may mimic other disorders, especially malignant biliary strictures; and the lack of specific imaging features. This article reports on a 51-year-old man with immunoglobulin G4–associated sclerosing cholangitis without autoimmune pancreatitis. He underwent resection of his extrahepatic bile duct with a hepaticojejunostomy. The diagnosis was confirmed after a histopathological examination. This case highlights the obstacles to making a preoperative diagnosis of immunoglobulin G4–associated sclerosing cholangitis.

Introduction

An isolated biliary stricture caused by neither trauma nor choledocholithiasis is often malignant and is presumed to correspond to cholangiocarcinoma. Despite improved imaging techniques, it is still difficult to differentiate benign from malignant biliary strictures reliably. A small proportion of patients initially diagnosed with malignant biliary strictures have proven to have benign strictures. In many cases, the exact pathogenesis of benign bile duct strictures in patients without previous histories of primary sclerosing cholangitis or abdominal pathology is uncertain. Immunoglobulin G4 (IgG4)–related lymphoplasmacytic sclerosing disease is an emerging disease. Recently, it has been shown to be responsible for autoimmune pancreatitis–induced strictures of the bile duct that mimicked cholangiocarcinoma. Autoimmune pancreatitis is a form of chronic pancreatitis characterised by a high serum IgG4 concentration and various extrapancreatic manifestations, including sclerosing cholangitis, sialoadenitis, retroperitoneal fibrosis and tubulonephritis.[1,2] It is apparent that tissue infiltration with abundant IgG4-positive cells is seen not only in autoimmune pancreatitis but also in other organs affected by autoimmune pancreatitis. Based on this observation, Kamisawa and Okamoto[3] proposed the term IgG4-related systemic disease to describe this condition. Although the pancreas is the most commonly affected organ in a case series describing IgG4-related systemic disease, the biliary tree is also commonly involved. This is especially so for people with autoimmune pancreatitis.[1,4,5] There have been several recent reports of patients with sclerosing cholangitis and increased serum IgG4 levels but no apparent pancreatic lesions.[6-8] Some authors have proposed that IgG4-related sclerosing cholangitis without pancreatic lesions may be a metachronous phenotype of sclerosing cholangitis associated with autoimmune pancreatitis.[9] Pathological studies have shown abundant infiltrations of IgG4-positive plasma cells in the bile duct walls. These have been given different names, including IgG4-related lymphoplasmacytic sclerosing cholangitis, autoimmune sclerosing cholangitis, and IgG4-associated cholangitis.[10-12] Although the sclerosing cholangitis seen in autoimmune pancreatitis needs to be differentiated from cholangiocarcinoma and primary sclerosing cholangitis, it is very difficult to discriminate between these diseases, particularly in those patients who have sclerosing cholangitis without autoimmune pancreatitis.

This article describes a patient with IgG4-associated sclerosing cholangitis without autoimmune pancreatitis.

Case report

A 51-year-old man presented in August 2008 to Pamela Youde Nethersole Eastern Hospital with a 3-week history of painless progressive jaundice associated with malaise and significant weight loss. Blood investigations revealed abnormal liver function tests with a serum bilirubin of 147 μmol/L, alkaline phosphatase of 437 IU/L, alanine aminotransferase

Key words
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Department of Surgery, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong
DTM Chung, MB, ChB, MRCS(Ed)
CN Tang, MB, BS, FRCS
ECH Lai, MB, ChB, FRACS
GPC Yang, MB, BS, FRACS
MKW Li, MB, BS, FRCS

Correspondence to: Dr DTM Chung
Email: tmchung@gmail.com

酷似膽管癌的免疫球蛋白G4相關性硬化性膽管炎

免疫球蛋白G4（IgG4）相關性淋巴漿細胞硬化病是一種新興的病。最近發現此病會導致因自身免疫性胰腺炎而引發的膽管狹窄，病況酷似膽管癌。要診斷IgG4相關性硬化性膽管炎需要有高度警覺性。鑑別診斷包括原發性硬化性膽管炎、膽管癌及胰臟癌。由於缺乏明顯病徵、症狀酷似其他疾病（尤其是惡性膽管狹窄）、或放射性影像不夠明顯，往往很難於手術前成功診斷此病。本文報告一名患上IgG4相關性硬化性膽管炎的51歲男子，他並沒有自體免疫胰腺炎。病人接受肝內膽管空腸吻合術以切除肝外膽管，經細胞病理學檢查才能確診病人患上此症。本病例指出術前診斷IgG4相關性硬化性膽管炎的困難。

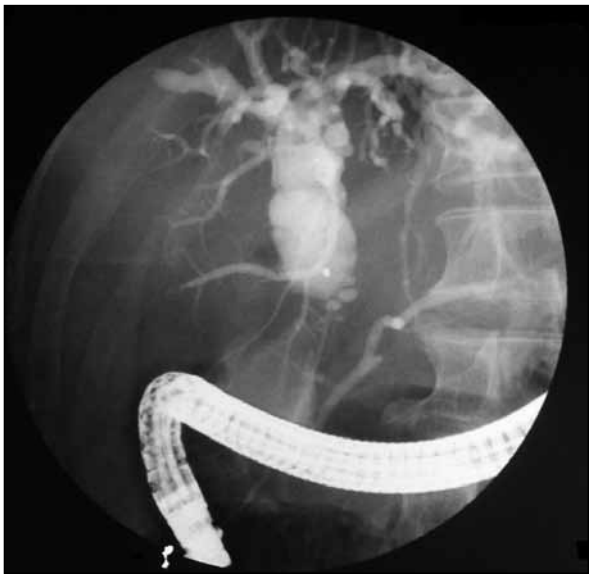

FIG 1. Cholangiogram showing the biliary stricture

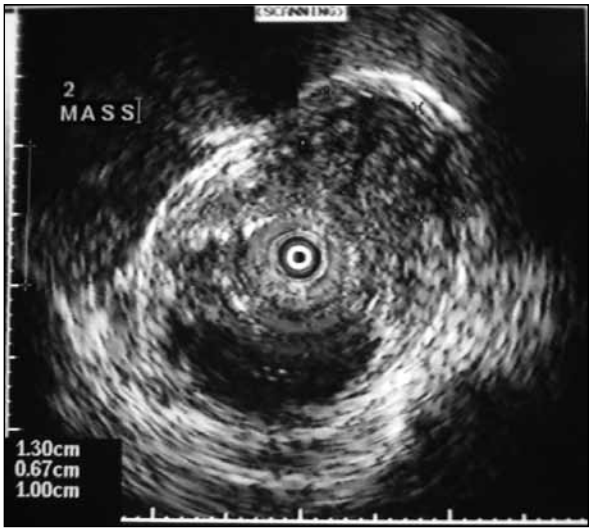

FIG 2. Intraductal ultrasound showing the biliary stricture with eccentric wall thickening

of 295 IU/L, and a normal serum amylase level. Ultrasonography of his abdomen showed mildly dilated intrahepatic ducts (IHD), a common bile duct (CBD) dilated to 1.5 cm, and a few CBD stones. Endoscopic retrograde cholangiopancreatography revealed a normal-looking papilla and pancreatic duct and a long stricture from the distal to mid-CBD with a markedly dilated proximal CBD and IHD (Fig 1). An internal biliary stent was inserted for biliary drainage and his liver function test improved subsequently. Contrast-enhanced computed tomography (CT) showed that there was no tumour mass compressing the bile duct and pancreas. His carbohydrate antigen 19-9 was elevated to 219 IU/mL (reference level, <37 IU/mL). An endoscopic intraductal ultrasound (IDUS) showed hyperechoic eccentric wall thickening in the mid-CBD region (Fig 2). A cytological examination of brushings taken from the biliary stricture revealed atypical cells. ^{18}F-fluorodeoxyglucose positron emission tomography showed a non-specific and patchy increase in metabolism at the mid-CBD region. A provisional diagnosis of cholangiocarcinoma was made and surgical exploration was carried out. Intraoperatively, the thickening of the CBD was found to extend into the common hepatic duct while the distal CBD, at pancreatic level, appeared normal. Abnormal-looking bile duct mucosa extending into the second-degree IHD was also seen during choledochoscopy. The extrahepatic bile duct was excised and a Roux-en-Y hepaticojejunostomy bypass was performed. A frozen section sent for confirmation of adequate resection margins was reported as negative for malignancy. His postoperative recovery was uncomplicated.

A histopathological examination of the tissue removed during surgery revealed no malignancy. There were inflammatory infiltrates mixing with histiocytes, lymphoplasma cells, neutrophils and eosinophils, and many reactive lymphoid follicles. Immunostaining revealed many IgG4-positive plasma cells infiltrating diffusely in the fibrously thickened gall bladder wall as well as in the CBD (up to 141 per high power field and an IgG4/IgG cell ratio of 37%). These features are compatible with IgG4-associated sclerosing cholangitis.

A postoperative test for autoimmune markers found that he was negative for antinuclear antibodies, anti-smooth muscle antibodies, anti-mitochondrial antibodies, and anti-neutrophil cytoplasmic antibodies. His complement levels (C3 and C4) were normal. His serum IgG levels were elevated (2240 mg/dL), but his sub-class serum IgG4 taken 5 weeks after surgery was normal (200 mg/dL).

When followed up 6 months postoperatively,

the patient remained well and reported no recurrence of his symptoms.

Discussion

Sclerosing cholangitis is a heterogeneous disease that may be associated with choledocholithiasis, biliary tumours, autoimmune disease or infection. Sclerosing cholangitis of unknown origin is called primary sclerosing cholangitis.[13] Immunoglobulin G4–associated sclerosing cholangitis is included within the sclerosing cholangitis group. The pathogenesis of IgG4-associated sclerosing cholangitis remains undetermined.

Diagnosing IgG4-associated sclerosing cholangitis requires a high index of suspicion. The differential diagnoses include primary sclerosing cholangitis, cholangiocarcinoma, and pancreatic cancer. The preoperative diagnosis of IgG4-associated sclerosing cholangitis is extremely difficult and is likely to be missed due to the lack of specific symptoms, a clinical presentation that may mimic other disorders—especially malignant biliary strictures—and the lack of specific imaging features. It is difficult to differentiate cholangiocarcinoma from IgG4-associated sclerosing cholangitis based solely on imaging with ultrasonography, CT, magnetic resonance imaging, endoscopic ultrasound, and IDUS. Histologically, the bile ducts are damaged by a dense transmural lymphoplasmacytic infiltrate, with many IgG4-positive plasma cells. Use of IgG4 immunostaining on cytology specimens is not recommended, however, because the density of IgG4-positive cells in the tissue cannot be determined from these specimens. Mild tissue IgG4 immunostaining can occur in other diseases.[14] Although a serum IgG4 increase is characteristic of IgG4-related cholangitis, it may not be diagnostic for the disease. Increased serum IgG4 levels should not be the sole basis for diagnosing IgG4-associated sclerosing cholangitis because its specificity and positive predictive value for IgG4-associated sclerosing cholangitis are not known. An IgG4 increase can occur in the absence of IgG4-related systemic disease.[15] Nevertheless, IgG4-associated sclerosing cholangitis should be suspected in unexplained biliary strictures associated with increased serum IgG4 and unexplained pancreatic disease. Other organ involvement is also an important clue to the diagnosis of IgG4-related cholangitis. Attention should be given to other organs that can be involved such as the salivary glands, retroperitoneum, lymph nodes, and kidneys.

Unlike primary sclerosing cholangitis, the biliary strictures in IgG4-associated sclerosing cholangitis, with or without autoimmune pancreatitis, respond well to steroids.[14] Nonetheless this treatment cannot be recommended if there is any suspicion that malignancy is present. An optimal steroid treatment regimen is yet to be defined. Most patients respond initially to steroids but relapse seems to be common. In patients with IgG4-associated sclerosing cholangitis, careful observation for relapse of IgG4-related sclerosing diseases is warranted both during and after withdrawal of the steroid therapy. A large cohort study (n=53) performed at the Mayo clinic found that 51% presented with biliary strictures confined to the intrapancreatic bile duct, and in the other 49% the proximal extrahepatic ducts and IHD were involved.[14] These patients were treated with steroids (n=30; median follow-up period, 29.5 months), with surgical resection (n=18; median follow-up period, 58 months), or conservatively (n=5; median follow-up period, 35 months). Relapses occurred in 53% after steroid withdrawal and in 44% of those who had surgery.

Conclusion

Making a preoperative diagnosis of IgG4-associated cholangitis is still a great challenge for clinicians. Differentiating IgG4-associated sclerosing cholangitis from carcinoma, especially in patients with no evidence of autoimmune pancreatitis, is very difficult without a thorough histological examination of a surgical specimen. Use of steroid treatment must be considered with caution to avoid the risks imposed by delaying the diagnosis and treatment of a malignant biliary structure.

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