**Immunoglobulin G4–associated sclerosing cholangitis mimicking cholangiocarcinoma**

**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 biliary 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 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.

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
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 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 1). A cytological examination of brushings taken from the biliary stricture revealed atypical cells.

A histopathological examination of the tissue removed during surgery revealed no malignancy. There were inflammatory infiltrates mixing with histiocytes, lymphoplasmacytic 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. 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. 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. 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. 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. 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.

References

8. Iida Y, Onitsuka A, Katagiri Y. Immunoglobulin G4-related sclerosing cholangitis without pancreatic involvement. Dig