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Introduction

Recently, IgG4-related sclerosing cholangitis (IgG4-SC) has attracted much attention with the emergence of clinical characteristics that distinguish it as a new clinical entity. IgG4-SC has a cholangiographic appearance similar to that of primary sclerosing cholangitis (PSC) and cholangiocarcinoma [1]. IgG4-SC respond well to steroid therapy (Fig. 1.1). In contrast, PSC is progressive and resistant to therapy, eventually involving both the intra- and extrahepatic bile ducts and resulting in biliary cirrhosis [2]. The value of steroid therapy has been questioned, and liver transplantation is the only effective measure for cure. Establishment of the concept of autoimmune pancreatitis (AIP) has meant that unnecessary surgery in the event of misdiagnosis of pancreatic

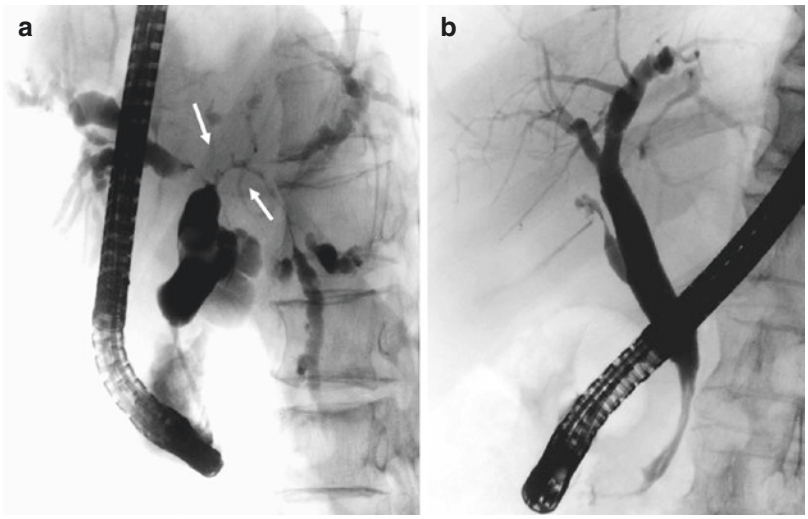

Fig. 1.1 Steroid therapy for type 2 IgG4-SC. (**a**) ERC showed diffuse stenosis in intrahepatic bile duct. (**b**) The diffuse stenosis dramatically improved by steroid therapy

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carcinoma can be avoided. Similarly, once a diagnosis of IgG4-SC can be established, then both liver transplantation under a diagnosis of PSC and hepatectomy under a diagnosis of cholangiocarcinoma can be avoided. Therefore, it is necessary to discriminate these diseases before choosing the most appropriate therapy.

Characteristic Features of IgG4-Related Sclerosing Cholangitis

Elevated serum IgG4 level is a characteristic feature of IgG4-SC [3]. In patients with IgG4-SC, the pancreas was the most common organ involved other than the bile duct. Patients with IgG4-SC show multiorgan involvement, including sclerosing sialadenitis, retroperitoneal fibrosis, and mediastinal lymphadenopathy. Based on histological and immunohistochemical examination of various organs, clinicopathological entity called "IgG4-related systemic disease" was proposed [4]. IgG4-SC is considered to be a biliary manifestation of IgG4-related disease. IgG4-RD including IgG4-SC was originally suspected to be an autoimmune disorder based on its frequent association with ANA positivity and steroid responsiveness. However, this possibility has been questioned. Unlike classic autoimmune disorders, patients with IgG4-RD are older (median age, 67 years) and 80% are male.

Two diagnostic criteria have been used in the diagnosis of IgG4-SC [5, 6]. Both criteria consist of imaging, serology, histology, other organ involvement, and responses to steroid therapy. If IgG4-SC is associated with AIP or other IgG4-related diseases, diagnosis is not so difficult. Otherwise, isolated IgG4-SC is difficult to diagnose. We should keep in mind several points for precise diagnosis. First, 10% of IgG4-SC cases show lower serum IgG4 level than cutoff value. Second, IgG4-SC show characteristic pathological findings but acquiring enough pathological sample for evaluation by bile duct biopsy is difficult because of superficial nature. Third, if the diagnosis remains nonconclusive, steroid trials may be considered; however, the possibility of malignancy should be carefully excluded before commencing immunosuppression.

Imaging suggestive for IgG4-SC are summarized in Fig. 1.2. We should evaluate imaging of IgG4-SC from two aspects, character of stenosis

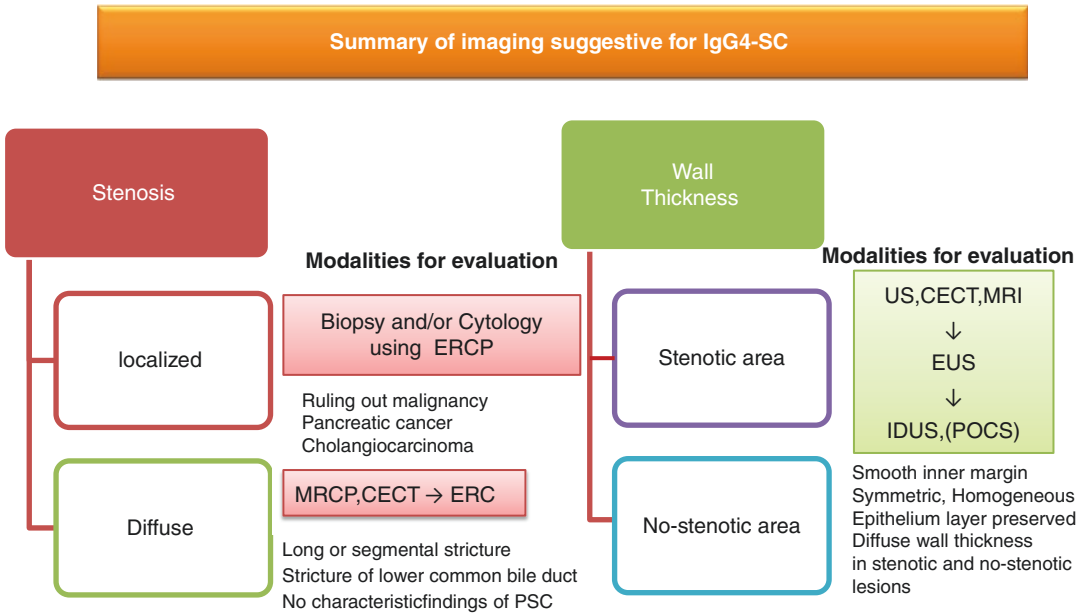


Fig. 1.2 Images suggestive for IgG4-SC. If stenosis is localized, bile duct biopsy is necessary in order to rule out cholangiocarcinoma. If stenosis is diffusely distributed, cholangiography can discriminate IgG4-SC from PSC. Diffuse bile duct wall thickness without injury of epithelium is characteristic for IgG4-SC

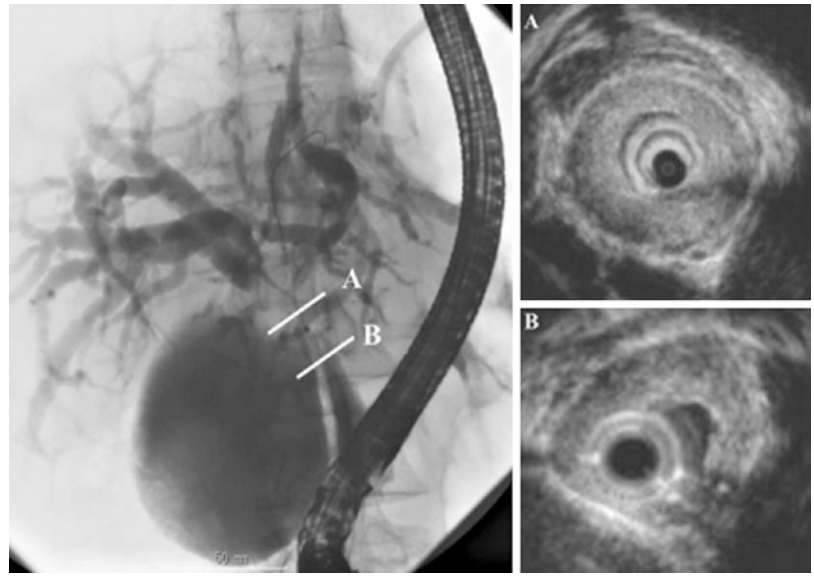


Fig. 1.3 Type 3 IgG4-SC and IDUS findings. ERC showed stenosis at the hilar hepatic lesion. IDUS showed symmetric and homogeneous wall thickness without epithelial injury both in the stenotic and non-stenotic lesions

and wall thickness. Imaging clearly reflects pathological characters that inflammation occurs mainly in stroma with normal mucosa surface. Severe infiltrating inflammatory cells induce long stricture in cholangiography on the contrary to short stricture due to fibrosis in PSC. If stenosis is localized, bile duct biopsy is necessary in order to rule out cholangiocarcinoma. If stenosis is diffusely distributed, cholangiography can discriminate IgG4-SC from PSC. If stenosis is localized, ruling out cholangiocarcinoma by bile duct biopsy is necessary. Bile duct wall thickness without injury of epithelium can be detected by intraductal ultrasonography (IDUS) (Fig. 1.3) or endoscopic ultrasonography (EUS).

The treatment strategy is basically similar to that for type 1 AIP. Steroid (prednisone at a dose of 0.6 mg/Kg/day) is the treatment of choice and generally leads to the rapid and consistent induction of disease remission. Although disease relapse is relatively common, IgG4-SC is considered a "benign" disease with a low risk of liver failure and biliary malignancy [7].

History and Nomenclature

Before the concept of AIP was established, the terms primary sclerosing cholangitis and sclerosing cholangitis associated with chronic pancreatitis/pancreatic pseudotumor were used. These disease entities were referred to as atypical primary sclerosing cholangitis to discriminate them from classic PSC [8]. The terms sclerosing cholangitis associated with AIP and autoimmune pancreatocholangitis have been applied in the context of AIP, and the terms lymphoplasmacytic sclerosing cholangitis, IgG4-related sclerosing cholangitis [9], and IgG4-associated cholangitis [6] have been employed in the context of IgG4-related autoimmune diseases based of their characteristic pathological changes.

Concept of Sclerosing Cholangitis

Classification of Sclerosing Cholangitis

Sclerosing cholangitis has been classified into two categories: PSC and secondary sclerosing cholangitis (SSC). IgG4-SC has sometimes been described as an isolated biliary tract lesion, even in the absence of pancreatic involvement, and has thus been established as a distinct clinical entity. Therefore, sclerosing cholangitis is now classified into three categories: PSC, IgG4-SC, and SSC [10, 11]. We have identified three reasons why IgG4-SC should be considered independently from other forms of SSC. First, steroid therapy is highly effective for IgG4-SC, in contrast to the other types of sclerosing cholangitis. Second, in comparison with the other forms,

IgG4-SC is frequently encountered in daily clinical practice. Third, the characteristics of IgG4-SC need to be fully discriminated from those of the other three intractable diseases, that is, pancreatic cancer PSC, and cholangiocarcinoma.

With regard to the diagnosis of sclerosing cholangitis, SSC should be ruled out first. Thereafter, IgG4-SC should be suspected; the serum IgG4 level, measured; and further exploration for pancreatic involvement or other IgG4-related systemic disease, conducted. Finally, compatibility with the criteria for PSC should be ascertained.

Primary Sclerosing Cholangitis

We have previously reported the differences between IgG4-SC and PSC [2]. Age at clinical onset was significantly older for patients with IgG4-SC. Among the chief complaints in IgG4-SC, obstructive jaundice, reflecting marked concentric stenosis of the large bile duct, was most frequently observed. However, approximately half of PSC patients in Japan are nonsymptomatic at diagnosis.

Secondary Sclerosing Cholangitis

SSC is a chronic cholestatic biliary disease that can develop after a diverse range of insults to the biliary tree. SSC is considered to develop as a consequence of known injuries or secondary to pathological processes of the biliary tree. The etiology of SSC can usually be identified, although the exact pathogenesis often remains speculative. The most frequently described causes of SSC are long-standing biliary obstruction, surgical trauma to the bile duct, and ischemic injury to the biliary tree in liver allografts.

Classification of IgG4-SC

Cholangiographic Classification

IgG4-SC displays various cholangiographic features similar to those of pancreatic cancer, PSC, and cholangiocarcinoma. The characteristic features of IgG4-SC can be classified into four types based on the stricture regions revealed by cholangiography and differential diagnosis (Fig. 1.4) [1]. Type 1 IgG4-SC displays stenosis only in the lower part of the common bile duct and thus should be differentiated from chronic pancreatitis, pancreatic cancer, and cholangiocarcinoma. Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts, should be differentiated from PSC and is further subdivided into two subtypes: type 2a, characterized with narrowing of the intrahepatic bile ducts with prestenotic dilation, and type 2b, characterized by the narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches, which is caused by marked lymphocytic and plasmacytic infiltrations into the peripheral bile ducts. Differential diagnosis between type 2a IgG4-SC and PSC is possible by endoscopic retrograde cholangiography (ERC) [12]. However, differential diagnosis between type 2b IgG4-SC and PSC with pruned tree appearance is difficult by ERC. Type 3 IgG4-SC is characterized by stenosis in the hilar hepatic lesions and the lower part of the common bile duct. Type 4 IgG4-SC presents with strictures of the bile duct only in the hilar hepatic lesions. The cholangiographic findings of types 3 and 4 IgG4-SC should be discriminated from those of cholangiocarcinoma. Bile duct biopsy is necessary for differential diagnosis between type 3 and 4 IgG4-SC and cholangiocarcinoma [13].

Inclusion of type 1 IgG4-SC into the IgG4-SC category has been disputed. Some researchers claim that the stricture of the lower common bile duct, which is observed in type 1 IgG4-SC, is caused by compression due to AIP [14]. This claim is based on the fact that type 1 IgG4-SC was not found in some cases of focal-type AIP with only body and tail involvement. On the contrary, others claim that type 1 IgG4-SC should be classified as one of the IgG4-SC types because of the following reasons. First, pathological examination of the bile duct wall obtained from surgically resected samples showed abundant IgG4-positive plasma cell infiltration, storiform

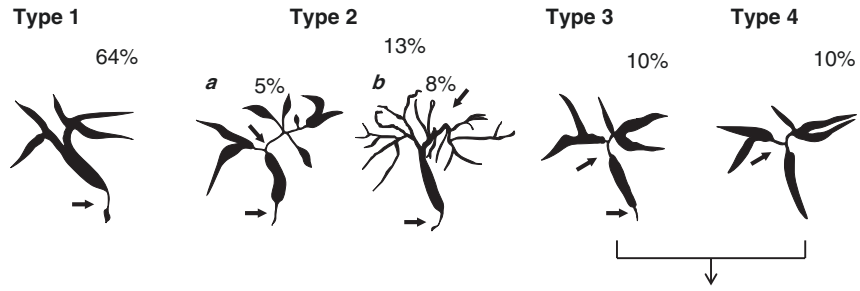
fibrosis, and obstructive phlebitis, which are characteristics of IgG4-SC-associated inflammation [9]. Second, the results of an IDUS study showed continuous thickening of the bile duct wall from the intrapancreatic to the extrapancreatic bile duct [13]. Third, isolated type 1 IgG4-SC has been reported [15]. In fact, it is difficult to identify which is the major factor contributing to the thickening of the bile duct wall—inflammation of the bile duct or compression due to AIP.

IgG4-SC With/Without AIP

IgG4-SC is frequently associated with AIP. A Japanese multicenter study revealed that 458 (87%) of 527 patients with IgG4-SC had AIP [7]. This association with AIP is useful when diagnosing IgG4-SC. However, some IgG4-SC cases are isolated from AIP and are difficult to diagnose [16].

Most reported cases of isolated IgG4-SC have hilar biliary strictures. We evaluated 344 patients with IgG4-SC according to our cholangiographic classification [17]. A total of 329 (95.6%) of the 344 IgG4-SC cases were associated with AIP (244 of 246 type 1 IgG4-SC cases [99.2%]; 51 of 56 type 2 IgG4-SC cases [91.1%]; 34 of 42 type 3 and 4 IgG4-SC cases [81.0%]). Type 3 and 4 IgG4-SC cases showed lower frequencies of association with AIP.

Isolated IgG4-SC with an intrapancreatic biliary stricture (type 1 IgG4-SC) is very rare. We encountered five cases of type 1 IgG4-SC that were not associated with AIP [17]. None of our cases had an enlarged pancreas, and only one showed an atrophied pancreas. None of the cases had an irregular narrowing of the main pancreatic duct. Four cases had a normal main pancreatic duct, and one showed slight dilation of the main pancreatic duct. Thickening of the bile duct wall in lesions without a luminal stenosis, which is a characteristic finding of IgG4-SC, was detected by abdominal computed tomography (CT) in all five cases and by IDUS in three cases. The IgG4



	Type 1	Type 2	Type 3	Type 4
Differential diagnosis	Pancreatic cancer Bile duct cancer Chronic pancreatitis	Primary sclerosing cholangitis	Bile duct cancer Gallbladder cancer	
Useful modalities	IDUS* (bile duct) EUS-FNA** (pancreas) Biopsy (bile duct)	Liver biopsy Colonoscopy (R/O coexistence of IBD ***)	EUS (bile duct, pancreas) IDUS (bile duct) Biopsy (bile duct)	

* IDUS：Intraductal ultrasonography
** EUS-FNA：Endoscopic ultrasound-guided fine needle aspiration
*** IBD: Inflammatory bowel disease

Fig. 1.4 The cholangiographic classification, frequency of IgG4-SC and differential diagnosis. Stenosis is located only in the lower part of the common bile duct in type 1; stenosis is diffusely distributed in the intra- and extrahepatic bile ducts in type 2. Type 2 is further subdivided into two types. Extended narrowing of the intrahepatic bile ducts with prestenotic dilation is widely distributed in type 2a. Narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches are widely distributed in type 2b; stenosis is detected in both the hilar hepatic lesions and the lower part of the common bile ducts in type 3; strictures of the bile duct are detected only in the hilar hepatic lesions in type 4. *IDUS* intraductal ultrasonography, *EUS-FNA* endoscopic ultrasound-guided fine needle aspiration, *IBD* inflammatory bowel disease

values of all three cases were within normal limits (<135 mg/dL). All three cases underwent surgery under suspicion of cholangiocarcinoma. The other two cases had high IgG4 values, and one case received steroid therapy. The other case was treated only with endoscopic biliary drainage. The pathological findings of the bile duct from surgical specimens of the three cases showed severe infiltration of lymphocytes, IgG4-positive plasmacytes, and prominent fibrosis, compatible with the findings of IgG4-SC, but no inflammatory changes compatible with AIP in adjacent pancreatic tissues. We concluded that isolated type 1 IgG4-SC cases are difficult to diagnose, particularly those with normal IgG4 values. We should be aware that isolated type 1 IgG4-SC are also one of the candidates in addition to a cholangiocarcinoma and pancreatic cancer when we diagnose a stenosis of intrapancreatic bile duct.

Early Stage/Advanced Stage

Advanced-stage IgG4-SC may sometimes be unresponsive to steroid therapy because cases of IgG4-SC show predominantly inflammatory nature at the early stage, followed by relatively less inflammation but marked fibrous scarring later in the course of the disease [18]. Similarly, AIP in advanced stage show sometimes calcification mimicking chronic pancreatitis, and stenosis of main pancreatic duct does not respond well to steroid therapy. This should be kept in mind when evaluating effectiveness of steroid therapy, especially in a steroid trial for IgG4-SC diagnosis.

Conclusion

Although disease relapse is relatively common, IgG4-SC is considered a "benign" disease with a low risk of liver failure and biliary malignancy. Therefore, differential diagnosis is important before starting treatment. As the concept of IgG4-SC prevails, our diagnostic ability has improved. Diagnosis of isolated IgG4-SC is still difficult. Bile duct biopsy and IDUS through ERCP are performed for ruling out cholangiocarcinoma and evaluating wall thickness. Further investigation for less invasive modality or more definite serological markers is necessary. New therapeutic strategies are also necessary because long-term steroid therapy induces several adverse events for aged people.

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