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MINIREVIEWS

Diagnosis of IgG4-related sclerosing cholangitis

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Abstract

IgG4-related sclerosing cholangitis (IgG4-SC) is often associated with autoimmune pancreatitis. However, the diffuse cholangiographic abnormalities observed in IgG4-SC may resemble those observed in primary sclerosing cholangitis (PSC), and the presence of segmental stenosis suggests cholangiocarcinoma (CC). IgG4-SC responds well to steroid therapy, whereas PSC is only effectively treated with liver transplantation and CC requires surgical intervention. Since IgG4-SC was first described, it has become a third distinct clinical entity of sclerosing cholangitis. The aim of this review was to introduce the diagnostic methods for IgG4-SC. IgG4-SC should be carefully diagnosed based on a combination of characteristic clinical, serological, morphological, and histopathological features after cholangiographic classification and targeting of a disease for differential diagnosis. When intrapancreatic stenosis is detected, pancreatic cancer or CC should be ruled out. If multiple intrahepatic stenoses are evident, PSC should be distinguished on the basis of cholangiographic findings and liver biopsy with IgG4 immunostaining. Associated inflammatory bowel disease is suggestive of PSC. If stenosis is demonstrated in the hepatic hilar region, CC should be discriminated by ultrasonography, intraductal ultrasonography, bile duct biopsy, and a higher cutoff serum IgG4 level of 182 mg/dL.

Key words: IgG4-related sclerosing cholangitis; Primary sclerosing cholangitis; IgG4; Sclerosing cholangitis

Core tip: IgG4-related sclerosing cholangitis (IgG4-SC) has become a third distinct clinical entity of sclerosing cholangitis. The diffuse cholangiographic abnormalities observed in IgG4-SC may resemble those observed in primary sclerosing cholangitis (PSC), and the presence of segmental stenosis suggests cholangiocarcinoma (CC). IgG4-SC responds well to steroid therapy, whereas PSC is only effectively treated with liver transplantation, and CC requires surgical intervention. IgG4-SC should be carefully diagnosed based on a combination of characteristic clinical, serological, morphological, and histopathological features after cholangiographic classification and targeting of a disease for differential diagnosis.

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INTRODUCTION

IgG4-related sclerosing cholangitis (IgG4-SC) is a characteristic type of sclerosing cholangitis, with an unknown pathogenic mechanism. Patients with IgG4-SC display increased serum IgG4 levels[1] and dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall[2]. Circular and symmetrical thickening of the bile duct wall is observed in the areas without stenosis that appear normal on cholangiography, as well as in the stenotic areas[3]. IgG4-SC has been recently recognized as an IgG4-related disease. IgG4-SC is frequently associated with autoimmune pancreatitis (AIP). IgG4-related dacryoadenitis/sialadenitis and IgG4-related retroperitoneal

fibrosis are also occasionally observed in IgG4-SC[4-7]. However, some IgG4-SC cases do not involve other organs[8]. IgG4-SC is most common in elderly men. Obstructive jaundice is frequently observed in IgG4-SC. The clinical and radiological features of IgG4-SC are resolved by steroid therapy, although its long-term prognosis is not clear[9-12]. The diffuse cholangiographic abnormalities observed in IgG4-SC may resemble those observed in primary sclerosing cholangitis (PSC), and the presence of segmental stenosis suggests cholangiocarcinoma (CC). IgG4-SC responds well to steroid therapy, whereas PSC is effectively treated only with liver transplantation, and CC requires surgical intervention. It is also necessary to rule out secondary sclerosing cholangitis (SSC) caused by diseases with an obvious pathogenesis.

Precise diagnosis is needed before choosing appropriate treatments. Therefore, this paper provides a review of the clinical and pathological characteristics of IgG4-SC, focusing on its differential diagnosis from other biliary diseases such as PSC and CC.

CLASSIFICATION OF SC

SC has been classified into two categories: PSC and 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, we propose that SC should now be classified into three categories: PSC, IgG4-SC, and SSC. We have identified three reasons why IgG4-SC should be considered independent of other forms of SSC. First, steroid therapy is highly effective for IgG4-SC, which is in contrast to the other types of SC. Second, in comparison with the other forms, IgG4-SC is the most 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 (PCa), PSC, and CC.

With regard to the diagnosis of SC, SSC should be initially ruled out. 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 PSC criteria should be ascertained.

PSC

The following diagnostic criteria for PSC, which were proposed by the Mayo Clinic, have been widely used[13]: typical cholangiographic abnormalities involving the intrabiliary and extrabiliary trees, compatible clinical and biochemical findings, and exclusion of other causes of SSC. Liver biopsy had been used in the past to help confirm diagnosis, but its diagnostic specificity and sensitivity have become controversial. Nevertheless, liver biopsy is useful in the diagnosis of small duct PSC, for patients with suspected PSC but normal cholangiographic findings, and for the exclusion of other cholestatic diseases.

Characteristic inflammatory bowel diseases (IBDs) are frequently observed in PSC patients. Standard ursodeoxycholic acid doses lead to improvements in biochemical abnormalities but not in histological findings, cholangiographic appearance, or patient survival. Liver transplantation is considered effective for end-stage liver disease because of PSC and is associated with improved patient survival. PSC usually leads to cirrhosis, with a mean survival time of 12-17 years.

IgG4-SC

Recently, IgG4-SC has attracted much attention with the emergence of clinical characteristics that distinguish it as a new clinical entity. The diffuse cholangiographic abnormalities observed in association with AIP may resemble those observed in PSC, and the segmental stenosis suggest CC. IgG4-SC responds well to steroid therapy compared with the other two types of SC.

We have previously reported on the differences between IgG4-SC and PSC[9]. The age at clinical onset is 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, is most frequently observed. However, in Japan, patients with PSC who present without symptoms after liver injury are identified by physical examination[14].

An elevated serum IgG4 level is a characteristic feature of IgG4-SC[15]. In patients with IgG4-SC, the pancreas is the most common organ involved other than the liver. Patients with IgG4-SC have multiorgan involvement, including sclerosing sialadenitis, retroperitoneal fibrosis, and mediastinal lymphadenopathy[4-7].

SSC

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.

The different types of SSC have been described in the diagnostic criteria established by the Mayo Clinic[13]. Two reviews of SSC cases have been published[16,17]. IgG4-SC was previously classified into SSC. We classified the etiology of SSC based on three review articles[13,16,17] (Table 1). There are few studies comparing patients with SSC and PSC. A 10-year retrospective review (1992-2002) by the Mayo Clinic identified 31 patients with SSC[18]. The documented etiologies in their series included surgical trauma from cholecystectomy, intraductal stones, recurrent pancreatitis, and abdominal injury. Nine of their patients with SSC ultimately required liver transplantation, and four died. In their series, when compared with matched controls with PSC, the patient transplant-free survival was significantly shorter.

Table 1 Etiology of secondary sclerosing cholangitis

Congenital	Caroli's disease
	Cystic fibrosis
Chronic obstruction	Choledocholithiasis
	Biliary stricutures (secondary to surgical trauma, choronic pancreatitis)
	Anastomotic stricutures in liver graft
	Neoplasms (benign, malignant, metastatic)
Infectious	Bacterial cholangitis
	Recurrent pyogenic cholangitis
	Parasitic infection (cryptosporidiosis, microsporidiosis)
	Cytomegalovirus infection
Toxic	Accidental alcohol, formaldehyde, hypertonic saline instillation in the bile ducts
Immunologic	Eosinophilic cholangitis
	Acquired immunodeficiency
Ischemic	Vascular trauma
	Post-traumatic sclerosing cholangitis
	Post-transplantation hepatic artery thrombosis
	Hepatic allograft rejection (acute, chronic)
	Intra-arterial, chemotherapy-related injury
	Transcatheter arterial embolization therapy
Infiltrative disorders	Systemic vasculitis
	Amyloidosis
	Radiation injury
	Sarcoidosis
	Systemic mastocytosis
	Hypereosinophilic syndrome
	Hodgkin's disease

IgG4-SC DIAGNOSIS

Cholangiographic classification

IgG4-SC displays various cholangiographic features similar to those of PCa, PSC, and CC. The characteristic features of IgG4-SC can be classified into four types based on the stricture regions revealed by cholangiography and differential diagnosis (Figure 1)[19,20]. Type 1 IgG4-SC displays stenosis only in the lower part of the common bile duct and thus should be differentiated from chronic pancreatitis, PCa, and CC. 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 plasmacyte infiltrations into the peripheral bile ducts. 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 CC.

Serum IgG4 level

Serum IgG4 level has been reported to be a useful marker for discriminating AIP from other pancreatic diseases. A cutoff IgG4 level of 135 mg/dL is widely used as part of the diagnostic criteria for AIP. However, twice the upper limit of normal is also recommended to discriminate AIP from PCa. In the international consensus diagnostic criteria for AIP, once or twice the upper limit of normal is included in levels 1 and 2 diagnoses, respectively[21].

Only a few reports have been published concerning the cutoff IgG4 level in the diagnosis of IgG4-SC. We published for the first time, the diagnostic criteria for IgG4-SC based on a comparative study[22]. The cutoff IgG4 level of 135 mg/dL is useful in discriminating IgG4-SC from PCa and PSC. However, this cutoff level displayed lower specificity in discriminating IgG4-SC from CC. Oseini *et al*[23] evaluated the utility of serum IgG4 level in distinguishing IgG4-SC from CC. They reported that among their 126 patients with CC, 17 (13.5%) had elevated (> 140 mg/dL) and four (3.2%) had a > 2-fold increase (> 280 mg/dL) in serum IgG4 levels. PSC was present in 31/126 CC patients, of whom seven (22.6%) had an elevated serum IgG4 level. The authors concluded that some patients with CC, particularly PSC, had elevated serum IgG4 levels and diagnosis using a twofold higher cutoff serum IgG4 level may not reliably distinguish IgG4-SC from CC. However, a cutoff level fourfold higher than the upper limit of normal had 100% specificity for IgG4-SC.

We recently established a cutoff serum IgG4 level to differentiate IgG4-SC from the three other diseases (type 1 IgG4-SC *vs* PCa, type 2 IgG4-SC *vs* PSC, and type 3 IgG4-SC *vs* CC) using serum IgG4 levels measured in nine Japanese high-volume centers[24]. The cutoff obtained from receiver operator characteristic (ROC) curves displayed similar sensitivity and specificity to those of 135 mg/dL when all the IgG4-SC cases and controls were compared. However, a new cutoff value was established when IgG4-SC subgroups and controls were compared. A cutoff level of 182 mg/dL can increase the specificity to 96.6% (a 4.7% increase) for distinguishing types 3 and 4 IgG4-SC from CC. A cutoff level of 207 mg/dL might be useful for completely distinguishing types 3 and 4 IgG4-SC from CC.

Alswat *et al*[25] demonstrated that serum IgG4 levels could efficiently detect patients with IgG4-SC after excluding SC patients with AIP. However, previously reported IgG4-SC cases without pancreatic involvement displayed no marked increase in serum IgG4 level compared with patients with AIP-associated IgG4-SC. Hamano *et al*[8] demonstrated modestly high serum IgG4 levels (119, 122, and 195 mg/dL) in three IgG4-SC cases without an obvious pancreatic mass.

Elevated serum IgG4 level is considered a characteristic feature of IgG4-SC[1]. However, Mendes *et al*[26] measured the serum IgG4 level in 127 patients with PSC and found that it was elevated in 12 (9%). The patients with elevated IgG4 levels had higher levels of total bilirubin and alkaline phosphatase, higher PSC Mayo risk scores, and lower incidence of IBD. It is important to note that the time to liver transplantation was shorter in

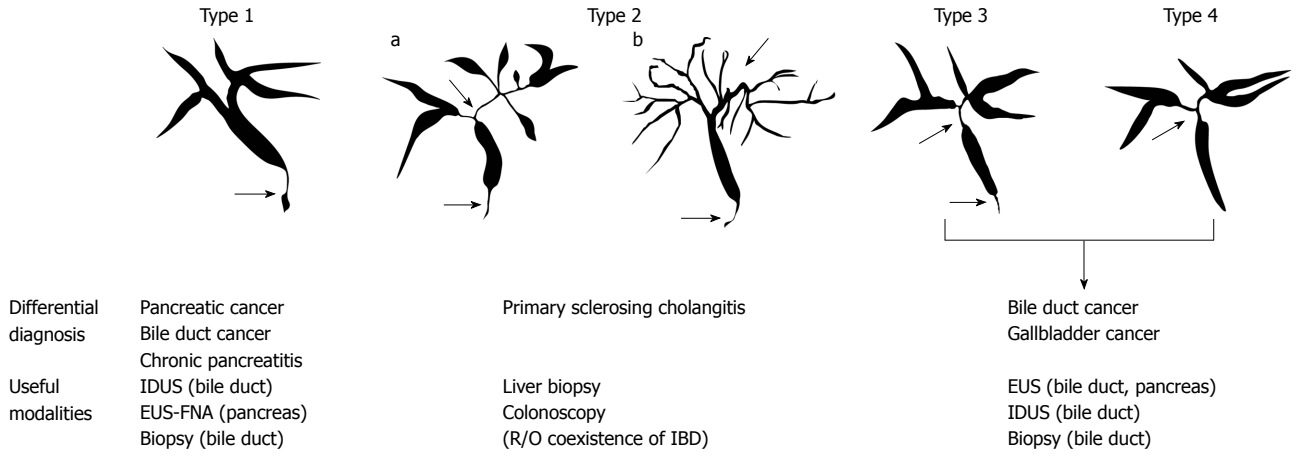

Figure 1 Cholangiographic classification of IgG4-related sclerosing cholangitis and differential diagnosis. Stenosis is located only in the lower part of the common bile duct in type 1; stenosis is diffusely distributed in the intra-and extra-hepatic bile ducts in type 2. Type 2 is further subdivided into two. 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.

the patients with elevated IgG4 levels (1.7 years *vs* 6.5 years, $P = 0.0009$). As only one of the patients in their series had an abnormal pancreatogram, the documented cases appeared to conform to the diagnosis of IgG4-SC. Therefore, clinical trials in which patients with PSC are evaluated for IgG4 and patients presenting elevated levels are treated with corticosteroids should be considered.

Other organ involvement

The concept of IgG4-related disease has been established internationally[27]. IgG4-SC is included in the IgG4-related disease category. Serum IgG4 level elevation and tissue infiltration with IgG4-positive plasma cells are common threads that connect a variety of apparently disparate conditions observed previously in multiple organs. Certain clinical and pathological features help define IgG4-related disease and distinguish it from its potential mimics. IgG4-related disease is a fibroinflammatory condition characterized by a tendency to form tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, frequent but not invariable elevations in serum IgG4 level, and a swift initial response to glucocorticoids, provided that tissue fibrosis has not supervened.

The pancreas was the first organ in which IgG4-related disease was identified, but the disease has now been described in virtually every organ system: the biliary tree, salivary glands, orbital tissues (*e.g.*, lacrimal gland, extraocular muscles, and retrobulbar space), kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid gland, pericardium, retroperitoneum, and skin.

Association with AIP is a useful finding in the diagnosis of IgG4-SC. In one study, 59 (95%) of 62 patients with IgG4-SC had associated AIP, with high prevalence[21]. Ghazale *et al*[15] reported an incidence rate of AIP association of 92% in 53 patients with IgG4-SC, which was a comparatively large sample. However, focal-type AIP sometimes displays similar imaging findings to those of PCa, making discrimination between the two diseases difficult[28]. The sensitivity rates of diagnostic criteria for AIP have been reported to range from 80% to 92%[29]. Therefore, useful diagnostic criteria need to be established for IgG4-SC when it is not associated with AIP or when diagnosis of AIP is unclear. IgG4-SC is occasionally associated with other systemic IgG4-related diseases including symmetrical dacryoadenitis/sialadenitis and retroperitoneal fibrosis. These associations are helpful in the accurate diagnosis of IgG4-SC.

Pathological features

In IgG4-SC, fibroinflammatory involvement is observed mainly in the submucosa of the bile duct wall, whereas the epithelium of the bile duct is intact[2]. However, slight injury and/or neutrophil infiltration are occasionally observed in IgG4-SC with associated secondary cholangitis. PSC should be ruled out if inflammation is observed, particularly in the epithelium of the bile duct wall. The characteristic pathological findings of IgG4-SC were first reported as "lymphoplasmacytic sclerosing pancreatitis with cholangitis"[30]. Abraham *et al*[31] reported frequent fibroinflammatory involvement of the gallbladder and common bile duct in patients with lymphoplasmacytic sclerosing pancreatitis. Zen *et al*[2] revealed that the bile duct wall in IgG4-SC had pathological features similar to those of AIP, displaying dense infiltrations of lymphocytes and IgG4-positive plasma cells, with extensive fibrosis and obliterative phlebitis. They classified IgG4-SC into six categories according to the extent of inflammation and association with an inflammatory pseudotumor. IgG4-positive plasma cells are sparse in the affected bile ducts in PSC, and the luminal side of the bile ducts, including lining biliary epithelial cells, is preferentially affected compared with IgG4-SC. In PSC, the fibrosis is denser and older, whereas in IgG4-SC, the entire bile

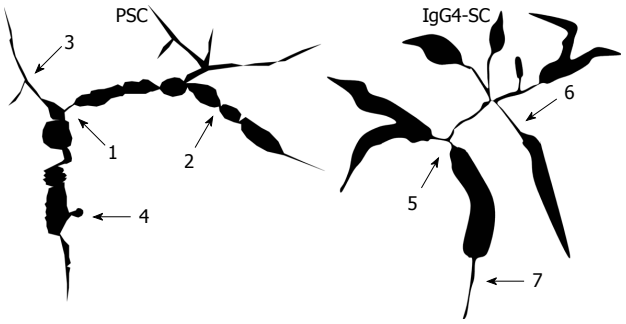

Figure 2 Schematic illustration of comparison of cholangiographic (primary sclerosing cholangitis *vs* IgG4-related sclerosing cholangitis) findings[28]. The schematic comparison of cholangiographic findings between IgG4-related sclerosing cholangitis (SC) and primary sclerosing cholangitis (PSC). IgG4-related SC displays segmental and long strictures and stricture of the lower common bile duct, whereas PSC displays band-like strictures (1-2 mm), beaded appearance (short and annular stricture alternating with normal or minimally dilated segments), pruned-tree appearance (diminished arbolization of intrahepatic duct and pruning), and diverticulum-like outpouching (outpouchings resembling diverticula, often protruding between adjacent strictures). 1: Band-like stricture; 2: Beaded appearance; 3: Pruned-tree appearance; 4: Dverticulum-like outpouching; 5: Segmental stricture; 6: Long stricture with prestenotic dilation; 7: Stricture of lower common bile duct.

duct wall and periductal tissue are affected. However, a recent study by Zhang *et al*[32] revealed that 23 (23%) of 98 liver explants with PSC had periductal infiltration with abundant IgG4-positive plasma cells [10/high-power field (HPF)] in the hilar area.

Differential diagnosis of IgG4-SC based on cholangiographic classification

IgG4-SC displays various cholangiographic features similar to those of PCa, PSC, and CC[9]. The differential diagnosis based on cholangiographic classification is sufficient in clinical practice because the useful modalities depend on the cholangiographic types (Figure 1)[20].

Type 1 IgG4-SC should be differentiated from chronic pancreatitis, PCa, and CC. The modalities useful for differential diagnosis are intraductal ultrasonography (IDUS)[3], endoscopic ultrasound-guided fine-needle aspiration for the pancreas[33], and cytological examination and/or biopsy of the bile duct[3,34].

Type 2 IgG4-SC should be differentiated from PSC. The modalities useful for differential diagnosis are cholangiography[35], evaluations for associated IBD[9,12], and liver biopsy[36,37]. Our discriminant analysis formula for cholangiographic features, including age, was able to discriminate type 2 IgG4-SC from PSC[35]. Band-like strictures, a beaded or "pruned tree" appearance, and diverticulum-like outpouching are significantly more frequent in PSC cases. In contrast, segmental strictures, long strictures with prestenotic dilation, and strictures of the lower common bile duct are significantly more common in IgG4-SC. These differences are illustrated in Figure 2. The characteristic cholangiographic features reflect the underlying pathological processes involved in each condition. In PSC, obliterative fibrosis is the main cause of biliary stenosis, creating short strictures. In contrast, in IgG4-SC, severe lymphoplasmacyte infiltration into bile ducts in the long region is the main cause of biliary stenosis, resulting in long strictures (Figure 3).

In contrast, Kalaitzakis *et al*[38] reported that diagnosing IgG4-SC by cholangiography displayed high specificity but poor sensitivity and may have led to the misdiagnosis of IgG4-SC as PSC or CC.

Associated ulcerative colitis is suggestive of PSC. IBD is present in only 0%-6% of patients with IgG4-SC[9,12,15]. IBD is usually not a feature associated with type 1 AIP, unlike the frequent association of IBD with type 2 AIP[23]. IBD associated with PSC represents a third phenotype in western countries[39]. Backwash ileitis, rectal sparing, and low disease activity appear to be features that characterize IBD when it is associated with PSC[39,40].

The histological features of IgG4-SC on liver biopsy are distinctive and, in conjunction with IgG4 immunohistochemical staining, help distinguish IgG4-SC from PSC[36,41]. We have already reported that liver needle biopsy is especially useful for distinguishing IgG4-SC from PSC in patients with cholangiographically evident intrahepatic biliary strictures[37]. Four (57%) of seven patients with type 2 IgG4-SC presented infiltration with $\geqslant$ 10 IgG4-positive plasma cells per HPF in liver biopsy samples, whereas none of the PSC patients presented this feature.

Types 3 and 4 IgG4-SC need to be discriminated from CC. The modalities useful for the differential diagnosis of types 3 and 4 IgG4-SC are endoscopic procedures[42] such as endoscopic ultrasonography, IDUS[3,43], cytological examination, and/or biopsy of the bile duct[3,34]. Although we described how type 2 IgG4-SC could be discriminated from PSC on the basis of characteristic cholangiographic features, cholangiography cannot discriminate the segmental stricture of types 3 and 4 IgG4-SC from CC. Therefore, we applied our discriminant analysis formula for cholangiographic features to discriminate between only type 2 IgG4-SC and PSC.

IDUS findings such as circular-symmetrical wall thickening, smooth outer margin, smooth inner margin, and homogeneous internal echo at the stenotic area were useful for the diagnosis of IgG4-SC. The most characteristic IDUS finding in the IgG4-SC cases was thickening of the bile duct wall, which appeared normal on cholangiography[3]. Bile duct wall thickening spread continuously from the intrapancreatic bile duct to the upper bile duct in most cases. To differentiate IgG4-SC from CC, 0.8-mm thickness of the bile duct wall that appeared normal on a cholangiogram was the best cutoff as indicated by ROC curves. The sensitivity, specificity, and accuracy were 95%, 90.9%, and 93.5%, respectively, when the cutoff value was 0.8 mm. No CC cases had a bile duct wall thicker than 1 mm. The sensitivity, specificity, and accuracy were 85%, 100%, and 87%, respectively, when the cutoff value was set at 1 mm. We considered a 1-mm thickness as an optimal cutoff wall thickness to completely exclude CC.

Ghazale *et al*[15] reported the usefulness of endoscopic biliary biopsy for diagnosis of IgG4-SC. They

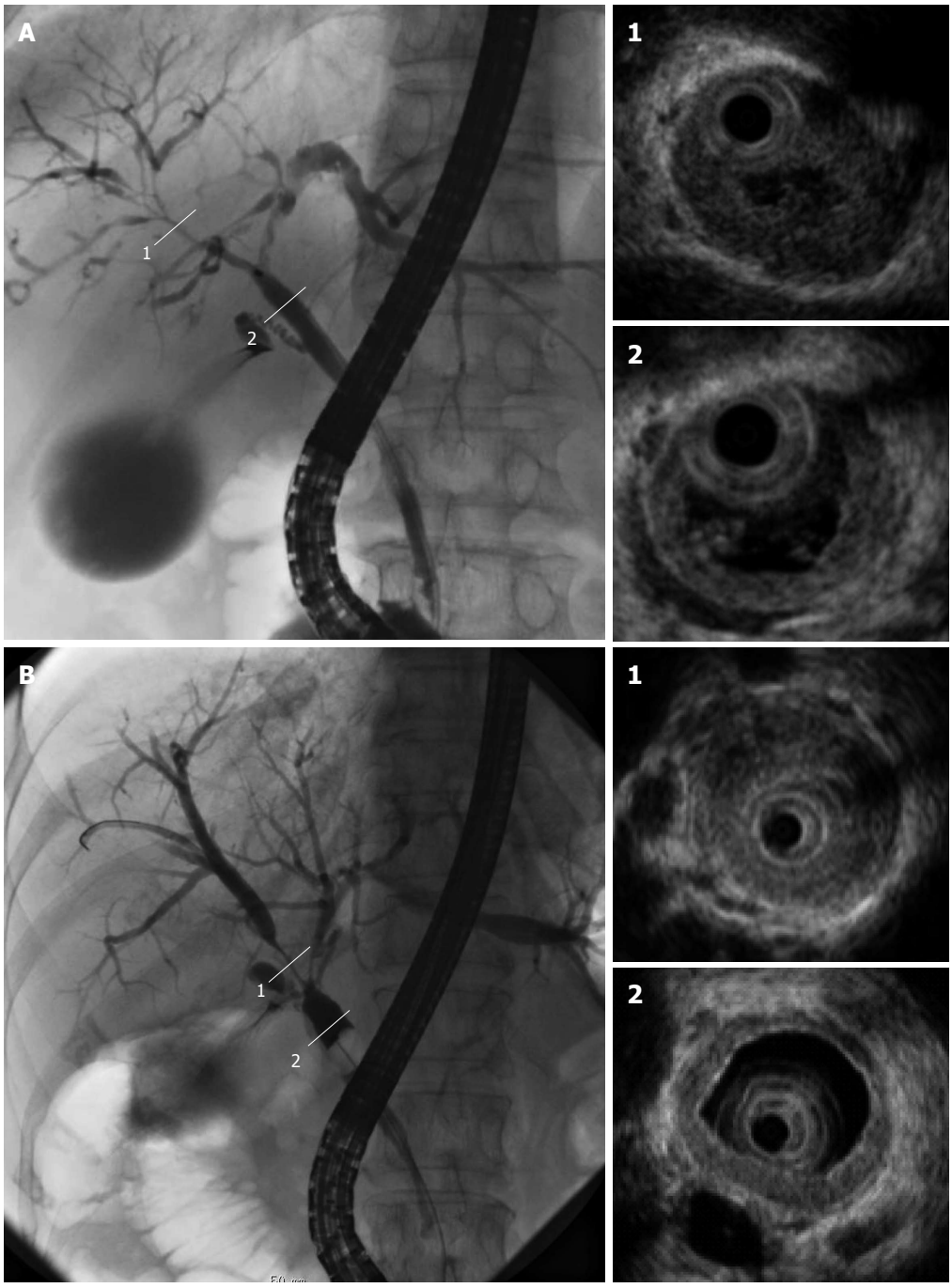

Figure 3 Cholangiogram displaying stenosis in the intrahepatic ducts (A-1) and hilar hepatic lesions (B-1); intraductal ultrasonography revealing bile duct wall thickening in areas with stenosis (1) and without (2).

reported that 14 (88%) of 16 patients had immunostaining results indicating abundant IgG4-positive cells (> 10 IgG4-positive cells/HPF) in bile duct biopsy specimens. Furthermore, they considered that the absence of malignant cells in the presence of an inflamed mucosa with many IgG4-positive plasma cells provided histological evidence to support the diagnosis of IgG4-SC. However, we were unable to diagnose any case as IgG4-SC on the basis of hematoxylin-eosin and elastin-van Gieson staining alone[3]. Abundant IgG4-positive plasma cells were observed in only three (18%) of 17 patients. We were able to diagnose IgG4-SC in only three patients (18%) on the basis of its characteristic histopathological features. However, it was possible to rule out CC by transpapillary biopsy. In addition, one of 11 CC cases presented with abundant IgG4-positive plasma cells. Zhang *et al*[32] also reported that abundant IgG4-positive plasma cells were evident in seven (18%) of 38 cases of CC. Harada *et al*[44] reported that CC cells could play the role of nonprofessional antigen-presenting cells and Foxp3-positive regulatory cells, inducing IgG4 reactions *via* the production of interleukin-10 indirectly and directly, respectively.

We could rule out CC by transpapillary biopsy. The superficial nature of endoscopic biopsy specimens lim-

its their usefulness for demonstrating the characteristic histological features of IgG4-SC. However, Kawakami *et al*[34] reported that the diagnostic rate from ampullary and bile duct biopsies was 52% (15/29 cases) based on the threshold of 10 IgG4-positive plasma cells per HPF, and that bile duct biopsy was valuable for patients with swelling of the pancreatic head. Ampullary biopsy is sometimes useful in the diagnosis of AIP and IgG4-SC[45,46].

Itoi *et al*[47] reported that cholangioscopy was useful in differentiating IgG4-SC from PSC and that monitoring patterns of proliferative vessels on video peroral cholangioscopy may be useful in differentiating IgG4-SC from CC.

Treatment and prognosis

Although some patients responded to biliary drainage or surgical resection, IgG4-SC displays a good response to steroid therapy, as is the case for pancreatic lesions.

Nishino *et al*[11] reported that bile duct stricture improved to various degrees in all 10 patients treated by steroid therapy but persisted in the lower part of the bile duct in four patients. Hirano *et al*[48] reported that steroid therapy could reduce AIP-related unfavorable events and that multivariate analysis indicated that steroid therapy and obstructive jaundice at onset were significant factors predictive of unfavorable events. Thus, early introduction of steroid therapy is recommended, especially for patients with obstructive jaundice. Ghazale *et al*[15] reported the clinical courses after steroid treatment (n = 30), surgical resection (n = 18), and conservative management (n = 5). Relapses occurred in 53% of cases after steroid withdrawal, whereas 44% relapsed after surgery and were further treated with steroids. The presence of proximal extrahepatic/intrahepatic strictures was predictive of relapse. Steroid therapy normalized liver enzyme levels in 61% of patients, and it was possible to remove biliary stents in 17 of 18 patients. Fifteen patients treated with steroids for relapse after steroid withdrawal responded to the treatment, and seven treated with additional immunomodulatory drugs reportedly remained in steroid-free remission. Topazian *et al*[49] reported that biliary strictures in one patient improved after rituximab therapy and thus the biliary stents were removed. However, the role of immunomodulatory drugs for relapse warrants further study. In one of our series, six of seven cases of IgG4-SC without steroid therapy and IgG levels > 2000 mg/dL were associated with significantly higher incidence of recurrence or progression[50].

Morphological and functional changes in the liver and bile ducts in IgG4-SC during long-term observation have not yet been reported. Our long-term follow-up of IgG4-SC cases without steroid therapy revealed that two patients developed portal obstruction and liver atrophy but no sign of liver cirrhosis or failure[51]. Ghazale *et al*[15] reported that four of 53 patients displayed portal hypertension and liver cirrhosis during their clinical courses. It is possible that persistent jaundice without steroid administration could result in liver failure, thus necessitating orthotopic liver transplantation. However, further study is needed to elucidate the long-term outcome of IgG4-SC.

Steroid trial

Although, generally, diagnosis should be made before starting therapy, a steroid trial is needed in some cases[52]. If a diagnosis cannot be clearly established in type 2 IgG4-SC, then a steroid trial is recommended. If malignancy is not confirmed by bile duct biopsy in types 3 and 4 IgG4-SC and bile duct wall thickening that appears normal on a cholangiogram, a steroid trial is an option. No reports on any steroid trial for IgG4-SC have been published thus far. A short-term steroid trial should be performed carefully only by specialists in pancreatic and biliary diseases. In addition, steroid pulse therapy is also an option[53]. Advanced-stage IgG4-SC may sometimes be unresponsive to steroid therapy because cases of AIP and IgG4-SC show a predominantly inflammatory nature at the early stage, followed by relatively less inflammation but marked fibrous scarring later. This should be kept in mind when attempting a steroid trial for IgG4-SC diagnosis[54]. The time frame for a steroid trial for IgG4-SC remains unknown. When a cholangiogram is indicative of type 1, 3 or 4 IgG4-SC, IgG4-SC should be discriminated from PCa or CC. It is important not to delay the timing of surgery by performing a long-term steroid trial. If a cholangiogram is indicative of type 2 IgG4-SC, IgG4-SC should be discriminated from PSC. Sufficient time should be devoted to a steroid trial only if an increased risk of biliary infection can be avoided.

Diagnostic criteria

Only three sets of diagnostic criteria for IgG4-SC have been proposed[15,20,24]. AIP should be clinically discriminated only from PCa. However, IgG4-SC should be discriminated from all of the three intractable diseases, that is, PCa, PSC, and CC. Therefore, diagnostic criteria that take into account the differential diagnosis between these three intractable diseases need to be established[22]. Our diagnostic criteria provide a concrete diagnostic algorithm for IgG4-SC (Figure 4). Association with AIP and other organ involvements are common useful diagnostic parameters in all three IgG4-SC types. Characteristic cholangiogram, liver biopsy and exclusion of IBD are useful parameters in type 2 IgG4-SC. IDUS findings, exclusion of malignancy by bile duct biopsy and a serum IgG4 cut-off level of 207 mg/dL were useful parameters in type 3 and 4 IgG4-SC. Although, generally, diagnosis should be made before starting therapy, a steroid trial is needed in some cases.

The HISORt criteria for the diagnosis of IgG4-SC[15] are based on the characteristic features of IgG4-SC on histological, imaging, and serological examination; other organ involvement; and response to steroid therapy, which parallel the HISORt criteria established for AIP[55].

The Research Committee of IgG4-related Diseases and the Research Committee of Intractable Diseases of Liver and Biliary Tract, in association with the Ministry

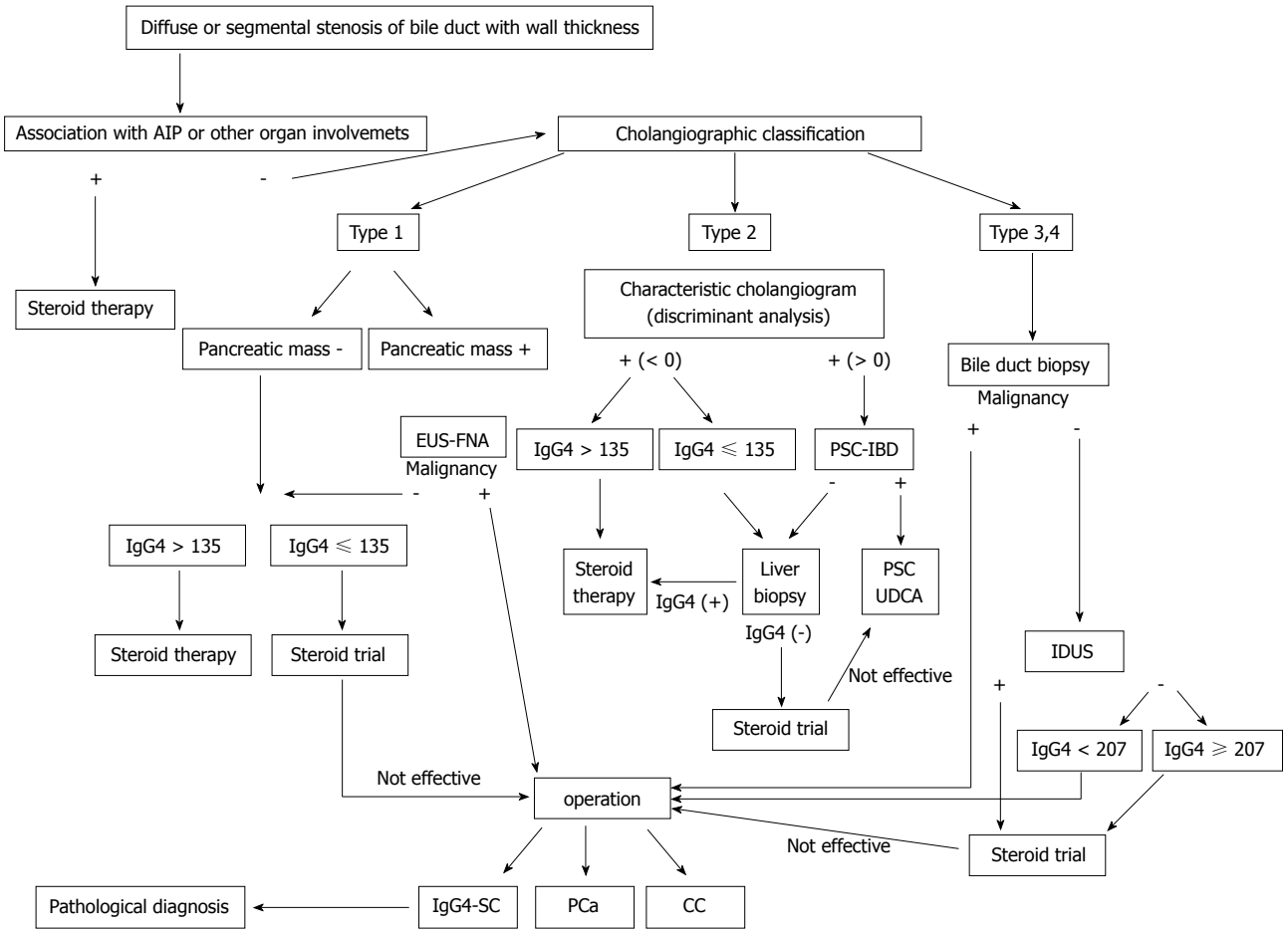

Figure 4 Algorithm for management of IgG4-related sclerosing cholangitis (cited from [22]). CC: Cholangiocarcinoma; PSC: Primary sclerosing cholangitis; IgG4-SC: IgG4-related sclerosing cholangitis; IDUS: Intraductal ultrasonography; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; IBD: Inflammatory bowel disease; UDCA: Ursodeoxycholic acid.

of Health, Labor and Welfare, Japan, and the Japan Biliary Association, proposed clinical diagnostic criteria for IgG4-SC in 2012[20]. These diagnostic criteria also include the concept of differential diagnosis based on cholangiographic classification.

CONCLUSION

Since IgG4-SC was first described, it has become a third distinct clinical entity of SC. IgG4-SC should be carefully diagnosed based on a combination of characteristic clinical, serological, morphological, and histopathological features after cholangiographic classification and targeting of a disease for differential diagnosis.

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