IgG4-Related Sclerosing Cholangitis: A Clinical and Imaging Review

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OBJECTIVE. The purpose of this article is to present the pathologic and clinical features of IgG4-related sclerosing cholangitis (ISC), illustrate the associated imaging findings, and discuss treatment of the disorder.

CONCLUSION. ISC is an inflammatory disorder involving the biliary system and resulting in strictures. Although often associated with autoimmune pancreatitis, it may be an isolated disease. Differentiation of ISC from other forms of cholangitis and cholangiocarcinoma is difficult but necessary for management. Imaging is important in diagnosing and assessing the extent of disease and planning a management strategy.

Keywords: autoimmune pancreatitis, IgG4-related disease, IgG4-related sclerosing cholangitis, primary sclerosing cholangitis, sclerosing cholangitis

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IgG4-related sclerosing cholangitis (ISC), or autoimmune cholangiopathy as it is also known, is a chronic inflammatory disease of the biliary system that occurs most commonly in association with other manifestations of IgG4-related systemic disease but can occur at times in isolation [1, 2]. In 1991, Kawaguchi et al. [3] first described this disease as lymphoplasmacytic sclerosing pancreatitis with cholangitis, and in 1995 Yoshida et al. [4] referred to it as autoimmune pancreatitis. Its association with elevated serum IgG4 levels was later identified, and the concept of IgG4-related autoimmune disease was proposed [5, 6]. IgG4-related disease is now recognized as a systemic disorder that can affect multiple organs, including the biliary system. ISC is a relatively new entity, and our understanding of the disease has therefore been evolving over the past decade. Although ISC is associated with autoimmune pancreatitis in 90% of cases, approximately 10% of cases are isolated [7]. ISC is seen in up to 39% of patients with autoimmune pancreatitis [8]. ISC is associated with type 1 autoimmune pancreatitis which shows the classsic lymphoplasmacytic infiltration, but it has not shown any association with type 2 autoimmune pancreatitis. Although to our knowledge no epidemiologic studies are available, ISC appears to be more prevalent in Japan than in other countries, with most of the published literature originating from that country [9]. The cause of ISC still is not clearly known, although autoimmune diseases and allergy have shown some association [1].

ISC often mimics biliary malignancy or other sclerosing cholangiopathies. Thus, a thorough knowledge of ISC is necessary to suspect the disease, perform appropriate investigations, and administer suitable treatment. The aim of this article is to illustrate the various imaging appearances of ISC that should aid in differentiating it from other diseases that mimic ISC, in addition to providing a brief description of its pathologic findings, clinical manifestations, diagnosis, and treatment options.

Pathologic Findings

The pathologic findings associated with ISC are distinctive and assist in making an accurate diagnosis [10–12]. Similar to other IgG4-related diseases, ISC is characterized by transmural lymphoplasmacytic infiltration in the walls of the biliary tree and peribiliary tissue with associated fibrosis [13]. The epithelium is typically normal (unlike in primary sclerosing cholangitis [PSC]). The triad of dense lymphoplasmacytic infiltration, obliterative phlebitis, and storiform interstitial fibrosis is characteristic of ISC (Fig. 1). Inflammation is mainly localized in the subepithelial layer with preserved mucosa. The diagnostic characteristic is the presence of IgG4-positive plasma cells (with more than 10 such cells present per high-power field in the biopsy sample), and the ratio of IgG4-positive cells to IgG-

positive cells should be more than 40% for a positive diagnosis to be made [11, 14, 15]. The lymphocytes are predominantly T cells with some B cells interspersed. In storiform fibrosis, the spindle cells radiate from the center like the spokes of a cartwheel. This finding may be missed in small samples, such as those obtained from needle biopsies. In obliterative phlebitis, infiltration of the lymphocytes and plasma cells in the wall and lumen of small- and medium-sized veins frequently results in the occlusion of such veins. Immunostaining tissue samples to determine the presence of IgG4 is increasingly recommended because it provides a strong confirmatory diagnosis [11]. However, studies have identified IgG4-positive cells even in PSC and cholangiocarcinoma, making this finding alone less specific [16, 17].

Additional findings include phlebitis without occlusion of the lumen and infiltration by eosinophils. Epithelioid cell granulomas and neutrophils are extremely unusual histologic findings and should point to an alternative diagnosis [18].

However, it is difficult to obtain adequate tissue from the bile ducts preoperatively, and pathologic analysis therefore seldom provides diagnostic evidence [19]. In cases of isolated ISC, diagnosis often relies on imaging and other supporting evidence.

Clinical Presentation

Most patients with ISC clinically present in their 7th or 8th decade of life [9, 20]. The disease is more commonly seen in men, with a male-to-female ratio of 4:1–8:1 [7, 20, 21]. Although no predisposing factors have been identified, ISC has been shown to be associated with a few allergic diseases, such as bronchial asthma, sinusitis, and drug allergies, in up to 20% of cases [22].

The presenting symptoms of ISC vary. The most common presentation is chronic or recurrent cholestatic jaundice, which may be seen in up to 75% of patients [23]. Associated symptoms include pruritus, fever caused by cholangitis, abdominal pain, and weight loss [14]. Sometimes the main presenting symptom may be due to another primary organ that is involved (e.g., the pancreas), and biliary involvement is detected incidentally. Autoimmune pancreatitis type 1, which is also an IgG4-related disease, predominantly presents with obstructive jaundice resulting from a mass in the head of pancreas, even without primary bile duct involvement. Uncommonly, the disease may be incidentally detected in the form of abnormal liver function test results or on imaging [24].

Laboratory investigations show elevated serum bilirubin and alkaline phosphatase levels in most patients with ISC. Serum alanine and aspartate aminotransferase levels may be mildly elevated. The serum IgG4 level is elevated in most patients with ISC [25]. Its sensitivity and specificity in diagnosing ISC depends on the cutoff level used. When a cutoff level of greater than 1.4 g/L is used, elevated levels are seen in 80% of patients with ISC. However, when the cutoff level is higher (> 2.8 g/L), the specificity is 90% but the sensitivity decreases to only 50% [25]. Furthermore, the IgG4 level may be increased in 10% of patients with PSC, 15% of patients with cholangiocarcinoma, and 5% of the healthy population [25–27]. A ratio of serum IgG4 to total IgG greater than 0.10 and a ratio of serum IgG4 to IgG1 of greater than 0.24 have also been suggested as useful in differentiating ISC from other cholangiopathies [26].

Imaging

Imaging is important not only in raising suspicion for ISC but also in detecting biliary involvement in IgG4-related systemic disease, defining the type and extent of biliary involvement, and assessing the response to therapy.

Sonography

Sonography (or ultrasound [US]) is the initial investigation used for most patients presenting with clinical symptoms suggestive of ISC. In the early stages of the disease, US findings are usually normal. Later in the course of the disease, however, US shows circumferential wall thickening of the bile duct (intrahepatic, extrahepatic, or both) and dilatation of intrahepatic bile ducts [28] (Fig. 2). One characteristic feature of ISC is that the lumen of the duct is often maintained despite the presence of wall thickening [29, 30]. Koyama et al. [31] described a trilaminar appearance of bile duct wall thickening in 64% of their patients and a parenchymal echo type of wall thickening in 36%. However, US has low sensitivity in detecting the disease and is suboptimal for assessing the extent of the disease. The findings are not specific and do not differentiate ISC from PSC or cholangiocarcinoma.

Associated diffuse wall thickening of the gallbladder may develop [28, 31]. US also helps in the identification of associated findings—most commonly, autoimmune pancreatitis in which a diffusely bulky pancreas is seen, often with a hypoechoic halo around it (Fig. 2B). In addition, US may occasionally be useful in acting as a guide for tissue sampling from the involved pancreas.

Intraductal US provides high-resolution images of the duct wall and reliably shows the extent of bile duct wall thickening [29]. On intraductal US, the involved segments show diffuse symmetric homogeneous wall thickening with smooth margins. The lumen is often preserved despite the wall thickening. On intraductal US, use of a cutoff value of 0.8 mm for bile duct wall thickness in areas without strictures (a characteristic feature of ISC) has a sensitivity and specificity of 95–100% and 91%, respectively, for differentiating ISC from cholangiocarcinoma [29, 32]. Endoscopic US also shows bile duct wall thickening in approximately 94% of patients with ISC [33, 34]. It is also useful in obtaining tissue samples either from the thickened bile duct or from the pancreas, if involved [19].

CT

CT with IV contrast medium, although not the investigation of choice for patients with biliary diseases, may show findings of biliary involvement when it is performed for the evaluation of abdominal pain or suspected autoimmune pancreatitis. It shows bile duct wall thickening and mild dilatation of proximal ducts.

Some studies have reported that CT findings differentiate ISC from infiltrative cholangiocarcinoma [35, 36]. The most important finding is circumferential symmetric wall thickening of the bile ducts, frequently involving the extrahepatic segments, with smooth outer and inner margins [30] (Fig. 3). The involved bile ducts show luminal narrowing; however, the lumen is often visible despite the wall thickening. The dilatation of bile ducts proximal to the strictures is less (usually < 9 mm) and often has a funnel shape [35, 36]. In addition, the thickened segment shows progressive homogeneous contrast enhancement, with more enhancement seen in the delayed phase [30].

The intrapancreatic bile duct segment is more commonly involved [35]. Associated skip lesions with involvement of the intrahepatic and extrahepatic bile ducts may be present. Yata et al. [35], in their comparative study of the imaging features of ISC and cholangiocarcinoma, found that the presence of a combination of the aforementioned findings on CT was 80% sensitive and specific in differentiating ISC from cholangiocarci-

TABLE 1: Classification of IgG4-Related Sclerosing Cholangitis Based on Cholangiographic Features

Type	Description	Frequency (%) [46]
1	Involvement of lower part of bile duct only	64
2a	Involvement of distal bile duct and intrahepatic bile duct with proximal dilatation	5
2b	Involvement of distal bile duct and diffuse intrahepatic bile duct without proximal dilatation	8
3	Involvement of distal bile duct and ducts at hepatic hilum	10
4	Involvement of ducts at hepatic hilum only	10

Note—Features were classified using the criteria identified by Nakazawa et al. [44].

noma and that the presence of dual-layered contrast enhancement of the bile duct wall (as opposed to single-layered enhancement) was 90% specific for cholangiocarcinoma.

The gallbladder shows diffuse hypoattenuated wall thickening in approximately 15% of patients [36] (Fig. 3B). Autoimmune pancreatitis is seen in more than 90% of patients with ISC [35] (Fig. 3). Involvement of other organs, like the kidneys and retroperitoneum, helps in suggesting a diagnosis.

MRI

MRI is the investigation of choice for assessing the biliary system in patients with suspected ISC and autoimmune pancreatitis. MRI findings are similar to CT findings and include bile duct wall thickening, single or multifocal involvement, smooth margins of wall thickening, long segment stricture, visible lumen in the thickened segments, and delayed homogeneous contrast enhancement [24, 37] (Figs. 4–6). Additional findings include bile duct wall thickening showing isointense to hypointense signal on T2-weighted images and diffusion restriction similar to that seen in autoimmune pancreatitis [28, 38] (Figs. 4–6). Masslike thickening of the hilar ducts presenting as a pseudotumor sometimes may be seen [39] (Fig. 6). This masslike thickening appears to be similar to some types of hepatic hilar inflammatory pseudotumor (e.g., the lymphoplasmacytic type) reported before the identification of its association with IgG4 [9, 39]. Nontypically, intraductal calculi may be present proximal to a stricture. Liver morphologic findings are usually normal, unlike in PSC [37]. Tokala et al. [37] suggested that a combination of findings of bile duct wall thickness greater than 2.5 mm, continuous involvement of the bile ducts, gallbladder involvement, and absence of hepatic parenchymal involvement was accurate in differentiating ISC from PSC.

Gallbladder involvement, seen in approximately 51% of patients, is usually in the form of diffuse wall thickening and enhancement [37]. Isolated gallbladder involvement without bile duct involvement is rare, with only a few cases reported. In isolated gallbladder involvement, wall thickening may be diffuse or focal, and it can mimic a carcinoma [40].

Associated findings, such as pancreatic involvement (seen in up to 90% of cases) (Figs. 4 and 5), renal lesions (nonenhancing hypoattenuated or hypointense lesions), retroperitoneal soft tissue, and lacrimal gland and salivary gland involvement assist in making a diagnosis. An additional role of MRI is in the follow-up of these patients to assess response to therapy [28].

PET

The role of FDG PET/CT in ISC, similar to that in IgG4-related systemic disease, is increasingly being evaluated [41, 42]. The involved bile ducts in ISC show uptake of FDG on PET/CT scans. Although it may not suggest the diagnosis of ISC in isolation, the presence of multiorgan uptake is helpful. Furthermore, PET/CT may help in suggesting which tissue to sample and in monitoring treatment response [41, 42]. However, the utility of PET/CT in the differentiation of ISC from PSC or malignancy is not yet clear.

ERCP

Previously, ERCP was commonly used in the diagnosis of ISC. It was not reliable in differentiating ISC from other similar lesions, with a sensitivity and specificity in diagnosing ISC of 45% and 88%, respectively [43]. However, with increasing understanding of the disease, and with the availability of MRI, which delineates the entire biliary system and shows the extent of the disease, extraluminal abnormalities, and other organ involvement, the utility of ERCP has been restricted to situations in which an intervention, like stent placement, is needed [22].

Nakazawa et al. [44] classified ISC into four different types on the basis of the cholangiographic appearance and location of strictures (Fig. 7). These types are described in Table 1. Different types mimic different diseases, with type 1 mimicking pancreatic carcinoma; type 2, PSC; and types 3 and 4, cholangiocarcinoma. This classification also helps in suggesting the next line of investigation: either intraductal US or endoscopic US combined with guided sampling, for types 1, 3, and 4, and liver biopsy, for type 2 [45]. The same classification can be applied to the cholangiographic appearance observed on MRCP.

Table 1 shows the frequency of different types of ISC when the disease is seen in association with autoimmune pancreatitis [46]. However, when ISC occurs in isolation, type 4 is most common, mimicking Klatskin tumor [7].

Newer Endoscopic Techniques

Few newer endoscopic techniques are now available that assist in making a diagnosis of ISC. Fluorescent in situ hybridization of the biopsy samples obtained has been shown to be helpful in differentiating ISC from cholangiocarcinoma and improving the sensitivity of routine H and E staining from 69.4% to 77.6% [47]. Cholangioscopy (Spyglass, Boston Scientific) allows direct visualization of the bile duct lesions and helps in obtaining biopsy specimens [48]. In ISC, it characteristically shows dilated and tortuous vessels in the bile duct wall and is useful in differentiating ISC from primary sclerosing cholangitis or cholangiocarcinoma [49]. Improvements in cholangioscopy, such as narrow band imaging, chromoendoscopy, and autofluorescence imaging, allow enhanced and more detailed visualization resulting in better characterization of bile duct lesions [50].

Diagnostic Criteria

Two proposed sets of diagnostic criteria for ISC exist in the literature. One is the HISORt (histologic findings, characteristic imaging features, positive serologic findings, other organ involvement, and response to steroid therapy) criteria, and the other is the Japanese criteria [9, 51, 52].

The HISORt criteria, which include diagnostic features similar to those used in the diagnosis of autoimmune pancreatitis, were

TABLE 2: HISORt Criteria for Diagnosis of IgG4-Related Sclerosing Cholangitis

Criteria	Description
Histologic findings	Characteristic lymphoplasmacytic infiltration (> 10 IgG4-positive plasma cells per high-power field), obliterative phlebitis, and storiform fibrosis
Imaging	Single or multiple bile duct strictures (intrahepatic, extrahepatic, or both), fleeting biliary strictures
Serologic finding	Elevated serum IgG4 level (> 135 mg/dL)
Other organ involvement	Pancreas (autoimmune pancreatitis), kidneys, retroperitoneum, salivary glands, or lacrimal glands
Response to steroid therapy	Improvement in liver function tests, bile duct strictures, or both

Note—HISORt = **h**istologic findings, characteristic **i**maging features, positive **s**erologic findings, **o**ther organ involvement, and **r**esponse to steroid **t**herapy.

defined by Ghazale et al. [51] and are presented in Table 2. Ghazale and colleagues suggested that a diagnosis of ISC can be made if histologic analysis reveals typical features, if features of autoimmune pancreatitis are present along with elevated serum IgG4 levels, or if there is a response to steroid therapy.

The Japanese criteria, which were recommended by Ohara et al. [52], not only include similar diagnostic features but also suggest different diagnostic categories (i.e., definitive, probable, and possible diagnoses) based on combinations of these features. The Japanese criteria are shown in Table 3.

These criteria show that imaging plays an important role in making the diagnosis, particularly when multiple organs are involved, which is often the case.

Differential Diagnosis

The imaging appearance of ISC is mimicked by diseases affecting the biliary system, most commonly PSC and cholangiocarcinoma. Differentiating among them is important for the appropriate management of patients.

Primary Sclerosing Cholangitis

PSC is mainly seen in younger patients. The intra- and extrahepatic bile ducts are involved in most cases [53]. Multiple biliary strictures are typically present, with a beaded appearance on MRCP (Fig. 8A). The strictures are often short in length, with only mild dilatation of the intervening segments observed [37, 38]. Ductal wall thickening is less than that seen with ISC. Bile duct diverticula, a characteristic feature, are seen on ERCP in 39% of patients and on MRCP in 12% [38]. The liver parenchyma shows hypertrophy of the caudate lobe and atrophy of the left lateral segments [54, 55]. In late stages of PSC, the appearance of the bile ducts resembles that of a pruned tree [53]. Associated inflammatory bowel disease, usually ulcerative colitis, is present in up to 80% of cases [56]. This disease responds poorly to steroids.

Cholangiocarcinoma

The infiltrating variety of cholangiocarcinoma mimics ISC on imaging. However, in cholangiocarcinoma, the duct involvement is unifocal, the wall thickening is asymmetric with a fuzzy or irregular outline, the stricture is short and eccentric, and the proximal dilatation is gross [35, 36] (Fig. 8B). These features have greater than 80% accuracy in differentiating cholangiocarcinoma from ISC.

Table 4 shows the differentiating features of ISC, PSC, and cholangiocarcinoma.

TABLE 3: Japanese Diagnostic Criteria for Diagnosis of IgG4-Related Sclerosing Cholangitis

Diagnostic Items or Diagnosis	Description
Diagnostic items	
(1)	Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of the bile duct wall
(2)	Hematological examination shows elevated serum IgG4 concentrations (≥ 135 mg/dL)
(3)	Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis
(4)	Histopathological examination shows:
(a)	Marked lymphocytic and plasmacyte infiltration and fibrosis
(b)	Infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF
(c)	Storiform fibrosis
(d)	Obliterative phlebitis
Option:	Effectiveness of steroid therapy
A specialized facility, in which detailed examinations such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be administered, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out.	
Diagnosis	
Definite diagnosis	(1) + (3) (1) + (2) + (4) a, b (4) a, b, c (4) a, b, d
Probable diagnosis	(1) + (2) + option
Possible diagnosis	(1) + (2)
It is necessary to exclude PSC, malignant diseases such as pancreatic or biliary cancers, and secondary sclerosing cholangitis caused by the diseases with obvious pathogenesis. When it is difficult to differentiate from malignant conditions, a patient must not be treated with facile steroid therapy but should be referred to a specialized medical facility.	

Note—HPF = high power field, PSC = primary sclerosing cholangitis. Reproduced from Ohara H, Okazaki K, Tsubouchi H, et al., Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012, *J Hepatobiliary Pancreat Sci* 2012; 19:536–542 with permission of John Wiley and Sons. Copyright 2012 Japanese Society of Hepato-Biliary-Pancreatic Surgery.

TABLE 4: Imaging Features Assisting in Differentiation of IgG4-Related Sclerosing Cholangitis (ISC), Primary Sclerosing Cholangitis (PSC), and Cholangiocarcinoma (CCA)

Imaging Feature	ISC	PSC	CCA
Location	Extrahepatic > intrahepatic	Extrahepatic plus intrahepatic mostly	Hilar more often than extrahepatic more often than intrahepatic
Length of involvement	Long, continuous	Short, multiple	Short, single
Duct wall thickening	Symmetric, often > 2.5 mm	Symmetric, usually < 2.5 mm	Asymmetric, > 5 mm
Margins of thickening	Sharp and smooth	Fuzzy and smooth	Fuzzy and irregular
Lumen of thickened segment	Often visible	Often occluded	Mostly occluded
Duct dilatation	Less (< 9 mm)	Mild	Gross
Contrast enhancement	Single layer	Uniform	Double layer
Skip lesions	Common	Less common	Rare
Liver parenchymal changes	Seen in late stages	Common	Rare
Others	Funnel-shaped dilatation	Pruned tree ducts, diverticula	Vascular invasion
Associations	Autoimmune pancreatitis type I	Inflammatory bowel disease	Usually none
Serum IgG4 level	Elevated in majority	Usually normal	Usually normal
Response to steroids	Good	Poor	No response

Recurrent Pyogenic Cholangitis

Recurrent pyogenic cholangitis is a type of biliary disease that causes bile duct strictures and hepatolithiasis and is associated with infection by *Clonorchis sinensis* or *Ascaris lumbricoides* [57]. It has been reported mainly in East Asian countries. MRCP typically shows dilated intrahepatic bile ducts, bile duct strictures, often intrahepatic strictures without much wall thickening, calculi within the dilated bile ducts, and morphologic changes like atrophy (of the left lateral or right posterior segments) or hypertrophy (of the caudate or left medial segments of the liver) [57, 58] (Fig. 8C). An abrupt change in the caliber of peripheral intrahepatic bile ducts often occurs.

Other biliary diseases that mimic ISC include ischemic cholangiopathy, infective causes like AIDS, tuberculosis, ascariasis, and eosinophilic cholangitis. Ischemic cholangiopathy is usually seen in the clinical setting of hepatic arterial injury (liver transplant and biliary or pancreatic surgeries) and mostly involves hilar ducts or mid common bile duct [59]. In AIDS cholangiopathy, papillary stenosis and long segment and multifocal strictures with enhancing walls are present. AIDS cholangiopathy is seen in patients with a CD4 count lower than 100 cells/mm^3. Eosinophilic cholangitis may be diagnosed in patients with peripheral eosinophilia, long segment bile duct stricture, and wall thickening of the cystic duct and gallbladder [60].

Treatment and Follow-Up

The mainstay of treatment for patients with ISC is corticosteroids, which produce good results [9, 20, 46, 51]. Without treatment, few patients (5–7.5%) have been shown to develop cirrhosis, and death occurs in up to 13% of patients [46, 51, 61]. Cholangiocarcinoma very rarely may develop in the involved biliary segment [62].

Treatment is started with high-dose corticosteroids (prednisolone, 30–40 mg/day) and is followed by gradual tapering of the dose, depending on the response. After remission occurs, a low maintenance dose (2.5–5 mg/day) is administered for 1–3 years [20]. The patients usually respond in 4–6 weeks, as shown by normalization of liver function test results, reduction in serum IgG4 levels, and improvement in biliary strictures (Fig. 9). Good clinical response and either improvement in or resolution of biliary strictures are seen in 97% of patients [51]. Biliary drainage (endoscopic or percutaneous) may be required for those with a bilirubin level higher than 5 mg/dL, cholangitis, or both. When the diagnosis is uncertain, a steroid trial is started after exclusion of malignancy [51, 63]. Its response is assessed within 1–2 weeks using liver function tests, serum IgG4 level, and MRCP or ERCP.

Bile duct involvement is a factor that predicts a high likelihood of relapse in patients with autoimmune pancreatitis and IgG4-related disease. Relapse of disease with bile duct strictures is common if steroid therapy is stopped after 8–12 weeks and is seen in up to 54% of patients [51]. In a large retrospective study by Tanaka et al. [46] that involved 527 patients, relapse of bile duct stenosis after treatment was seen in 104 patients (19.7%). These patients may be treated with another course of steroids or other immunomodulatory drugs or with rituximab [51].

Follow-up of these patients involves clinical evaluation, liver function tests, and assessment of the serum IgG4 level after 4–8 weeks of steroid treatment [51]. Although no protocol has been recommended, imaging may be performed using either US or MRCP, preferably the latter, especially for patients in whom a stent was placed. MRCP shows improvement in the biliary involvement and strictures better than does US (Fig. 9).

Conclusion

In conclusion, ISC is an uncommon but increasingly recognized disorder affecting the biliary system, usually occurring as a part of IgG4-related disease or sometimes in isolation. Clinical and laboratory findings and characteristic imaging features, as described previously in this article, frequently assist in making an accurate diagnosis. A few other conditions mimic ISC and histologic confirmation often is necessary. Treatment with steroids is effective.

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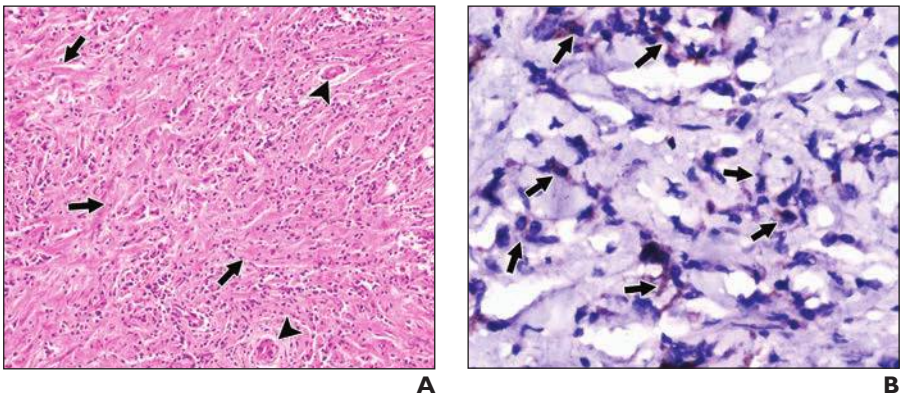


Fig. 1—57-year-old woman with IgG4-related sclerosing cholangitis who had histologic analysis of bile duct sample performed.
A, Photomicrograph (H and E, ×200) shows lymphocyte and plasma cell infiltrate with extensive fibrosis in storiform pattern (*arrows*) and obliterative phlebitis (*arrowheads*).
B, Photomicrograph (immunohistochemical stain for IgG4 antigen [MRQ-44, dilution 1:400, Bio SB], ×400) shows IgG4-positive plasma cells (> 10 cells per high-power field) (*arrows*).

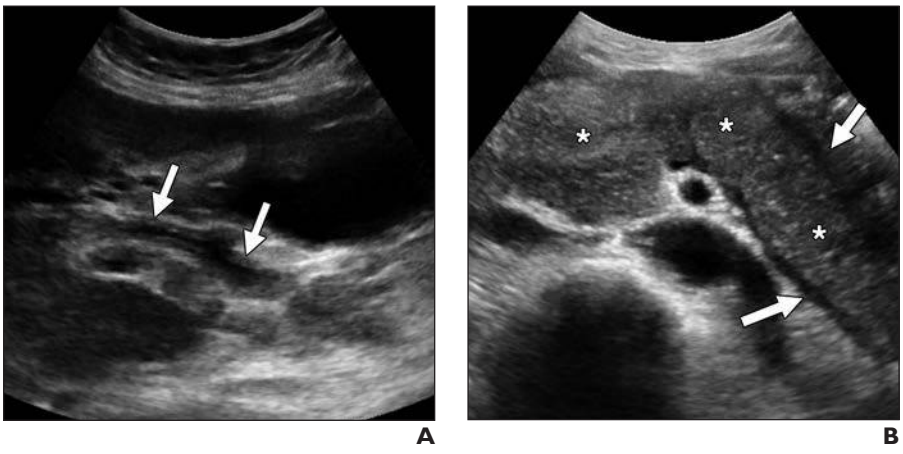


Fig. 2—64-year-old man with autoimmune pancreatitis and IgG4-related sclerosing cholangitis.
A, Longitudinal ultrasound image of common bile duct shows diffuse, circumferential wall thickening with sharp margins (*arrows*). Lumen is still visible.
B, Axial ultrasound image shows diffuse enlargement of pancreas (*asterisks*) with hypoechoic halo (*arrows*).

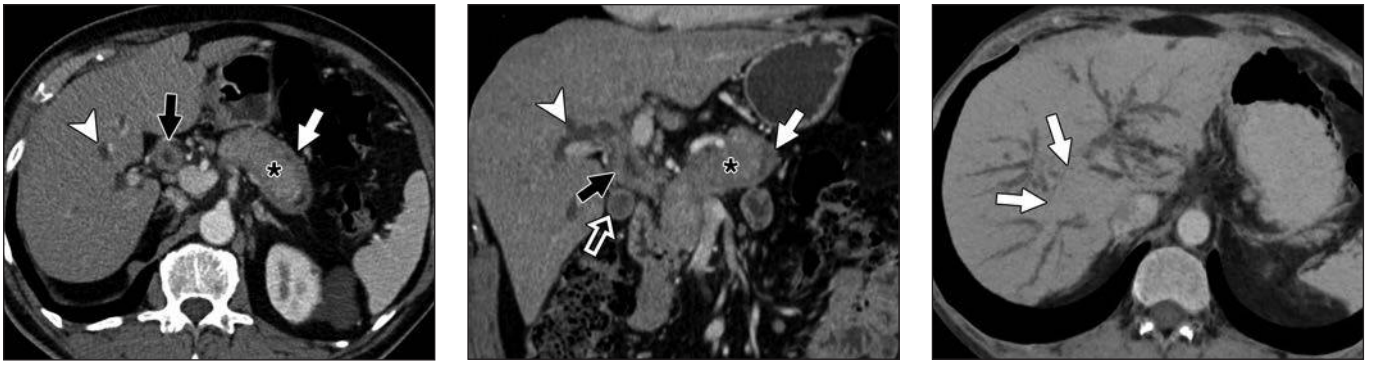


Fig. 3—CT appearances of biliary involvement.
A and **B,** 66-year-old man with autoimmune pancreatitis. Axial (**A**) and coronal (**B**) contrast-enhanced CT images show diffusely bulky pancreas (*asterisk*) with hypoattenuated halo (*solid white arrow*). There is uniform, well-marginated wall thickening of common bile duct (*solid black arrow*) with dilatation of intrahepatic bile ducts (*arrowhead*) suggesting IgG4-related sclerosing cholangitis (ISC). Mild wall thickening of gallbladder is also seen (*open white arrow*, **B**).
C, 44-year-old man with ISC. Axial minimum-intensity-projection CT image shows stricture involving primary and right secondary biliary confluence (*arrows*) with proximal dilatation.

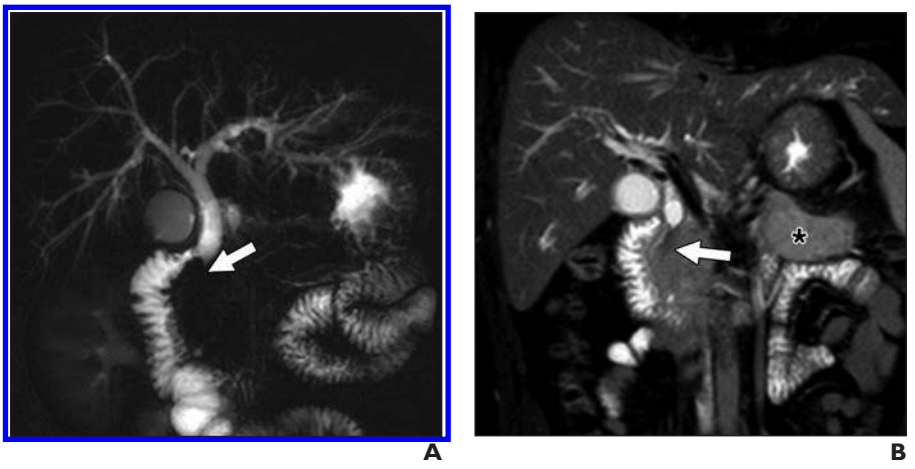


Fig. 4—33-year-old man with autoimmune pancreatitis.
A, MRCP image shows abrupt tapering of distal common bile duct (CBD; *arrow*) with proximal biliary dilatation. Pancreatic duct is poorly visualized.
B, Coronal T2-weighted MR image shows hypointense wall thickening of distal CBD (*arrow*) with diffuse bulky pancreas (*asterisk*).

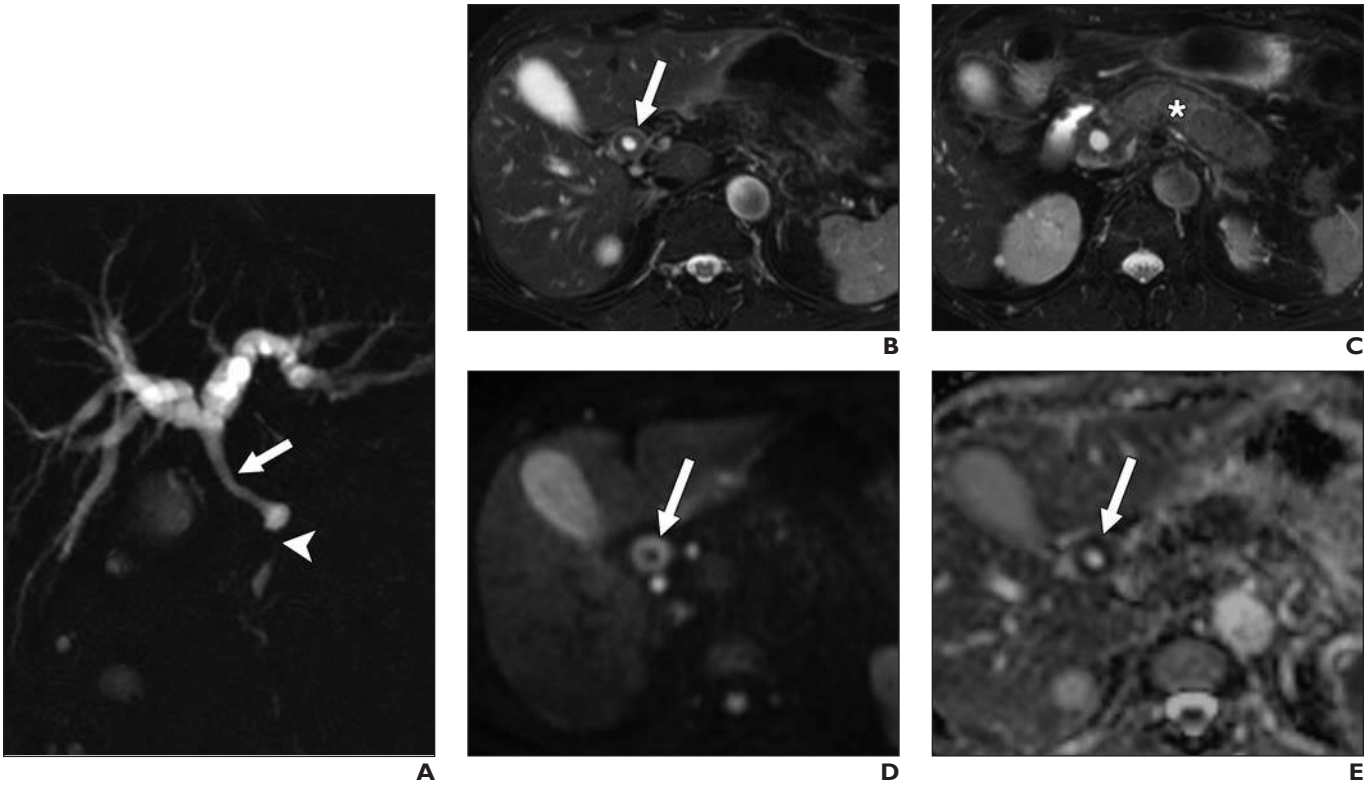


Fig. 5—66-year-old man with IgG4-related sclerosing cholangitis (ISC).
A, MRCP image of patient with ISC shows tight stricture of distal common bile duct (CBD; *arrowhead*) and smooth long-segment narrowing of proximal CBD (*arrow*).
B and **C,** Axial T2-weighted fat-saturated MR images depict thickened wall of CBD with hypointense signal and sharp margins (*arrow*, **B**) and diffusely bulky pancreas showing hypointense halo (*asterisk*, **C**).
D and **E,** DW image (**D**) and apparent diffusion coefficient map (**E**) show diffusion restriction of CBD wall (*arrow*).

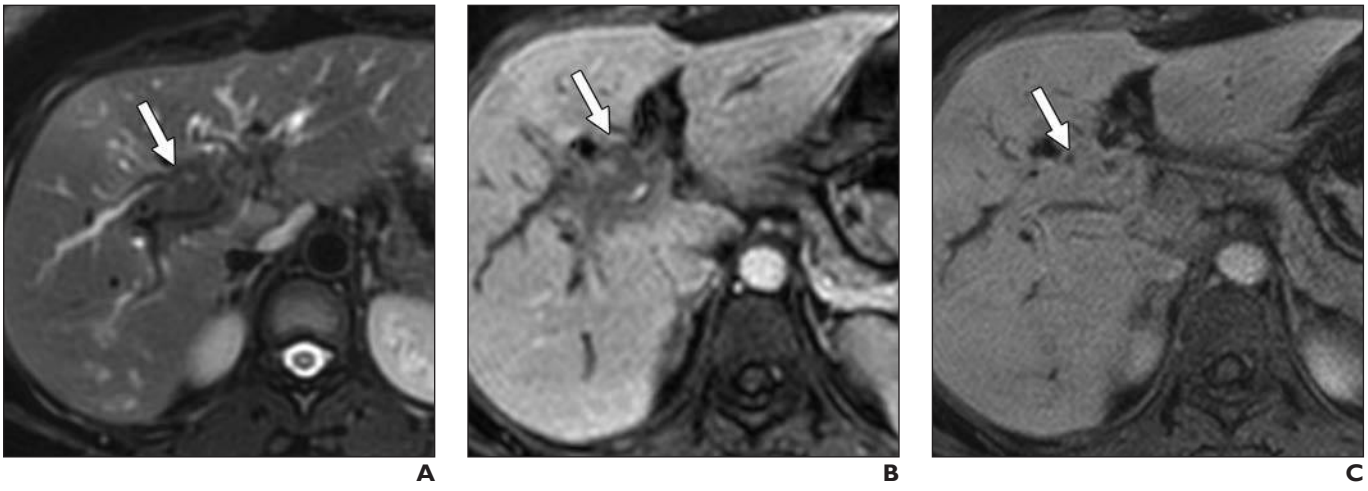


Fig. 6—29-year-old woman with proven case of masslike IgG4-related sclerosing cholangitis.
A, Axial T2-weighted MR image shows hypointense mass (*arrow*) at hepatic hilum involving primary biliary confluence and encasing vessels at porta hepatis, mimicking malignancy.
B and **C,** Venous (**B**) and delayed phase (**C**) dynamic contrast-enhanced T1-weighted images show progressive enhancement of mass (*arrow*).

(Fig. 6 continues on next page)

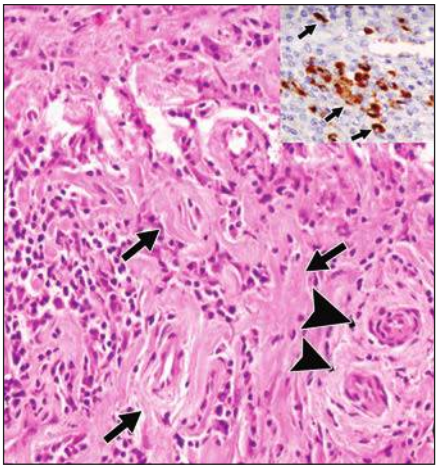


Fig. 6 (continued)—29-year-old woman with proven case of masslike IgG4-related sclerosing cholangitis.
D, Photomicrograph (H and E, ×200) shows lymphoplasmacytic infiltrate with extensive fibrosis (*arrows*) and obliterative phlebitis (*arrowheads*). Inset shows photomicrograph (IgG4 immunostain [MRQ044, dilution 1:400, Bio SB], ×400) of IgG4-positive plasma cells (*arrows*) present in significant numbers.

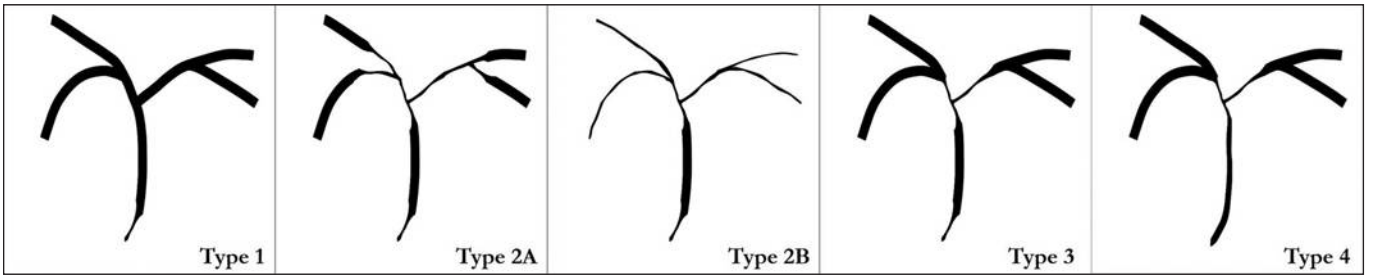


Fig. 7—Schematic of classification of IgG4 sclerosing cholangitis on basis of cholangiographic appearance and location of strictures as outlined by Nakazawa et al. [44] (see also Table 1).

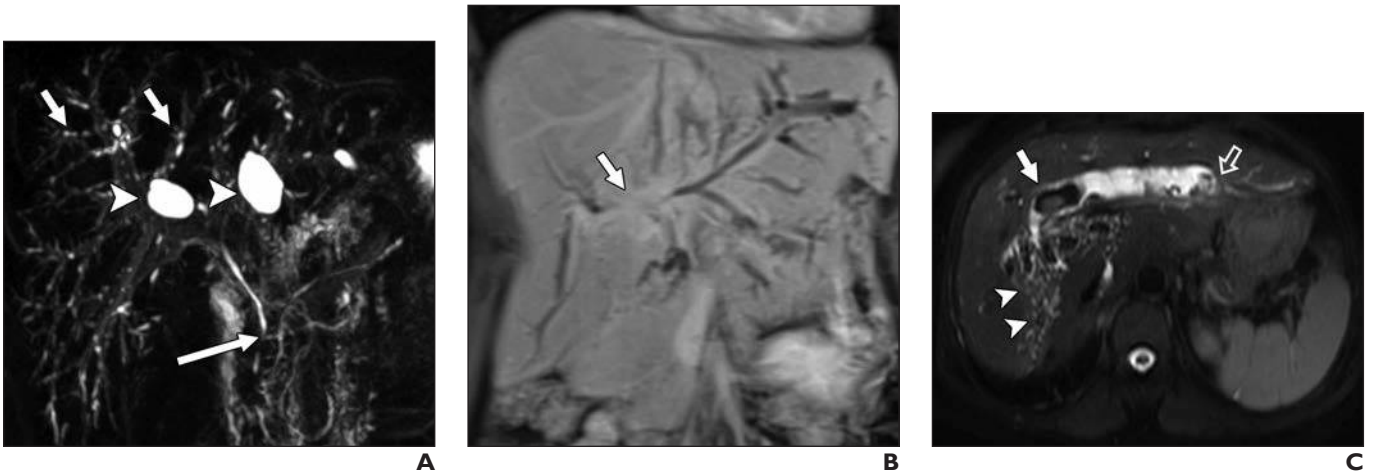
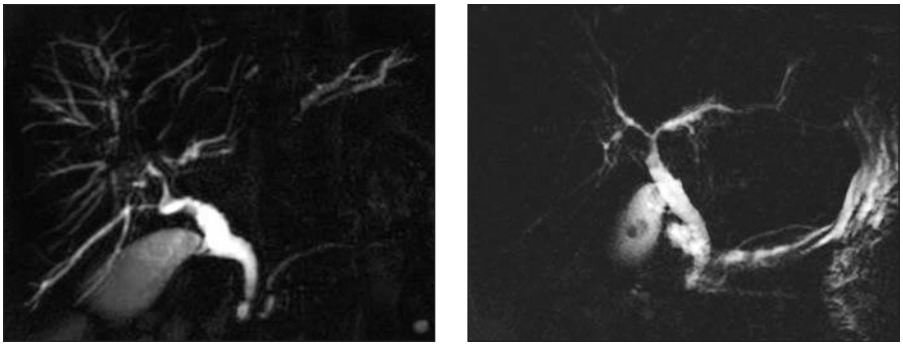


Fig. 8—Differential diagnosis.
A, 25-year-old woman with primary sclerosing cholangitis. MRCP image shows diffuse involvement of intrahepatic bile ducts with beaded appearance (*short arrows*), cystic dilatations (*arrowheads*), and extrahepatic duct stricture (*long arrow*).
B, 43-year-old woman with hilar cholangiocarcinoma. Coronal contrast-enhanced T1-weighted MR image shows infiltrative enhancing soft-tissue mass (*arrow*) with ill-defined margins involving hepatic hilum and bilobar secondary biliary confluence resulting in intrahepatic bile duct dilatation.
C, 36-year-old woman with recurrent pyogenic cholangitis. Axial T2-weighted MR image shows dilated left hepatic duct (*solid arrow*) caused by stricture at hilum, with multiple hypointense calculi. Right lobe is atrophic and shows ducts filled with calculi (*arrowheads*). Characteristic feature is abrupt change in caliber of involved dilated segment at periphery (*open arrow*).



A B

Fig. 9—57-year-old woman with IgG4-related sclerosing cholangitis.
A and **B,** MRCP images obtained before (**A**) and after (**B**) treatment with steroids for 6 months. Multifocal intrahepatic and extrahepatic strictures have significantly improved in follow-up scan (**B**).

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2. Kumble S. Madhusudhan, Pramod K. Garg. 2020. Reply to "Differential Diagnosis of IgG4-Related Sclerosing Cholangitis". *American Journal of Roentgenology* **215**:2, W24-W24. [Citation] [Full Text] [PDF] [PDF Plus]