Diagnostic Criteria

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Hirotaka Ohara, Itaru Naitoh, Kazuki Hayashi,
Katsuyuki Miyabe, and Takahiro Nakazawa

Diagnostic Criteria of IgG4-Related Sclerosing Cholangitis

Introduction

IgG4-related sclerosing cholangitis (IgG4-SC) is a characteristic type of sclerosing cholangitis with an unknown pathogenic mechanism. IgG4-SC patients have increased serum IgG4 levels [1] and dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall [2]. IgG4-SC is frequently associated with autoimmune pancreatitis (AIP) and generally shows a good prognosis and responds to steroid therapy [3–7].

As various cholangiographic features of IgG4-SC are similar to those of primary sclerosing cholangitis (PSC), pancreatic cancer, and cholangiocarcinoma [8, 9], it can be difficult to discriminate IgG4-SC from these progressive or malignant diseases on the basis of cholangiographic findings alone [10, 11]. Therefore, these three diseases should be taken into account in the diagnostic criteria for IgG4-SC.

Diagnostic Criteria

Two sets of diagnostic criteria for IgG4-SC have been proposed. The HISORt criteria were originally developed for AIP and adapted for IgG4-SC [7] (Table 7.1). These criteria are based on histological findings, imaging, serological examination, other organ involvement, and response to steroid therapy.

A second set of diagnostic criteria for IgG4-SC has been proposed by a Japanese group [12] (Table 7.2). Diagnosis of IgG4-SC is based on the following four criteria: (1) characteristic biliary imaging findings, (2) elevation of serum IgG4 concentration, (3) coexistence of IgG4-related diseases except those of the biliary tract, and (4) characteristic histopathological features. The effectiveness of steroid therapy is an optional extra diagnostic criterion used to confirm a diagnosis of IgG4-SC. Furthermore, the typical cholangiographic features are shown schematically and diseases to be discriminated from IgG4-SC and the necessary examinations for diagnosis are described to facilitate clinical application of these diagnostic criteria [12] (Fig. 7.1).

H. Ohara (✉)
Department of Community-Based Medical Education, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
e-mail: hohara@med.nagoya-cu.ac.jp

I. Naitoh · K. Hayashi · K. Miyabe
T. Nakazawa
Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Table 7.1 Diagnostic criteria with histologic and imaging findings, serum tests, organ manifestation pattern, and response to immunosuppressive therapy (HISORt criteria) for IgG4-related sclerosing cholangitis (cited from [7])

Feature	Characteristics
Histology of bile duct	Lymphoplasmacytic sclerosing cholangitis on resection specimens (lymphoplasmacytic infiltrate with >10 IgG4-positive cells/HPF within and around bile ducts with associated obliterative phlebitis and storiform fibrosis)[a]
Imaging of bile duct	One or more strictures involving intrahepatic, proximal extrahepatic, or intrapancreatic bile ducts fleeting/migrating biliary strictures
Serology	Increased levels of serum IgG4
Other organ involvement[b,c]	Pancreas, classic features of autoimmune pancreatitis on imaging or histology[d]; suggestive pancreatic imaging findings, focal pancreatic mass/enlargement without pancreatic duct dilatation, multiple pancreatic masses, focal pancreatic duct stricture without upstream dilatation, pancreatic atrophy Retroperitoneal fibrosis Renal lesions: single or multiple parenchymal low-attenuation lesions (round, wedge-shaped, or diffuse patchy) Salivary/lacrimal gland enlargement
Response to steroid therapy	Normalization of liver enzyme levels or resolution of stricture[e]

[a]Bile duct biopsy specimens often do not provide sufficient tissue for a definitive diagnosis. In such specimens, IgG4 immunostaining showing >10 IgG4-positive cells/HPF is suggestive of IgG4-related sclerosing cholangitis (IgG4-SC); however, the specificity of this finding is not known
[b]IgG4 immunostaining of involved organs shows >10 IgG4-positive cells/HPF
[c]The presence of inflammatory bowel disease (IBD) suggests primary sclerosing cholangitis rather than IgG4-SC; however, the absence of IBD does not help diagnose IgG4-SC in an individual patient
[d]Diffusely enlarged pancreas with delayed enhancement and capsule-like rim. Diffusely irregular, attenuated main pancreatic duct multiple strictures or long stricture without upstream dilatation
[e]Complete resolution of stricture may not be seen in all patients, especially those early in the course of treatment (<6 weeks) or with predominantly fibrotic strictures

Table 7.2 Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012 (cited from [12])

A. Diagnostic criteria
1. Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of bile duct wall
2. Hematological examination shows elevated serum IgG4 concentrations ($\geq$135 mg/dl)
3. Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis
4. Histopathological examination shows: (1) Marked lymphocytic and plasmacyte infiltration and fibrosis (2) Infiltration of IgG4-positive plasma cells, >10 IgG4-positive plasma cells/HPF (3) Storiform fibrosis (4) 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 administrated, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out.
B. Diagnosis
Definite diagnosis: 1 + 3, 1 + 2 + 4 (1) (2), 4 (1) (2) (3), 4 (1) (2) (4) Probable diagnosis: 1 + 2 + option Possible diagnosis: 1 + 2

Note: It is necessary to exclude primary sclerosing cholangitis, malignant diseases such as pancreatic or biliary cancers, and secondary sclerosing cholangitis caused by the diseases with obvious pathogenesis. If IgG4-related sclerosing cholangitis cannot be clinically ruled out, a patient must not be treated with facile steroid therapy but should be referred to a specialized medical facility
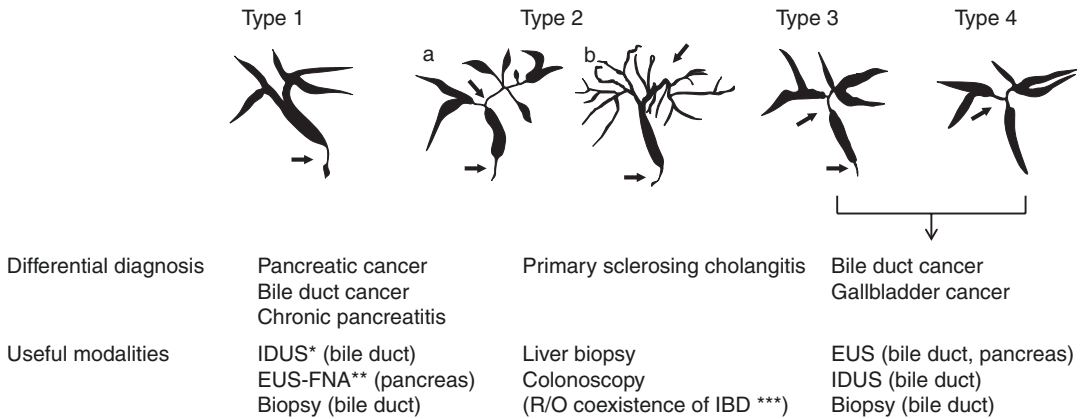
	Type 1	Type 2		Type 3	Type 4
		a	b		

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)

Fig. 7.1 The 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 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 is 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; and 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

Diagnostic Imaging Findings

Narrowing of the Bile Duct

IgG4-SC shows 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. 7.1) [13].

Type 1 IgG4-SC shows stenosis only in the lower part of the common bile duct, which should be differentiated from chronic pancreatitis, pancreatic cancer, and cholangiocarcinoma. IgG4-SC associated with AIP frequently shows a stricture in the lower common bile duct. This stricture can originate from thickening of the bile duct or the effect of pancreatic inflammation and/or edema [14].

Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts, should be differentiated from PSC. Band-like stricture, a beaded and pruned tree appearance, and diverticulum-like outpouching are significantly more frequent in PSC. In contrast, segmental strictures, long strictures with prestenotic dilation, and strictures of the lower common bile duct are significantly more common in IgG4-SC. Type 2 is subdivided into Type 2a, which involves narrowing of the intrahepatic bile ducts with prestenotic dilation, and Type 2b, which involves narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches. The latter is caused by marked lymphocytic and plasmacyte infiltration into the peripheral bile ducts.

Type 3 IgG4-SC is characterized by stenosis in both the hilar hepatic lesions and the lower part of the common bile duct. Type 4 IgG4-SC shows strictures of the bile duct only in hilar hepatic lesions. The cholangiographic findings of Types 3 and 4 should be discriminated from those of cholangiocarcinoma.

Thickening of the Bile Duct

Abdominal ultrasonography (US) [15], abdominal computed tomography [16], abdominal magnetic resonance imaging, endoscopic ultrasonography, and intraductal ultrasonography (IDUS) [17] show circular-symmetric wall thickening, smooth outer and inner margins, and homogenous internal echo. These characteristic features are recognized not only in the stenotic areas or occasionally in the gallbladder but also in areas without stenosis that appear normal on

cholangiogram. Bile duct wall thickening extends continuously from the intrapancreatic bile duct to the upper bile duct in most IgG4-SC cases. To differentiate IgG4-SC from cholangiocarcinoma, a bile duct wall thickness of 0.8 mm that appears normal on a cholangiogram is the optimum cutoff established by a study on IDUS [17]. Patients with PSC also have widespread thickening of the bile duct, which shows IDUS findings of an irregular inner margin, diverticulum-like outpouching, and disappearance of three layers [18].

Hematological Examination

An elevated serum IgG4 level is a diagnostic criterion for IgG4-SC [1]. The cutoff serum IgG4 levels are 140 mg/dl (nephelometric method) in the HISORt criteria [7] and 135 mg/dl in the Japanese criteria [12].

However, an elevated serum IgG4 level is also observed in atopic dermatitis, pemphigus, asthma, etc.; in particular, elevated serum IgG4 levels are also observed in PSC and some malignant cholangiopancreatic diseases (e.g., pancreatic cancer and cholangiocarcinoma) [19, 20]. Oseini et al. evaluated the utility of serum IgG4 level to discriminate IgG4-SC from cholangiocarcinoma [20]. They concluded that some patients with cholangiocarcinoma, particularly PSC, had elevated serum IgG4 levels, and diagnosis using a twofold higher cutoff serum IgG4 level (>280 mg/dl) may not reliably distinguish IgG4-SC from cholangiocarcinoma. A cutoff level fourfold higher than the upper limit of normal (> 560 mg/dl) had 100% specificity for IgG4-SC.

A Japanese multicenter study was performed to establish a serum IgG4 cutoff value to differentiate IgG4-SC from pancreatic cancer, PSC, and cholangiocarcinoma [21]. A total of 344 IgG4-SC patients were enrolled, together with 245, 110, and 149 patients with pancreatic cancer, PSC, and cholangiocarcinoma, respectively, as controls. The cutoff values from receiver operating characteristic (ROC) curves showed similar sensitivity and specificity to that of 135 mg/dl when all IgG4-SC cases and controls were compared. Of the pancreatic cancer, PSC, and cholan-

giocarcinoma cases, 5.7%, 12.7%, and 8.1%, respectively, had serum IgG4 levels higher than the cutoff value. A serum IgG4 cutoff value of 182 mg/dl increased the specificity to 96.6% for distinguishing Types 3 and 4 IgG4-SC from cholangiocarcinoma, and a cutoff of 207 mg/dl enabled discrimination of Types 3 and 4 IgG4-SC from cholangiocarcinoma.

Other Organ Involvement

IgG4-SC is frequently associated with AIP. Ghazale et al. reported that 49 of 53 patients with IgG4-SC had AIP [7]. In a Japanese multicenter study, 329 of 344 (95.6%) IgG4-SC cases were associated with AIP [21]. Association with AIP is useful for diagnosis of IgG4-SC. However, some IgG4-SC patients do not have AIP and are thus difficult to diagnose; most isolated IgG4-SC cases have hilar biliary strictures [22–24].

Occasionally, IgG4-SC is associated with other systemic IgG4-related diseases, including IgG4-related symmetrical dacryoadenitis/sialadenitis, IgG4-related retroperitoneal fibrosis, and IgG4-related kidney disease [25–28]. These associations can also assist diagnosis of IgG4-SC. Inflammatory bowel disease is usually not an associated condition, unlike its frequent association with PSC [29].

Pathological Findings of the Bile Duct

In IgG4-SC cases, fibroinflammatory involvement is observed mainly in the submucosa of the bile duct wall, whereas the bile duct epithelium is intact [30]. However, slight injury and/or neutrophil infiltration are occasionally observed in cases of IgG4-SC with secondary cholangitis. PSC should be excluded if inflammation is observed, particularly in the bile duct wall epithelium.

Endoscopic transpapillary bile duct biopsy is performed to rule out cholangiocarcinoma. Ghazale et al. reported that the immunostaining results of 14 (88%) of 16 patients indicated abundant IgG4+ cells in bile duct biopsy specimens [7]. However, it is difficult to obtain

enough biliary tract tissue to assess the histology of IgG4-SC biopsy specimens (e.g., storiform fibrosis and obliterative phlebitis) [13]. We were able to diagnose IgG4-SC in only 3 (18%) of 17 patients on the basis of its characteristic histopathological features [17]. In addition, 1 of 11 cholangiocarcinoma cases presented abundant IgG4+ plasma cells. Zhang et al. also reported abundant IgG4+ plasma cells in 7 (18%) of 38 cases of cholangiocarcinoma [31]. It is important to note that the superficial nature of endoscopic biopsy specimens limits their usefulness for demonstrating the characteristic histological features of IgG4-SC.

Ampullary biopsy is occasionally useful in the diagnosis of IgG4-SC patients with swelling of the pancreatic head caused by AIP [32]. Liver biopsy can be useful for diagnosing IgG4-SC cases with intrahepatic bile duct strictures [33, 34].

Exclusion of Secondary Sclerosing Cholangitis

It is necessary to rule out the following features of secondary sclerosing cholangitis: common bile duct stone, cholangiocarcinoma, trauma, biliary tract surgery, congenital biliary anatomy, corrosive cholangitis, ischemic bile duct stenosis, AIDS-related cholangitis, and biliary injury due to intra-arterial chemotherapy.

Effectiveness of Steroid Therapy

In the HISORt criteria, response to steroid treatment is defined as a decrease in liver enzyme levels to less than twofold the upper limit of normal and/or improvement in biliary strictures [7]. In the Japanese criteria, this optional diagnostic criterion should be applied only to IgG4-SC cases in which the effect of steroid therapy can be evaluated by imaging modalities after negative workup for malignancy [12]. Accordingly, clinical conditions or hematological findings cannot be evaluated by this method. It is sometimes difficult to obtain sufficient biopsy specimens from patients suffering from diseases not only of the biliary tract but also of other organs, such as the pancreas, lachrymal gland, salivary gland, and retroperitoneum. However, efforts should be made to collect sufficient tissue samples for diagnosis, and steroid trials should be avoided [12].

The effectiveness of steroid therapy should be cautiously evaluated because some malignant lesions improve after steroid administration [35]. If neoplastic lesions cannot be clinically ruled out after steroid therapy, a reevaluation should be performed to rule out malignant cholangiopancreatic diseases.

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