12 Differential Diagnosis from Primary Sclerosing Cholangitis

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Introduction

Primary sclerosing cholangitis (PSC), a chronic progressive disease of unknown etiology, is characterized by fibrosis and strictures involving the intra- and extrahepatic bile ducts [1, 2]. PSC is a distinct entity from IgG4-related sclerosing cholangitis (IgG4-SC), but some IgG4-SC masquerades as PSC by way of similar manifestations, such as frequent stenosis of both intra- and extrahepatic bile ducts, bile ductal wall thickening, male predominance, cholestatic liver dysfunction, and initial mild symptoms [3–7]. The differential diagnosis between PSC and IgG4-SC is clinically important because their treatment modalities and prognosis are very different [2, 7, 8]. Timely diagnosis of IgG4-SC can lead clinicians to prescribe adequate corticosteroid therapy that can reverse bile duct strictures/wall thickening and cholestatic liver dysfunction and could potentially prevent future advanced liver disease [2]. A proper diagnosis of PSC, in turn, is crucial for optimizing the surveillance of the disease progression to hepatic decompensation and the need for liver transplantation.

Interval screening for cholangiocarcinoma is also recommended for patients with PSC, because this disorder is associated with a lifetime risk of cholangiocarcinoma of around 7–14% [9]. The incidence of cholangiocarcinoma does not correlate with the duration of the PSC period, and approximately one-third of detected cholangiocarcinomas in PSC are identified within the first year of PSC diagnosis [10, 11]. A misclassification of PSC as IgG4-SC may result in inadvertent corticosteroid treatment and delay of the optimal surveillance, whereas a misclassification of IgG4-SC as PSC may result in missing the window for the steroid treatment and subsequent reversal of the disease progression. Discernment of the differences in the features of IgG4-SC versus PSC is therefore essential.

Differentiation by Clinical Features

Age

Age of presentation is a very important factor for differentiation between IgG4-SC and PSC (Table 12.1). PSC tends to be a disease of young adult and middle-aged persons, whereas IgG4-SC tends to be a disease of the elderly. The median age at diagnosis ranged from 35 to 45 years in patients with PSC [2, 7, 10, 12, 13], whereas this

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Table 12.1 Important points for differentiating between PSC and IgG4-SC

	Favor PSC	Favor IgG4-SC
Age	<40 years[a]	>60 years
Inflammatory bowel disease	Presence[a]	–
Serum IgG4	<140 mg/dL	>560 mg/dL[a]
Serum IgG4:IgG1 ratio[b]	<0.24	>0.24
pANCA	Positive	–
Association with autoimmune pancreatitis/IgG4-related disease	–	Presence[a]
Cholangiogram	Beaded appearance, diverticulum-like outpouching, pruned tree appearance	Longer stricture and more prestenotic dilatation, distal CBD stricture
Cholangioscopy	Scarring and pseudodiverticula	Dilated and tortuous vessel
Intraductal ultrasonography	Irregular inner margin, disappearance of three layers	Symmetrically thickened wall with smooth margin
Histology and immunohistochemistry	Onion-skin fibrosis and periportal sclerosis, sometimes IgG4-positive cell infiltration	Dense and richly IgG4-postive lymphoplasmacytic infiltration, marked fibrosis with storiform pattern, and obliterative phlebitis
Tissue IgG4+:IgG+ plasma cell ratio	<0.40	>0.40 {with IgG4+ plasma cells >10/HPF (biopsy) or 50/HPF (resection)}
Steroid responsiveness[c]	–	Positive[a]

[a]Reported specificity >90%
[b]In the setting of serum IgG4 level between 140 and 280 mg/dL
[c]Defined by radiographic resolution or marked improvement in the bile duct strictures and wall thickening after steroid therapy

range was 60 to 70 years in patients with IgG4-SC [5, 7, 14]. Interestingly, very few cases of IgG4-SC have been reported in young adults less than 40 years of age [2, 5, 7, 15]. A Japanese PSC cohort showed a second age peak at 65 years, but the diagnosis of PSC is uncommon over the age of 60 years in most populations. Patients with sclerosing cholangitis who are under the age of 40 years and who have no evidence of secondary causes are almost always afflicted with PSC, whereas those aged more than 60 years favor an IgG4-SC diagnosis.

Gender is generally not helpful for differentiation, as both of these sclerosing cholangiopathies show male predominance. The ratio of male predominance is 1.5:1 in PSC and 4-7:1 in IgG4-SC [8].

Association with Inflammatory Bowel Disease

The ratio of association with inflammatory bowel disease (IBD) differs somewhat between Western and Eastern countries, which probably reflects the basic prevalence of IBD. IBD is associated with majority of PSC patients, at a ratio of 60–80% in Western countries and 30–50% in Japan and Korea [1, 2, 7, 16–18]. By contrast, IBD is seldom associated with IgG4-SC, at a ratio of 5% in Western countries and 0% in Japan and Korea [2, 5, 14, 15, 19]. Patients with sclerosing cholangitis of unknown origin may show a presence of IBD that favors the diagnosis of PSC rather than IgG4-SC, especially in the areas with a low prevalence of IBD.

Concurrent or History of IgG4-Related Disease

IgG4-SC lies within a spectrum of IgG4-related diseases, with the pancreas most commonly affected. IgG4-related pancreatitis, or so-called type 1 autoimmune pancreatitis (AIP), is commonly associated with the IgG4-SC patient population, at a ratio of 70–92% [2, 5, 15]. Although

other autoimmune conditions coexist, PSC is seldom associated with pancreatic involvement [20]. Patients with sclerosing cholangitis of unknown origin may have concurrent or a history of AIP-/IgG4-related disease that may lead directly to a diagnosis of IgG4-SC. In the clinical setting, when differentiating between IgG4-SC and PSC, a meticulous evaluation of extrabiliary manifestations of Ig4-related disease should be performed when reviewing computed tomography scans or magnetic resonance images.

Differentiation by Serology

Serum IgG4

Despite the disease nomenclature of "IgG4"-SC, the assessment of serum IgG4 in isolation does not straightforwardly differentiate IgG4-SC from PSC. Recent research has shown that 9–26% of patients with classic PSC had elevated serum IgG4 levels (>135 mg/dL or >140 mg/dL) [2, 7, 12, 21–24]. Among patients with IgG4-SC, 60–90% had elevated serum IgG4 levels [2, 5, 7, 8]. Application of a cutoff value for serum IgG4 of 560 mg/dL, which is four times the upper limit of normal (ULN), gives a specificity of 100% for IgG4-SC [21]. For mildly elevated serum IgG4 levels (1–2 × ULN), a ratio of serum IgG4/IgG1 > 0.24 might be helpful for the differentiation of PSC from IgG4-SC [21].

pANCA

The most prevalent autoantibody in PSC is a particular type of perinuclear anti-neutrophil cytoplasmic antibody (pANCA) [18]. This pANCA is not typically used for the diagnosis of PSC because it is not specific for PSC; it is also observed in ulcerative colitis and autoimmune hepatitis [1, 18]. However, pANCA may have a role in the differentiation of PSC from IgG4-SC because it is observed in 40–60% of patients with PSC but in less than 10% of patients with IgG4-SC [2, 8].

Differentiation by Imaging

Cholangiogram

Characteristic cholangiographic features might also allow differentiation between IgG4-SC and PSC. The typical cholangiographic features for PSC are a beaded appearance, diverticulum-like outpouching, and a pruned tree appearance [25, 26]. The distinctive cholangiographic features of IgG4-SC that differentiate it from PSC are a distal CBD stricture, longer stricture, and more prestenotic dilatation [25–27]. However, these cholangiographic features can be observer dependent. A blinded multicenter study by worldwide specialists revealed that the cholangiogram had a high specificity (88%), poor sensitivity (45%), and slight interobserver agreement (kappa 0.18) for the diagnosis of IgG4-SC [28]. This poor sensitivity of cholangiographic findings suggests that many patients with IgG4-SC may be misdiagnosed with PSC or cholangiocarcinoma if the cholangiogram is used in isolation for the diagnosis. Apart from cholangiography, an endobiliary biopsy should be routinely performed at the time of endoscopic retrograde cholangiopancreatography (ERCP), in the setting of obstructive jaundice/cholangitis or a dominant stricture.

Cholangioscopy/Intraductal Ultrasonography

Direct endoscopic visualization of the biliary tree may aid in the differentiation between PSC and IgG4-SC. Characteristic cholangioscopic features of PSC include scarring and pseudodiverticula, whereas dilated and tortuous vessels are characteristic in IgG4-SC [29]. These dilated and tortuous vessels in IgG4-SC can be differentiated from the tumor vessels of cholangiocarcinoma by assessment of the patterns of proliferative vessels [29].

The intraductal ultrasonographic findings also differ between IgG4-SC and PSC [30]. Irregular inner margins, diverticulum-like outpouching, and the disappearance of the three layers are specific intraductal ultrasonographic findings for

PSC, when compared with IgG4-SC [30]. By contrast, intraductal ultrasonography of IgG4-SC shows a symmetrically thickened bile duct wall with smooth margins and preservation of the three layers [30].

Differentiation by Histology

If a resected specimen is available, histologic differentiation is mostly possible. The characteristic features of PSC include onion-skin fibrosis and periportal sclerosis [8]. The surface epithelium of the thickened bile duct, when infiltrated by lymphoplasmacytes in PSC, is often inflamed and shows edema, sloughing, erosion, and neutrophilic infiltration [24]. By contrast, the transmural lymphocyte infiltration in IgG4-SC spares the biliary lining epithelium [24]. The characteristic features of IgG4-SC include dense and richly IgG4-postive lymphoplasmacytic infiltration, marked fibrosis with a storiform pattern, and obliterative phlebitis in accordance with type 1 AIP [24]. Recent research has revealed that liver explants from classic PSC show IgG4 positivity in 23% of the tissues [24]. A consensus statement on the pathology of IgG4-related disease stipulates >10/HPF as the cutoff for the number of IgG4+ plasma cells in pancreas and bile duct for biopsy and >50/HPF for surgical specimens [31]. Moreover, the ratio of IgG4+ to IgG+ plasma cell >40% is mandatory for histologic diagnosis of IgG4-related disease [31].

An endoscopic intraductal forceps biopsy obtained from the biliary stricture in most cases does mostly not show these histologic features due to its small sample size. Variable sensitivities of IgG4 immunostaining of an endobiliary biopsy for diagnosing IgG4-SC have been reported, ranging from 18 to 88% due to the small sample size and possible patchy involvement [5, 32–34]. IgG4 immunostaining of endobiliary biopsy specimens was positive for IgG4-SC patients, independently of the presence of elevated serum IgG4 levels [35]. However, IgG4 immunostaining of endobiliary biopsy specimens from patients with PSC also showed up to 18% positivity for tissue IgG4 [2, 33]. This tissue IgG4 positivity should therefore be viewed in conjunction with the entire clinical, imaging, and serological features of each individual patient.

Differentiation by Steroid Trial

The use of steroid responsiveness as a diagnostic tool may be important, as steroid responsiveness is the most distinguishing clinical feature between IgG4-SC and PSC [2]. Some researchers have argued that a small portion of patients with PSC show positive steroid responsiveness, but the positive steroid responsiveness of PSC is only an isolated biochemical response, especially in patients with overlap syndrome between PSC and autoimmune hepatitis [22, 36–38]. The resolution of biliary strictures following corticosteroid treatment alone is not observed in PSC, but is typically seen with IgG4-SC. The reversal of the biliary strictures of PSC can be obtained by balloon dilatation and/or biliary stenting [22]. For differentiation of IgG4-SC from PSC by a steroid trial (steroid use as a diagnostic trial), the definition of steroid responsiveness is of utmost importance. Positive steroid responsiveness can be defined as radiographic resolution or a marked improvement in the bile duct strictures and wall thickening in response to steroid therapy [2]. A biochemical response alone after steroid therapy should not be designated as a positive steroid responsiveness for the purposes of this differentiation.

Proposal of Strategy for Differentiation by Combination of Features

The interpretation of serum/tissue IgG4 and the cholangiographic and histologic features as a means of differentiating between IgG4-SC and PSC may occasionally require a substantial amount of experience by the clinician, especially when a serum/tissue IgG4 is elevated in a patient with presumed PSC or when IgG4 is normal in a

patient with presumed IgG4-SC. Our group has overcome this difficulty through the development of a simple scoring system for the discrimination of IgG4-SC from PSC that we can use in daily clinical practice [2]. The selected variables (estimated scores) include other organ involvement (yes, 3 points; no, 0 points), beaded appearance on cholangiography (yes, 0 points; no, 2 points), and age (<30 years, 0 points; 30–39 years, 1 point; 40–49 years, 2 points; 50–59 years, 3 points; ≥60 years, 4 points). The patients are classified, according to the sums of each score, into three categories: 0–4 points, probable PSC; 5–6 points, indicating a steroid trial; 7–9 points, probable IgG4-SC.

Our scoring system can be used as a basis for a clinical algorithm for patients with multifocal intrahepatic/hilar biliary strictures, with a focus on the differentiation between IgG4-SC and PSC (Fig. 12.1). The exclusion of cholangiocarcinoma is the step of utmost importance, because some imaging features of IgG4-SC overlap those of cholangiocarcinoma and because PSC is associated with a potential risk of cholangiocarcinoma. An endobiliary biopsy should be routinely performed at the time of ERCP in the setting of obstructive jaundice/cholangitis or dominant stricture. A liver biopsy can be performed in the presence of a tumefactive periductal nodule/mass. Serum CA 19-9 should be serially measured at baseline and during follow-up.

In the next stage of the evaluation, patients should undergo serum IgG4 measurement. If the serum IgG4 level shows an elevation greater than twofold, a steroid trial is indicated. If the serum IgG4 level is normal or shows an elevation of less than twofold, our scoring system is applied to these patients. For a steroid trial, prednisone 0.6–1.0 mg/kg (body weight) is administered for 2 weeks. Steroid responsiveness should be assessed based on follow-up imaging and the CA 19-9 level. When a steroid trial results in no response on imaging, an endobiliary/liver biopsy with IgG4 immunostaining could be considered. When the serum CA 19-9 rises even after biliary decompression, cholangiocarcinoma should be differentiated by means of a meticulous rebiopsy.

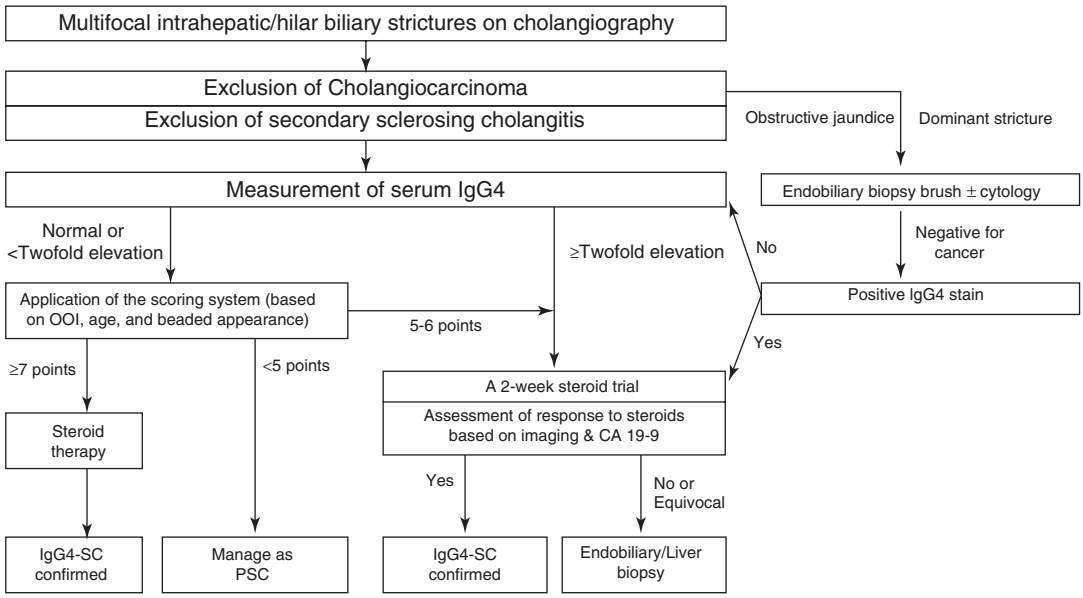

Fig. 12.1 Clinical algorithm for distinguishing IgG4-SC from PSC (adapted from J Gastroenterol 2017;52:483–493). OOI, other organ involvement (presence of IgG4-related extrabiliary lesions). The scoring system and the detailed description of algorithm are stated in the body text

Conclusion

Discernment of the differences between IgG4-SC and PSC is essential for clinicians. PSC tends to be a disease of young adult and middle-aged persons (median 35–45 years), whereas IgG4-SC is a disease of the elderly (median 60–70 years). The presence of IBD favors the diagnosis of PSC rather than IgG4-SC. A concurrent or history of AIP may lead to a straightforward diagnosis of IgG4-SC. Serum IgG4 is elevated in some patients with PSC; however, an elevation of more than 4x ULN is specific for IgG4-SC. Typical cholangiographic features for PSC include a beaded appearance, diverticulum-like outpouching, and a pruned tree appearance, whereas distinctive cholangiographic features of IgG4-SC, which differentiate it from PSC, are a distal CBD stricture, longer stricture, and more prestenotic dilatation. Tissue IgG4 should be interpreted in the appropriate clinical context on the basis of clinical features, imaging, and histopathological appearance. Positive steroid responsiveness is defined as radiographic resolution or a marked improvement in the bile duct strictures and wall thickening in response to steroid therapy. A correct diagnosis occasionally requires a constellation of multidisciplinary investigation.

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