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AUTOIMMUNE, CHOLESTATIC, AND BILIARY DISEASES (S GORDON AND CL BOWLUS, SECTION EDITORS)

IgG4-Related Sclerosing Cholangitis

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Abstract
Purpose of Review IgG4-related sclerosing cholangitis (ISC) is a frequent occurrence. However, its diagnosis is difficult. This review summarizes the clinical features, pathogenesis, differential diagnosis, and management of ISC.
Recent Findings A precise diagnosis of ISC is important. Diagnosis is based on the Japanese criteria which has recently been provided. The characteristic features of plasma cell infiltration and raised IgG4 levels along with classical histopathological and imaging findings help in diagnosis. Steroid therapy is very effective in ISC. Immunomodulatory drugs have also shown promising results.
Summary Diagnostic approach of ISC mainly involves imaging modalities. Japanese diagnostic criteria is important in its diagnosis. It is also extremely important to differentiate IgG4 sclerosing cholangitis from various other cholangiopathies. Steroid therapy stays the treatment of choice. The role of other immunomodulators needs to be researched and reciprocated in clinical setting before it replaces steroid therapy.

Keywords Autoimmune cholangiopathy · Primary sclerosing cholangitis · Biliary strictures

Introduction

The recognition of IgG4-related disease as a systemic condition came into being after initial similarities between autoimmune pancreatitis (AIP) and IgG4 were found out. This prompted studying the pathologies in detail, as a result of which IgG4-related fibroinflammatory conditions in other organs outside pancreas were found. Mikulicz disease (head and neck), Küttner tumor (salivary gland), interstitial pneumonitis (lungs), interstitial nephritis (kidney), and Riedel thyroiditis (thyroid) were all found to have one thing in common, i.e., increased serum IgG4 concentrations, and pathologically, there was presence of IgG4-positive plasma cells [1]. IgG4-related sclerosing cholangitis (ISC) also known as autoimmune cholangiopathy is a chronic inflammatory disease of the biliary system which is commonly seen as part of IgG4-related systemic disease [2••]. The diagnosis of ISC is based on well-established diagnostic criteria [3••]. However, sometimes, differentiating it from primary sclerosing cholangitis and cholangiocarcinoma becomes difficult [3••]. The correlation of ISC and autoimmune pancreatitis is of paramount importance as it has been observed that around 90% of cases also have autoimmune pancreatitis, in particular, type 1 autoimmune pancreatitis showing the classic lymphoplasmacytic infiltration [4•]. ISC is seen in up to 39% of patients with autoimmune pancreatitis [5]. The etiopathogenesis of ISC is still not clearly understood. Therefore, we hereby describe the pathogenesis, clinical features, differential diagnosis, and management of ISC.

Pathogenesis

The association of AIP with IgG4-SC is evident from the two parallel immunological responses that are thought to underlie the pathophysiology of these diseases: a pro-inflammatory, tissue-destructive process and an anti-inflammatory feedback response, which probably relates to IgG4 production [6•]. In pro-inflammatory process, similar to most idiopathic inflammatory diseases, AIP also shows association with specific

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polymorphisms in immune-related genes (e.g., HLA, CTLA4, and FRCL3) [7]. This points towards the broader inference that the immune reactions in patients with IgG4-RD are triggered due to repetitive exposure to unidentified immunogens and increased genetic susceptibility [8]. Potential autoantigens in autoimmune pancreatitis include ductal antigens (e.g., carbonic anhydrase II) [9], pancreatic enzymes (e.g., amylase and trypsinogens) [10], protease inhibitors (e.g., SPINK1) [10], and annexin A11 [11]; however, none of these antigens is widely accepted as autoantigens of autoimmune pancreatitis. Conforming to Newton's third law, an anti-inflammatory feedback process is set in motion which works in order to decrease the tissue-destructive effect of the immune reactions. Circulating and tissue resident Tregs were originally the indicators that such anti-inflammatory reactions were occurring. The activation of immune-suppressive reactions was originally suggested by the expansion of circulating and tissue resident Tregs [12, 13]. Histologically, large numbers of Tregs are observed in the pancreas and bile duct affected by IgG4-related disease, and these Tregs have upregulated expression of anti-inflammatory cytokines such as interleukin 10 and transforming growth factor β (TGFβ).

Clinical Features

Unlike other autoimmune diseases, ISC exhibits male predeliction with male-to-female ratio of 4:1. Patients in their 60s or older constitute more than 90% of the cases [14]. A history of allergic disorders as bronchial asthma, chronic sinusitis, and drug allergies is seen in about 20% patients. Seventy-five percent of patients present with chronic or recurrent cholestatic jaundice and may have cholangitis and weight loss [15, 16]. Occasionally, these patients may come with the symptoms of another primary organ involved. Autoimmune pancreatitis type 1, even without primary bile duct involvement, may present with obstructive jaundice due to mass in the head of pancreas. Type 1 AIP most frequently shows close association with intrapancreatic IgG4-related sclerosing cholangitis, which likely illustrates the direct extension of the inflammatory process from the pancreas. This also suggests that lower bile duct is involved as a secondary event [17, 18]. Since isolated lower duct ISC is extremely uncommon, one has to be careful when making a diagnosis of ISC in patients with lower duct cholangitis. In contrast, proximal ISC (e.g., hilar ducts and intrahepatic bile ducts) may occur either independently or in association with pancreatitis [19]. True isolated ISC cholangiopathy is exceptionally rare as most patients of ISC present with IgG4-RD in other organs outside the pancreatobiliary system. In a retrospective study of 527 patients with ISC, 35% patients had jaundice, 13% had pruritus, and 28% of patients were asymptomatic [20•].

Differential Diagnosis

The differential diagnosis of ISC is important as it mimics the clinical presentation of PSC and cholangiocarcinoma (Table 1). It is also important to exclude secondary sclerosing cholangitis due to biliary surgery, stones, trauma, ischemic injury, AIDS cholangiopathy, and intra-arterial chemotherapy. Some ISC cases were resected on suspicion of cholangiocarcinoma. Therefore, for the accurate diagnosis of ISC, imaging, serology, histopathology, presence of other IgG4-related diseases, and response to steroid therapy are required as per the diagnostic criteria [3••].

Primary Sclerosing Cholangitis

ISC and PSC have differentiating clinical features. PSC has close association with inflammatory bowel disease and 80% patients with PSC have history of ulcerative colitis. PSC is also more likely in patients younger than 40 years [21]. In PSC, multiple short biliary strictures are present involving intra- and extrahepatic bile ducts [22] with a beaded appearance on MRCP. The intervening segments are mildly dilated [23, 24]. Ductal wall thickening is lesser as compared with ISC. ERCP and MRCP shows characteristic feature of bile duct diverticula in 39% and 12% patients, respectively [24]. The liver parenchyma shows hypertrophy of the caudate lobe and atrophy of the left lateral segments [25, 26]. Bile duct shows prune tree appearance in the late stages of PSC [22]. Histopathology shows predominantly mucosa-targeted tissue damage with ulceration and xanthogranulomatous inflammation. There may be presence of IgG4-positive plasma in a smaller number and in localized areas.

Cholangiocarcinoma

This is an important differential diagnosis particularly in cases of localized or obstructive cholangitis. In cholangiocarcinoma, the duct involvement is unifocal, asymmetric wall thickening, irregular outline, short, and eccentric stricture with proximal dilatation [27, 28]. If imaging features are inconclusive, use of tissue examination such as bile duct biopsy along with biliary cytology might be required. A failed response to steroid therapy within 2–3 weeks favors a diagnosis of cholangiocarcinoma.

Differential diagnosis of ISC also includes various biliary strictures as ischemic cholangiopathy, AIDS cholangiopathy, tuberculosis, ascariasis, and eosinophilic

Table 1 Differential diagnosis of IgG4 sclerosing cholangitis

Parameter	IgG4 sclerosing cholangitis	Primary sclerosing cholangitis	Cholangiocarcinoma
Clinical features	Older age ≥ 60 years M:F—4:1 Obstructive jaundice Pancreatitis Pain abdomen Multi-organ involvement	Younger age < 40 years Slightly more in males Fatigue Advanced-stage cirrhosis Associated-inflammatory bowel disease	Older age No sex preference Obstructive jaundice Weight loss
Serology	IgG4 > 135 mg/dL in 80%	IgG4 increased in 10% with lower levels	IgG4 increased in 15% with lower levels
Pathology	Characteristic triad-lymphoplasmacytic infiltration (> 10 IgG4-positive plasma cells per high-power field), obliterative phlebitis, storiform fibrosis	Fibro-obliterative lesions with mild lymphocytic infiltration-onion skin fibrosis	Adenocarcinoma
Imaging	Strictures-extrahepatic > intrahepatic, long, continuous, duct wall thickening-symmetric > 2.5 mm, lumen of thickened segment-visible, skip lesions seen, liver parenchymal changes seen in late stages, funnel shaped dilatation	Strictures-extrahepatic and intrahepatic, short, multiple, duct wall thickening-symmetric < 2.5 mm, lumen of thickened segment-occluded, skip lesions less commonly seen, liver parenchymal changes common, pruned tree ducts, diverticula	Stricture-hilar more often than extrahepatic, extrahepatic > intrahepatic, short, single, duct wall thickening-asymmetric > 5 mm, lumen occluded, skip lesions rare, liver parenchymal changes rare, vascular invasion may be seen
Response to steroid	Good	Poor	No

cholangitis. Liver transplant and biliary or pancreatic surgeries may result in ischemic cholangiopathy due to hepatic arterial injury which results in hilar or mid common bile duct strictures [29]. AIDS cholangiopathy usually causes papillary stenosis and long segment and multifocal strictures in patients with a CD4 count lower than 100 cells/mm^3. Peripheral eosinophilia, long segment bile duct stricture, and wall thickening of the cystic duct and gallbladder indicate eosinophilic cholangitis [30].

Diagnostic Criteria

The diagnosis of ISC is based on 2 diagnostic criteria: HISORt (histologic findings, characteristic imaging features, positive serologic findings, other organ involvement, and response to steroid therapy) criteria and the Japanese criteria [3, 31, 32]. The HISORt criteria include the following: 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; and response to steroid therapy—improvement in liver function tests, bile duct strictures, or both [32•]. Japanese diagnostic criteria for the diagnosis of ISC is given in Table 2 [3••].

Autoantibodies

The diagnosis of ISC requires evaluation of serum IgG4 elevations. This is the most sensitive and specific non-invasive examination [15, 32, 33]. A previous study demonstrated that approximately 80% of patients with ISC had elevated levels of IgG4, using a cutoff value of 135 or 140 mg/dL [34]. However, the IgG4 level may be increased in 10% of patients with PSC, 15% of patients with cholangiocarcinoma, and 5% of the healthy population [34–36]. To increase the diagnostic specificity to more than 90%, a twofold higher cutoff value (270 or 280 mg/dL) may be used [34]. However, this comes at a cost as the sensitivity is reduced to 50%. Another method is to calculate the ratio of IgG4 to total IgG or IgG1 [14, 35]. A ratio criterion like IgG4/IgG > 0.10 or IgG4/IgG1 > 0.24 is beneficial for differentiating ISC from neoplastic and non-neoplastic cholangiopathies [14, 35]. Other immunological alterations seen in these patients, though not very specific, are hyper γ-globulinemia (50%), hyper IgG (60–70%), antinuclear antibodies (40–50%), rheumatoid factor (20%), and eosinophilia (15–25%) [37, 38].

Imaging Characteristics

Imaging plays an important role in the diagnosis of ISC. Ultrasonography (US), computed tomography (CT), magnetic resonance (MR), endoscopic retrograde cholangiography (ERC), intraductal ultrasonography (IDUS), endoscopic

Table 2 Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012

Diagnostic items
(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 (≥ 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.

HPF, high-power field; PSC, primary sclerosing cholangitis

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ultrasound (EUS), positron emission tomography (PET), and cholangioscopy are helpful in differentiating ISC from other diseases.

Ultrasound

US is usually the initial imaging performed. As most of these patients present with obstructive jaundice, it is important to verify the presence or absence of biliary obstruction [15, 32]. US shows circumferential thickening of the bile duct wall (intrahepatic, extrahepatic, or both) and dilatation of intrahepatic bile ducts [39] with maintained lumen.

Intraductal Ultrasound

Intraductal US provides high-resolution images and proves a highly specific and sensitive (95–100% and 91% respectively) tool for differentiating ISC from cholangiocarcinoma when using a cutoff value of 0.8 mm for bile duct wall thickness in areas without strictures (a characteristic feature of ISC) [40, 41].

Endoscopic Ultrasound

EUS demonstrates bile duct wall thickening in about 94% of patients with ISC [42, 43]. EUS-guided tissue sampling either from the thickened bile duct or from the pancreatic mass [44] is helpful in arriving at a diagnosis of ISC.

CT/MR

CT and MR are useful for evaluating pancreatobiliary diseases. As most of the patients have associated type 1 AIP, the diagnostic approach should focus on the pancreatic lesion. Diffuse enlargement, capsule-like rim around the pancreas, and irregular narrowing of the main pancreatic duct are classical findings seen in pancreas [45, 46]. CT and MR imaging also sometimes depicts IgG4-RD in other intra-abdominal organs, as peripheral cortical nodules, round or wedge-shaped renal cortical lesions, mass-like lesions, and pelvic wall thickening within the kidneys; soft-tissue masses surrounding the aorta and its branches in the retroperitoneum and mesentery; and lymphadenopathy [47–50]. The image findings that point towards the diagnosis of ISC include hyperenhancement during the late arterial phase, homogeneous hyperenhancement during the delayed phase, multifocal biliary strictures, a markedly thickened bile duct wall (mean wall thickness, 4.9 mm), a smooth outer margin, a narrow but visible lumen, concurrent gallbladder wall thickening, and no vascular invasion [28, 51–53]. In contrast, findings more likely to suggest cholangiocarcinoma are hyperenhancement relative to the liver during the venous phase, strictures longer than 12 mm, asymmetric narrowing segments, and indistinct outer margins [54, 55]. Imaging features that help in diagnosing ISC over PSC are a single-layer bile duct wall thickness greater than 2.5 mm, multifocal strictures, long and continuous involvement of the bile duct, diffuse gallbladder wall thickening, and the absence of liver parenchymal changes [23, 28, 52, 53, 56].

ERCP

ERCP is not the primary investigation of choice in the patients as it carries a risk of pancreatitis and its sensitivity and specificity in diagnosing ISC are 45% and 88%, respectively [57]. Therefore, ERCP is indicated in these patients only when an intervention, like stent placement, is needed [58]. Classification of ISC on the basis of cholangiographic appearance and location of strictures has been described by Nakazawa et al. [59]: type 1: involvement of lower part of bile duct only mimicking pancreatic carcinoma, cholangiocarcinoma, and chronic pancreatitis; type 2: stenosis is diffusely distributed in the intra- and extrahepatic bile ducts mimicking PSC. Type 2 is further subdivided into 2 types: 2a—

extended narrowing of the intrahepatic bile ducts with prestenotic dilation; 2b—narrowing of the intrahepatic bile ducts without prestenotic dilation; type 3: stenosis is detected in both the hilar hepatic lesions and the lower part of the common bile ducts; and type 4: strictures of the bile duct are detected only in the hilar hepatic lesions. Types 3 and 4 mimic cholangiocarcinoma (Fig. 1).

PET

PET/CT shows uptake of FDG in ISC. It is not diagnostic of ISC; however, the presence of multi-organ FDG uptake is helpful in suggesting tissue sampling and therapeutic response monitoring [60, 61].

Cholangioscopy

Direct visualization of the bile duct lesions on cholangioscopy shows characteristic dilated and tortuous vessels in the bile duct wall. This feature is useful in differentiating ISC from primary sclerosing cholangitis or cholangiocarcinoma [62, 63]. 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 [64].

Histopathology

Histopathology shows the distinct triad of transmural lymphoplasmacytic infiltration, obliterative phlebitis, and storiform interstitial fibrosis with normal epithelium [65]. Distinctive feature of ISC is the presence of an increased number of IgG4-positive plasma cells (with more than 10 such cells present per high-power field in the biopsy sample), along with the ratio of IgG4-positive cells to IgG-positive cells of more than 40% [16, 66, 67]. In storiform fibrosis, the spindle cells radiate from the center like the spokes of a cartwheel. The histopathological findings are of little use and the diagnostic approach still heavily relies on imaging modalities because of the preoperative difficulty in obtaining tissue samples of the bile duct lesion.

Treatment

Rapid and consistent induction of disease remission (shown by normalization of liver function test results, reduction in serum IgG4 levels, and improvement in biliary strictures) is achieved with immunosuppressive therapy involving high-dose steroids (prednisone at a dose of 30–40 mg per day) which is also considered the treatment of choice [8, 32, 33]. There is some difference in opinion as far as the regimen is concerned. In Asian countries including Japan, after achieving remission, high-dose steroid administration is followed by a slow taper over several months to a low maintenance dose (equivalent of 2.5–10 mg of prednisone per day), which is continued for at least 1–3 years [68, 69]. Whereas, in the West, once there is successful induction of remission and the tapering period (typically 5 mg each weak), the steroid therapy is completely withdrawn [32, 70, 71]. The patients usually respond in 4–6 weeks. In a study of 527 patients with ISC in Japan, they found the disease to be benign and most patients

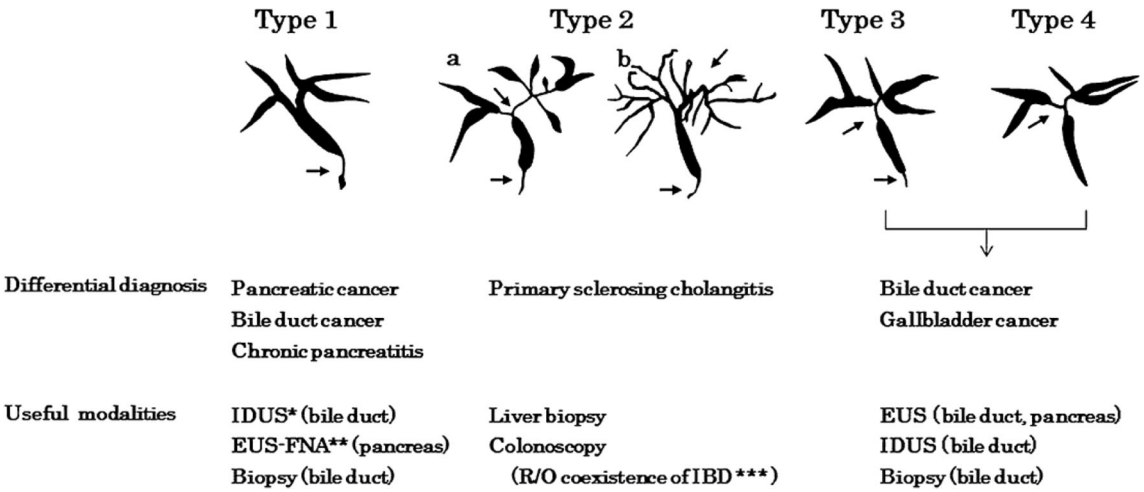

Fig. 1 The cholangiographic classification of IgG4-related sclerosing cholangitis and differential diagnosis. Stenosis is located only in the lower part of the common bile duct in type 1; stenosis is diffusely distributed in the intra- and extrahepatic bile ducts in type 2. Type 2 is further subdivided into 2 types: extended narrowing of the intrahepatic bile ducts with prestenotic dilation is widely distributed in type 2a; narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches are widely distributed in type 2b. Stenosis is detected in both the hilar hepatic lesions and the lower part of the common bile ducts in type 3, 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. Note: 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

(90%) responded to treatment with prednisolone and few developed decompensated cirrhosis or cholangiocarcinoma [20•]. Uncertainty in diagnosis warrants a steroid trial after exclusion of malignancy [32, 72]. In this case, the patient is re-evaluated after 1–2 weeks using liver function tests, serum IgG4 level, and MRCP or ERCP. When corticosteroids fail to show the desired effect, the diagnosis of ISC needs to be double-checked. This is in spite of the fact that some cases of corticosteroid refractory ISC have been documented.

Rituximab, a monoclonal CD20 antibody leading to B cell depletion, has shown favorable results as a treatment for IgG4-RD [70, 73–75]. Rituximab appears to be effective for inducing and maintaining remission; therefore, it may be worth considering for patients with corticosteroid refractory ISC and those at high risk of relapse [70, 74, 76]. There are two protocols for rituximab therapy—B cell lymphoma dosing protocol (375 mg/m^2 body surface area (BSA) weekly for 4 weeks, followed by infusions every 2–3 months) [70]. The second protocol is the same as that for rheumatoid arthritis (1000 mg/dose 2 weeks apart) [75].

Conclusions

IgG4-related sclerosing cholangitis (ISC) is seen in about 60% of the patients with IgG4-related disease. Preoperative diagnosis is often difficult. Primary sclerosing cholangitis (PSC) and cholangiocarcinoma are frequent mimickers of this disease. The characteristic features of plasma cell infiltration and raised IgG4 levels along with classical histopathological and imaging findings help in diagnosis. Steroid therapy and immunomodulatory drugs have shown promising results in ISC.

Compliance with Ethical Standards

Conflict of Interest None

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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