J Gastroenterol (2016) 51:295–312
DOI 10.1007/s00535-016-1163-7

The Japanese Society of Gastroenterology

REVIEW

IgG4-related sclerosing cholangitis: all we need to know

Yoh Zen[1] · Hiroshi Kawakami[2] · Jung Hoon Kim[3]

Received: 24 December 2015 / Accepted: 24 December 2015 / Published online: 27 January 2016

Abstract Our knowledge and experience of IgG4-related sclerosing cholangitis (ISC) have expanded in the last decade. ISC is one of the common organ manifestations of IgG4-related disease (IgG4-RD); approximately 60 % of patients with this systemic condition have ISC in the proximal and/or distal bile ducts. ISC needs to be discriminated from primary sclerosing cholangitis, cholangiocarcinoma, and other rare forms of lymphoplasmacytic cholangiopathy (e.g., follicular cholangitis and sclerosing cholangitis with granulocytic epithelial lesions). Its diagnosis requires a multidisciplinary approach, in which serology, histology, and imaging play crucial roles. Treatments with high-dose corticosteroids typically lead to the rapid and consistent induction of disease remission. Another promising therapeutic approach is B-cell depletion with rituximab. Although disease relapse is relatively common, provided that appropriate treatments are administered, ISC is considered a "benign" disease with a low risk of liver failure and biliary malignancy. Its molecular pathology is characterized by Th2-dominant immune reactions, regulatory T-cell activation, and CCL1-CCR8 interactions. Particular subsets of B cells such as plasmablasts and regulatory B cells also expand. A recent global proteomic study demonstrated that three significantly activated immunological cascades in ISC were all B-cell- or immunoglobulin-related (Fc-gamma receptor-mediated phagocytosis, B-cell receptor signaling pathway, and Fc-epsilon receptor I signaling pathway), suggesting the crucial roles of B cells in the underlying immune reactions. Despite the expansion of our knowledge of the pathophysiology of ISC, the exact role of IgG4 remains unclear. A better understanding of its immunopathology will offer some potential drug targets for this emerging biliary disease.

Keywords Autoimmune pancreatitis · IgG4-related disease · T cells · B cells · Rituximab

Abbreviations

AIP	Autoimmune pancreatitis
EUS	Endoscopic ultrasound
GEL	Granulocytic epithelial lesion
IgG4-RD	IgG4-related disease
ISC	IgG4-related sclerosing cholangitis
PSC	Primary sclerosing cholangitis

Introduction

The relationship between IgG4 and type 1 autoimmune pancreatitis (type 1 AIP) was elucidated in 2001 [1]. Subsequent pathological studies identified similar IgG4-

✉ Yoh Zen
yohzen@med.kobe-u.ac.jp

Hiroshi Kawakami
hiropon@med.hokudai.ac.jp

Jung Hoon Kim
jhkim2008@gmail.com

[1] Department of Diagnostic Pathology, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-Cho, Kobe 650-0017, Japan

[2] Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan

[3] Department of Radiology and Institute of Radiation Medicine, Seoul National University College of Medicine, Seoul, Korea

related fibroinflammatory conditions in various organs outside the pancreas [2–10], eventually leading to the recognition of a systemic condition named IgG4-related disease (IgG4-RD) [11, 12]. During this process, the bile duct appeared to be one of the target organs commonly affected by this condition [13–15]. Sclerosing cholangitis is a central biliary manifestation of IgG4-RD [13–15]. Although our clinical experience and knowledge of IgG4-related sclerosing cholangitis (ISC) have expanded rapidly in the last decade, many questions remain to be answered. One example is that isolated ISC without other organ involvement is still challenging to diagnose in clinical practice. Another question is whether ISC increases the risk of cholangiocarcinoma in the long term. The exact role of IgG4 in the pathogenesis of ISC is also poorly understood.

In this review, we summarize our current understanding of the clinical and molecular features of this emerging biliary disease and also discuss future perspectives.

Pancreatobiliary manifestations of IgG4-RD

The pancreatic manifestation of IgG4-RD is currently termed type 1 AIP or IgG4-related pancreatitis [16, 17]. It is important to note that another type of AIP (type 2 AIP) is outside the spectrum of IgG4-RD. The term AIP is used to describe this less common form of pancreatitis, given that its imaging features are nearly indistinguishable from those of type 1 AIP and both types respond similarly to steroid therapy [18]. However, these two conditions are entirely distinct in their pathophysiology; type 2 AIP is not related to IgG4.

IgG4-related disease may develop in various organs, and the incidence of each organ manifestation varies widely [19]. Pancreatitis is the leading manifestation of this systemic condition, being diagnosed in 60 % of patients with IgG4-RD [20]. The second most common manifestation is sialadenitis (34 %), followed by tubulointerstitial nephritis (23 %), dacryoadenitis (23 %), and periaortitis (20 %) [20]. An important aspect is that 95 % of patients with IgG4-RD have at least one of the top-five manifestations [20]. In terms of biliary involvement, given that the intrapancreatic bile duct is damaged in most patients with IgG4-related pancreatitis, lower duct cholangitis is also common. In contrast, the frequency at which the proximal bile ducts (e.g., hilar ducts and intrahepatic bile ducts) are affected is markedly lower, and, thus, this manifestation is ranked as sixth (13 %) [20].

IgG4-related sclerosing cholangitis develops in close association with type 1 AIP. Intrapancreatic ISC is mostly associated with AIP, suggesting that lower duct involvement is not a primary disease, and more likely represents a direct extension of the inflammatory process from the pancreas [21, 22]. Since isolated lower duct ISC is extremely uncommon, caution is needed when considering this condition for patients with lower duct cholangitis, but without pancreatitis. In contrast, proximal ISC (e.g., hilar ducts and intrahepatic bile ducts) may occur either solely or in association with pancreatitis [23]. Among 142 consecutive cases of IgG4-related pancreato-cholangitis, pancreatitis with or without intrapancreatic biliary involvement was detected in 78 % of cases, pancreatitis and proximal ISC in 20 %, and isolated proximal ISC in 2 % (Fig. 1) [20]. Most patients with isolated ISC have IgG4-RD in other organs outside the pancreatobiliary system, suggesting that true isolated cholangiopathy is exceptionally rare in IgG4-RD. Since this figure is based on data obtained from general hospitals, the incidence of isolated ISC is expected to increase up to 8 % in tertiary referral centers [14]. In most patients with both pancreatitis and proximal cholangitis, these two conditions develop simultaneously. Proximal bile duct involvement may also appear at the time of relapse in patients with type 1 AIP, while ISC prior to the development of type 1 AIP is much less common [24].

The overall prevalence rate of type 1 AIP in Japan is estimated to be 4.6 per 100,000 population with an annual incidence rate of 1.4 [25]; therefore, the prevalence and incidence of proximal ISC are expected to be 1.0 and 0.3 per 100,000 population, respectively.

Clinical features

Unlike classic autoimmune diseases, ISC more commonly develops in males with a male-to-female ratio of 4:1. More than 90 % of patients are diagnosed with ISC in their 60s or older [20]. Approximately 20 % of patients have a history of allergic disorders such as bronchial asthma, chronic sinusitis, and drug allergies. Up to 15 % of patients with IgG4-RD also have hypothyroidism and/or Hashimoto's thyroiditis [26]. Although some patients rarely have other autoimmune diseases (e.g., rheumatoid arthritis and inflammatory bowel disease), they are more likely to be an incidental association with no proven pathogenetic relevance.

Patients with ISC typically present with obstructive jaundice [14, 15, 27]. This presentation is particularly common in patients with concomitant pancreatitis. Nonspecific symptoms such as abdominal pain may trigger the diagnosis of this condition. In patients with multi-organ lesions, bile duct involvement is sometimes detected unexpectedly by imaging studies. Unlike PSC, which is often diagnosed at the advanced stage (e.g., liver cirrhosis), this presentation is uncommon in ISC.

Serum IgG4 elevations are the most sensitive and specific non-invasive examination for the diagnosis of

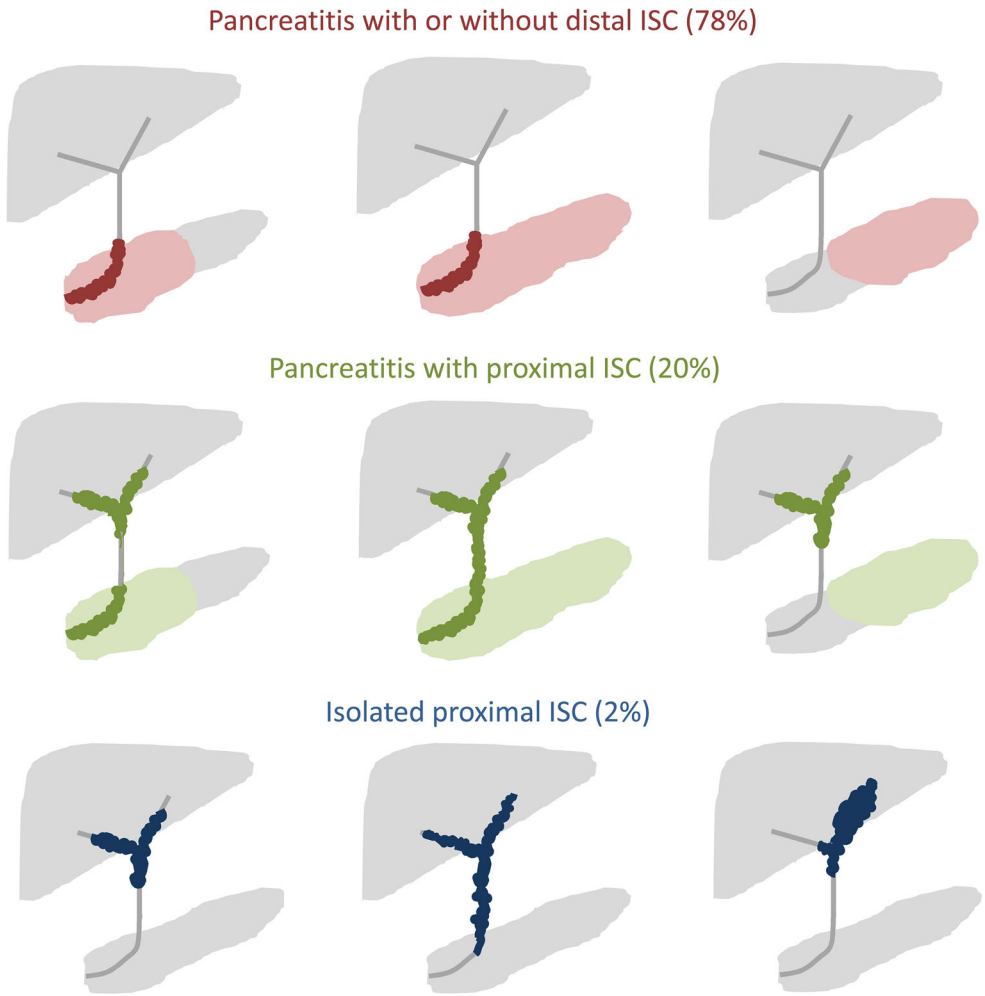


Fig. 1 Schematic view of pancreatobiliary manifestations and their incidences in IgG4-RD

ISC [14, 15, 27]. By using a typical cut-off value of 135 or 140 mg/dl, a previous study demonstrated that approximately 80 % of patients with ISC had elevated levels of IgG4 [28]. However, a caveat is that its specificity appears to be lower than initially considered. IgG4 may be elevated in patients with PSC (~10 %) or cholangiocarcinoma (~15 %), and even a non-selected cohort of patients (~7 %) who visit hospitals for various reasons [28–30]. One possible approach to increase diagnostic specificity is to use a twofold higher cut-off value (270 or 280 mg/dl) [28]. This approach increases specificity to more than 90 %; however, sensitivity is reduced to 50 %. Another method is to calculate the ratio of IgG4 to total IgG or IgG1 [20, 31]. A ratio criterion such as IgG4/IgG > 0.10 or IgG4/IgG1 > 0.24 is useful for discriminating ISC from other neoplastic and non-neoplastic biliary diseases [20, 31]. This additional calculation is helpful particularly when IgG4 elevations are less than twice the upper limit of the normal range.

Other serological abnormalities that have been reported in patients with ISC include IgG elevations (~60 %), hyper-γ-globulinemia (~50 %), antinuclear antibodies (ANAs) (~40 %), and rheumatoid factor (~20 %) [32]. Autoantibodies that are specific to other conditions (e.g., anti-mitochondrial antibody [AMA] and anti-neutrophil cytoplasmic antibody [ANCA]) are typically undetected. Serum eosinophilia and/or IgE elevations have been observed in up to 30 % of cases [33, 34].

Imaging findings

The findings of an imaging analysis frequently trigger a clinical suspicion of ISC; therefore, imaging studies are important to avoid the overdiagnosis and underdiagnosis of this condition. ISC may mimic other biliary disorders such as PSC, cholangiocarcinomas, and pancreatic cancers on imaging based on the extent and site of the biliary stricture [35, 36]. Imaging modalities that are commonly used in the

diagnostic process of ISC include ultrasonography (US), computed tomography (CT), magnetic resonance (MR), endoscopic retrograde cholangiography (ERC), intraductal ultrasonography (IDUS), and peroral video cholangioscopy (PVCS).

US

Since patients with ISC typically present with obstructive jaundice, US is initially performed on most patients with ISC in order to confirm the presence or absence of biliary obstruction [14, 15].

CT/MR

Once biliary strictures are suspected, CT and MR are performed in order to better characterize pancreatobiliary abnormalities (Fig. 2). Although CT is commonly used to evaluate pancreatobiliary diseases, MR imaging with MR cholangiopancreatography generally provides more comprehensive information in this clinical setting [37, 38]. This non-invasive approach is useful not only for evaluating the location, distribution, and degree of the biliary strictures by MR cholangiopancreatography, but also for demonstrating other abnormalities such as bile duct wall thickening and unusual enhancement patterns using pre-contrast and dynamic contrast-enhanced MR images. In patients with concomitant AIP, the pancreas shows imaging abnormalities highly specific for the diagnosis (e.g., diffuse enlargement, capsule-like rim around the pancreas, and irregular narrowing of the main pancreatic duct) [39, 40]; therefore, the diagnostic approach needs to primarily target the pancreatic lesion. CT and MR imaging also sometimes depict IgG4-RD in other intra-abdominal organs unexpectedly. Common examples are round or wedge-shaped renal cortical lesions, peripheral cortical nodules, mass-like lesions, and pelvic wall thickening in the kidneys; soft-tissue masses surrounding the aorta and its branches in the retroperitoneum and mesentery; and lymphadenopathy [41–44]. An imaging diagnosis of ISC becomes highly challenging in patients with no recognizable lesion in other organs [45, 46].

The image findings useful for the diagnosis of ISC include multifocal biliary strictures, a markedly thickened bile duct wall (mean wall thickness, 4.9 mm), a smooth outer margin, a narrow but visible lumen, hyperenhancement during the late arterial phase, homogeneous hyperenhancement during the delayed phase, concurrent gallbladder wall thickening, and no vascular invasion (Fig. 2) [47–50]. In contrast, findings more likely to suggest cholangiocarcinoma are strictures longer than 12 mm, asymmetric narrowing segments, indistinct outer margins, and hyperenhancement relative to the liver during the venous phase [51, 52]. When the biliary stricture of ISC involves the intra- and extrahepatic bile ducts, it may mimic PSC. Imaging features that favor ISC over PSC are multifocal strictures, a single-layer bile duct wall thickness greater than 2.5 mm, long and continuous involvement of the bile duct, diffuse gallbladder wall thickening, and the absence of liver parenchymal changes [47, 49, 50, 53, 54].

ERC

Although ERC is superior to MR cholangiography for demonstrating luminal changes in the bile duct, ERC is clearly more invasive than MR with a risk of post-ERC acute pancreatitis. The incidence of ERC used in patients with suspected ISC varies widely among regions because of the different guidelines applied, distinct insurance systems, and physicians' preferences. Dilation after confluent stricture (>10 mm) is a characteristic feature of ISC [35]. Classic cholangiographic findings of PSC, such as a band-like stricture, a beaded appearance, pruned tree appearance, and diverticulum-like outpouching are rare in ISC [35]. These differences in imaging findings likely represent histopathological features in which mucosal damage is more extensive in PSC, while the fibroinflammatory process transmurally affecting the duct wall characterizes ISC.

IDUS

This modality helps to demonstrate circumferential thickening of the bile duct wall, smooth outer and inner margins, and a homogeneous luminal echo [55]. These features, which are characteristic of ISC, are observed not only in stenotic areas but also in non-stenotic parts of the bile duct or even the gallbladder. Similar findings may also be obtained by endoscopic ultrasound (EUS). A caveat is that cholangiocarcinomas with extensive intraepithelial tumor spread may exhibit similar abnormalities.

PVCS

A common finding in ISC is dilated tortuous vessels not associated with partially enlarged vessels [56]. Cholangiocarcinomas may also show dilated and torturous vessels, but also have partially enlarged vessels. Another beneficial aspect of this modality is the opportunity to perform bile duct biopsy under cholangioscopy [57].

Pathology

Large duct cholangiopathy

The affected ducts show diffuse and circumferential wall thickening, with the overall appearance resembling a pipe

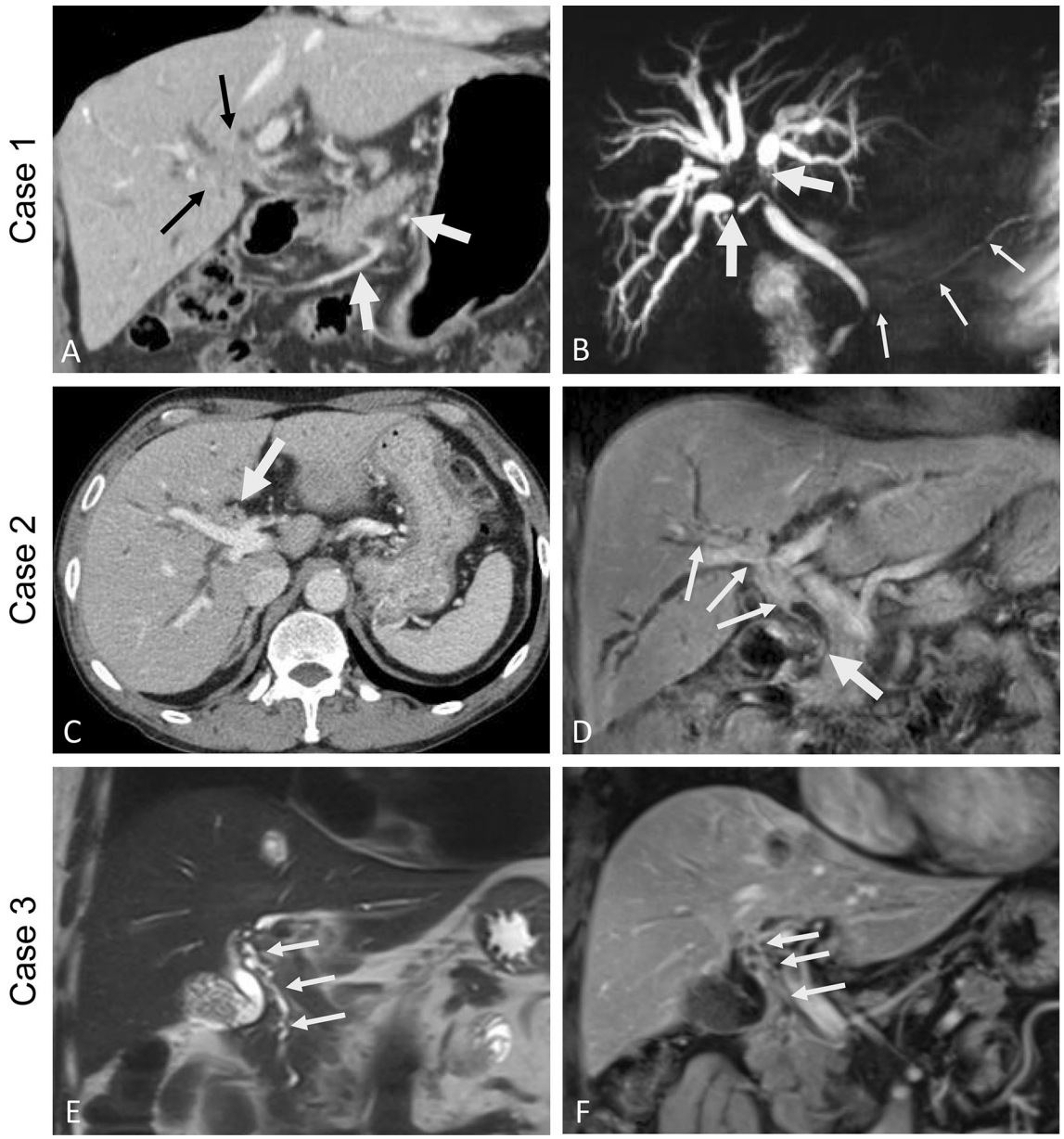


Fig. 2 Imaging features of ISC. *Case 1*, proximal ISC with AIP: **a** Contrast-enhanced CT with a coronal plan demonstrates enhanced wall thickening of the perihilar bile duct (*black arrows*) and peripancreatic fat stranding around the head of the pancreas (*white arrows*). **b** MR cholangiopancreatography shows severe stricture of the perihilar bile duct with associated upstream biliary dilatation (*large arrows*). Focal narrowing of the distal common bile duct and irregular narrowing of the main pancreatic duct (*small arrows*) are also noted. *Case 2*, proximal ISC with AIP: **c** Contrast-enhanced CT demonstrates enhanced wall thickening of the perihilar bile duct (*arrow*). **d** Contrast-enhanced MRI with a coronal plan shows diffusely enhanced wall thickening of the extra- and intrahepatic bile ducts (*small arrows*). Focal narrowing of the distal common bile duct is also noted (*large arrow*). *Case 3*, isolated ISC: **e** T2-weighted MR image with a coronal plan shows a long-segment stricture involving the extrahepatic bile ducts (*arrows*) with associated upstream biliary ductal dilatation. **f** Contrast-enhanced MRI with a coronal plan demonstrates diffuse enhanced wall thickening of the extrahepatic bile ducts (*arrows*)

stem (Fig. 3a) [58]. The mucosal surface is relatively smooth with no ulceration or intraductal granulation tissue. In some cases, ISC manifests as periductal mass lesions typically involving perihilar ducts, referred to as an IgG4-related inflammatory pseudotumor [59]. Since mass-forming ISC mimics hilar cholangiocarcinoma on imaging, surgical resection has sometimes been performed for suspected malignancies.

IgG4-related sclerosing cholangitis histologically exhibits transmural fibroinflammatory processes, in which

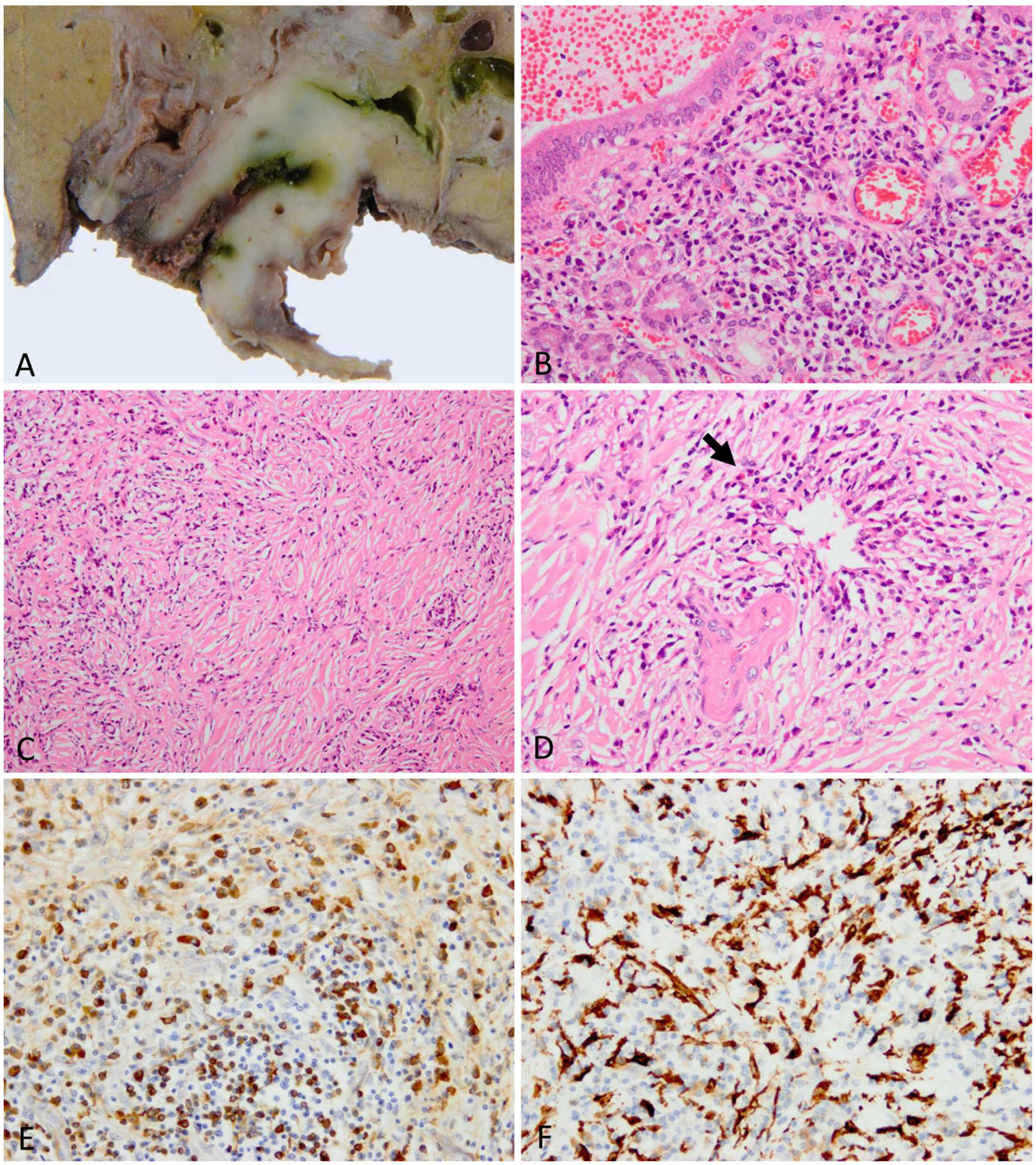


Fig. 3 Pathology of ISC. **a** The hilar bile duct with ISC shows extensive wall thickening. **b** Plasma cell-rich inflammation is noted beneath the intact lining epithelium. **c** Collagen fibers are arranged in a storiform pattern. **d** Lymphoplasmacytic phlebitis (*arrow*) represents an early sign of obliterative phlebitis. **e** IgG4 immunostaining demonstrates many IgG4-positive plasma cells. **f** Although macrophages are not conspicuous on H&E-stained sections, CD163 immunostaining reveals abundant M2-type macrophages

inflammation and fibrosis are evenly distributed from the mucosal surface to subserosa [23]. Another feature is that the lining surface epithelium and peribiliary glands are intact despite the severe fibroinflammatory process [23, 58]. Infiltrating inflammatory cells are mainly lymphocytes and plasma cells (Fig. 3b). Eosinophilic infiltration is also noted in most cases, whereas neutrophils, abscess, and necrosis are not. Some degree of fibrosis is always present, even in patients who present acutely. A characteristic pattern of fibrosis is called storiform fibrosis, in which collagen fibers are arranged in an irregularly whorled pattern (Fig. 3c). The fibroinflammatory process is pronounced around veins, leading to partial or complete obliteration, and this histological finding is called obliterative phlebitis (Fig. 3d). Inflammation also sometimes extends along nerve fibers.

Immunostaining for IgG4 reveals the massive infiltration of IgG4-positive plasma cells (Fig. 3e). These cells are

expected to be diffusely present, and focal aggregation is not typical for this condition. The cut-off values for IgG4-positive plasma cells proposed for ISC are >50 cells/hpf for surgical specimens and >10 cells/hpf for biopsy samples [60]. The ratio of IgG4-positive to total IgG-positive plasma cells is greater than 40 % [60]. This ratio criterion helps to discriminate ISC from other biliary diseases with the non-specific infiltration of IgG4-positive plasma cells.

Small duct cholangiopathy

The main target of ISC appears to be the large bile ducts; however, the inflammatory process extends into the intrahepatic bile ducts along periductal connective tissue and Glisson's capsule in up to 30 % of cases [61, 62]. Small duct ISC always accompanies large duct disease with no cases of pure small-duct ISC (like small-duct PSC) being reported [62]. Small duct involvement may be confirmed by liver biopsy. Histologically, affected portal tracts are enlarged with a dense inflammatory infiltrate consisting mainly of lymphocytes and plasma cells [58, 62]. Eosinophils are also present. A bile ductular reaction is noted particularly in patients with biliary obstruction. Reactive bile ductules are associated with neutrophilic infiltration. Therefore, although neutrophilic infiltration is generally regarded as a histological finding against the diagnosis of IgG4-RD, this is not the case in liver needle biopsies. Bile ducts are slightly damaged, as evidenced by an irregularity in the lining epithelium, whereas bile duct loss is less likely to occur even in cases of longstanding ISC. Most cases do not have typical obliterative phlebitis in small portal tracts. Microscopic small nodules consisting of fibrosis and inflammatory infiltrates may form around the portal tracts. This finding, which was originally called portal inflammatory nodules, likely represents storiform fibrosis at this site, and is highly specific for the diagnosis of ISC [63]. Immunostaining demonstrates the infiltration of IgG4-positive plasma cells (>10 cells/hpf) in the affected portal tracts with an increase in the ratio of IgG4/IgG-positive cells to greater than 40 %.

Diagnostic approach

One of the two diagnostic criteria proposed for ISC is called the HISORt criteria, which were originally designed for type 1 AIP; however, its application was further expanded to the biliary disease [14, 64, 65]. Another diagnostic criterion for ISC was proposed by Japanese investigators [66]. Although there are minor differences between the two proposals, the overall multidisciplinary approach is the same. Features on imaging, serology, histology, other organ involvement, and responses to steroid therapy need to be considered for a diagnosis. It is important to note that >95 % of patients with ISC have concomitant type 1 AIP. In these cases, the diagnostic approach is toward the pancreatic disease because IgG4-related pancreatitis is easier to diagnose than ISC in most cases. The diagnosis of type 1 AIP needs to follow the International Consensus Diagnostic Criteria [67]. In patients with suspected isolated ISC, serum IgG4 elevations and imaging features are not sufficient to reach a concrete diagnosis; therefore, other organ involvement needs to be confirmed and/or a tissue diagnosis performed. If the diagnosis remains non-conclusive even with histology, steroid trials may be considered; however, the possibility of malignancy should be carefully excluded before commencing immunosuppression.

Differential diagnosis

Cholangiocarcinoma

Many earlier cases of ISC underwent surgery for suspected malignancies, suggesting the leading differential diagnosis of ISC to be cholangiocarcinoma, particularly in cases of localized or mass-forming cholangitis. The serological test for IgG4 is not always conclusive for this differential diagnosis as described above. If imaging features are also not diagnostic, a tissue examination is needed. In this clinical setting, bile duct biopsy and biliary cytology are more useful than liver needle biopsy (Fig. 4a, b) [68]. Although some patients may require steroid trials, if imaging abnormalities do not improve in the first 2–3 weeks after the initiation of steroid therapy, the diagnosis of ISC will be questioned.

Primary sclerosing cholangitis (PSC)

Clinical features differ between ISC and PSC. PSC is more likely in patients younger than 40 years and those who have a history of inflammatory bowel disease. Cholangiography is also useful; however, the findings obtained need to be reviewed by experienced radiologists or endoscopists [35, 69]. From a histological point of view, this differential diagnosis is relatively straightforward if resected bile duct specimens are available [58]. Unlike ISC, which is a transmural fibroinflammatory process, PSC generally shows more mucosa-targeted tissue damage with ulceration and xanthogranulomatous inflammation. Obliterative phlebitis and storiform fibrosis support the diagnosis of ISC, while neutrophilic infiltration and fibro-obliteration of the bile ducts are more consistent with PSC. Small veins are often obliterated in PSC, but are not associated with an inflammatory infiltrate [70]. Although IgG4-positive plasma cells may be present in PSC [70, 71],

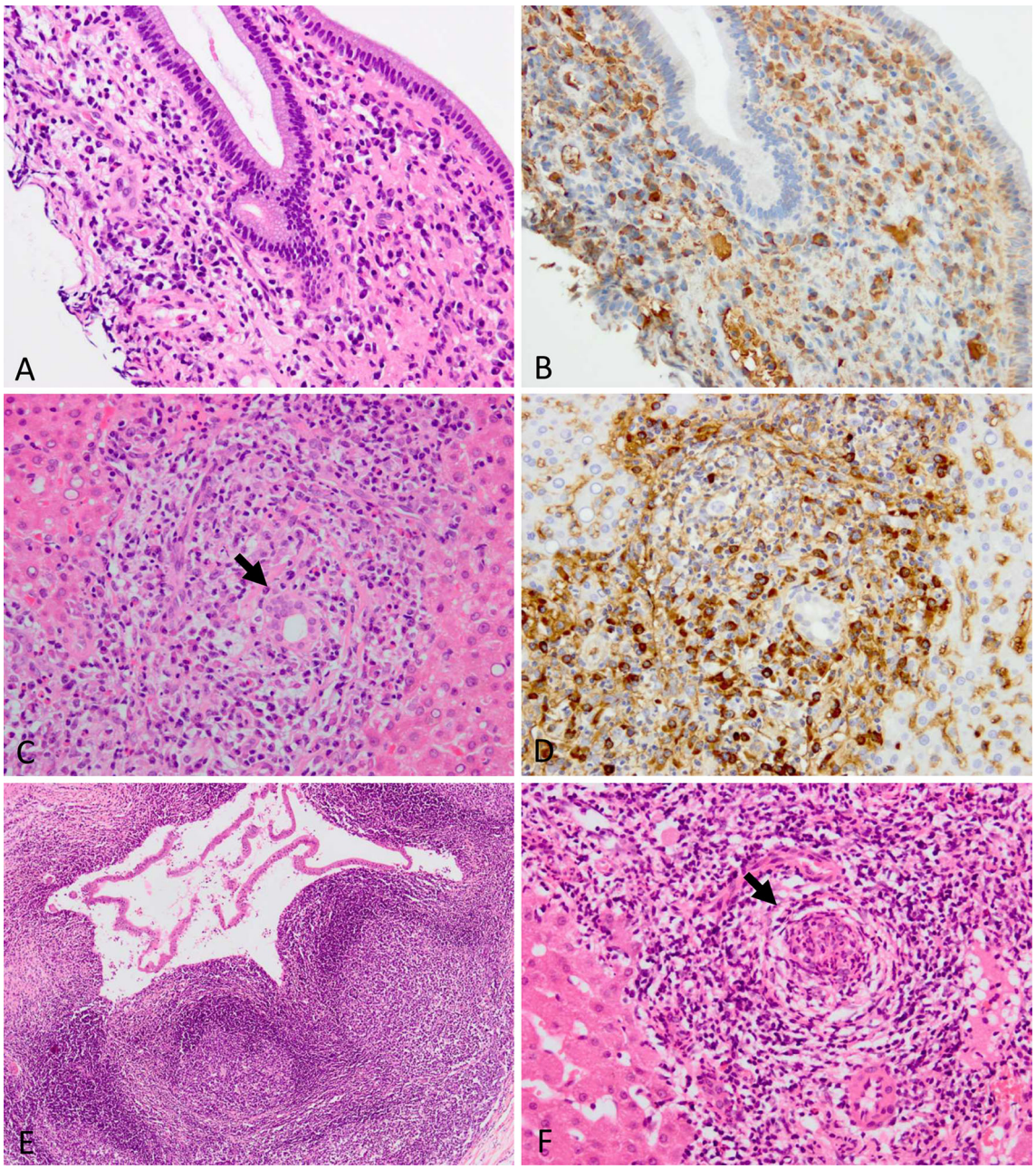


Fig. 4 Biopsy findings and differential diagnoses of ISC. **a** Bile duct biopsy shows the infiltration of lymphocytes and plasma cells in the bile duct stroma. The lining epithelium is well preserved. **b** Many plasma cells appear to be positive for IgG4, indicating the diagnosis of ISC. **c** In this liver biopsy, the portal tract is expanded with a dense inflammatory infiltrate containing lymphocytes, plasma cells, and eosinophils. The *arrow* indicates a slightly damaged bile duct; however, bile duct injury is less conspicuous than that in PSC. **d** IgG4 immunostaining shows many IgG4-positive plasma cells, in keeping with ISC. **e** Follicular cholangitis is characterized by dense lymphocytic infiltration with many lymphoid follicles. **f** Sclerosing cholangitis with GEL shows intraepithelial neutrophilic infiltration and periductal fibrosis (*arrow*)

their number and ratio to IgG-positive plasma cells are markedly smaller than those in ISC. More importantly, IgG4-positive plasma cells are not diffusely present in PSC [70, 71].

Although this differential diagnosis becomes more difficult in biopsy samples, liver needle biopsies often assist in determining the nature of sclerosing cholangitis. Histological findings in both conditions include portal inflammation, a bile ductular reaction, and copper-associated protein deposition in periportal hepatocytes; therefore, these are not useful for the discrimination [61]. Fibro-obliterative changes such as periductal concentric fibrosis

and bile duct loss suggest PSC over ISC, while the presence of IgG4-positive plasma cell infiltration (>10 per high-power field) indicates ISC (Fig. 4c, d) [58, 72]. In our experience, liver biopsies suggest either condition in approximately 40 % of patients who have sclerosing cholangitis of an unknown cause.

Follicular cholangitis

Follicular cholangitis is another form of lymphoplasmacytic cholangitis. This condition is estimated to be rare with less than a dozen cases being reported [73–76]. Patients typically lack any serological autoimmune abnormalities or associated immune-mediated conditions in other organs. A tissue examination is essential for a conclusive diagnosis. Follicular cholangitis usually affects perihilar large bile ducts, but broad cholangiopathy mimicking ISC or PSC is rarely encountered [73]. A characteristic histological feature is duct-centered inflammation associated with many lymphoid follicles (Fig. 4e). Fibrosis is less conspicuous than ISC. The inflammatory infiltrate in follicular cholangitis is more lymphocytic and less plasmacytic than that in ISC. A similar inflammatory process rich in lymphoid follicles may develop in the pancreas and gallbladder, referred to as follicular pancreatitis and follicular cholecystitis, respectively [73, 77]. Whether or not serum IgG4 levels can be elevated in this condition is unknown. As all cases reported so far were diagnosed by tissue examination of the resected tissue, steroid responsiveness is another unanswered question.

Sclerosing cholangitis with granulocytic epithelial lesion (GEL)

GEL is a pathognomonic histological finding of type 2 AIP [78, 79]. It is characterized by a large number of neutrophils infiltrating the lining epithelium of the pancreatic duct. A similar neutrophil-rich duct injury was recently identified in a subset (2 %) of "primary" sclerosing cholangitis cases, particularly in pediatric cases [80]. Five patients in the original study showed a good response to steroids and were in remission for a number of years, indicating that GEL serves as a histological sign of steroid responsiveness in patients with sclerosing cholangitis [80]. Histologically, a large number of neutrophils infiltrate the epithelial layer of the small bile ducts, leading to an irregular configuration of the lining epithelium (Fig. 4f). Other histological findings such as periductal concentric fibrosis are basically similar to those in PSC. GEL histologically differs from suppurative cholangitis in that neutrophils are mainly present in the epithelial layer, but not inside the duct lumen. Although reactive bile ductules also commonly have neutrophilic infiltration, bile duct GEL is distinct from reactive bile ductules because GEL originates from the principal bile ducts, not the ductules. The recognition of this entity suggests that steroid-responsive sclerosing cholangitis is not always ISC.

Non-IgG4-related inflammatory pseudotumors

Mass-forming ISC is called an IgG4-related inflammatory pseudotumor [59]. Two subtypes of hepatic inflammatory pseudotumors have been recognized to date; one is IgG4-related, while the other, named the fibrohistiocytic type, is not. Unlike the IgG4-related type, which typically affects hilar bile ducts, the fibrohistiocytic type more commonly occurs in the liver parenchyma exhibiting nodular lesions [59]. Histologically, the non-IgG4-related fibrohistiocytic type shows an extensive xanthogranulomatous reaction. Although IgG4-positive plasma cells may moderately increase in number, these two conditions are distinguishable from each other based on H&E-stained sections. The IgG4/IgG-positive cell ratio does not exceed 40 % in the fibrohistiocytic type [59]. Similar to mass-forming ISC, non-IgG4-related pseudotumors sometimes show spontaneous regression; however, it currently remains unclear whether steroid therapy is effective.

Hepatic pseudolymphoma

This is another mass-forming inflammatory condition in the liver [81]. Patients with hepatic pseudolymphoma sometimes have autoimmune diseases outside the liver or a history of malignancy. In this condition, solitary or multiple inflammatory nodules are formed within the liver parenchyma. Unlike ISC, hilar duct involvement is uncommon. Histologically, this condition is more lymphoid in appearance with no increases in the number of IgG4-positive plasma cells [81].

Treatment and outcome

The treatment strategy is basically similar to that for type 1 AIP [17]. Immunosuppressive therapy with high-dose steroids (prednisone at a dose of 30–40 mg per day) is the treatment of choice, and generally leads to the rapid and consistent induction of disease remission (Fig. 5a) [14, 17, 27]. 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 [82, 83]. In contrast, in the West, steroid therapy is completely withdrawn after the successful induction of remission and the tapering period (typically 5 mg each weak) [14, 84, 85]. A

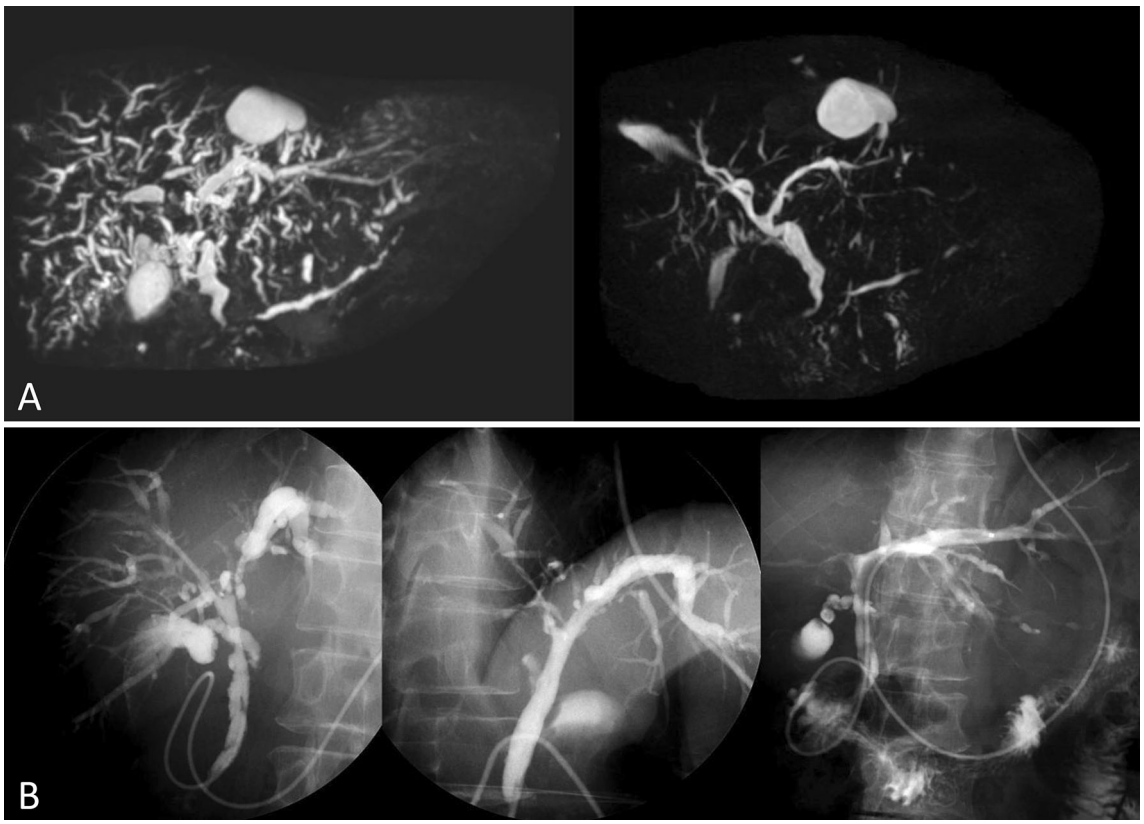


Fig. 5 Treatment effects of corticosteroids on ISC. **a** Bile duct damage is markedly improved by a 2-week treatment with corticosteroids. (*Left*, before treatment; right, after treatment). **b** Cholangiographic findings in a case of histology-proven ISC show persistent biliary strictures even with steroid therapy for 4 years (*Left*, before treatment; *middle*, after 1 month; *right*, after 4 years)

retrospective study of type 1 AIP showed that the relapse rate was slightly higher in patients with maintenance steroids than in those with no maintenance therapy [86]. Although rare cases of ISC refractory to corticosteroids have been documented (Fig. 5b), the diagnosis of ISC needs to be double-checked when the effects of corticosteroids are less than expected.

Disease relapse occurs in approximately 30–50 % of patients either during the steroid taper or after the discontinuation of steroids, particularly in the first couple of years [17]. Known risk factors for relapse include increased IgG4 levels and the presence of proximal bile duct strictures [87]. Relapsed disease develops either at the same site as the original disease or in a different portion of the biliary tree [87]. New lesions may also appear in other organs. Additional high-dose steroids remain highly successful for the re-induction of remission in patients with relapse [87]. Other approaches include immunomodulators such as azathioprine, 6-mecrpatopurine, and mycophenolate mofetil. However, no reliable data is available in terms of how effective these drugs are in the re-induction of remission in patients with relapsed ISC [87].

Rituximab, a monoclonal CD20 antibody leading to B-cell depletion, has been increasingly recognized as a promising treatment for IgG4-RD [87–90]. The first reported patient with IgG4-RD who was given rituximab had relapsed ISC [88]. His steroid-refractory biliary disease was treated with rituximab, and remission was successfully achieved [88]. Based on the findings of subsequent studies including a recent phase I/II study, rituximab appears to be effective for inducing and maintaining remission; therefore, it may be worth considering for patients with previous intolerance to high-dose steroids and those at high risk of relapse [87, 89, 91]. It is important to note there are two protocols for rituximab therapy. The B-cell lymphoma dosing protocol consists of 375 mg/m^2 body surface area (BSA) weekly × 4 weeks, followed by infusions every 2–3 months [87]. The second protocol, which was used in the phase I/II study, is the same as that for rheumatoid arthritis (1000 mg/dose 2 weeks apart) [90]. According to the limited data available, the remission rate was similar between the two (80–90 % in patients including many with difficult-to-treat disease), whereas the relapse rate appeared to be slightly higher with the rheumatoid arthritis approach.

In terms of long-term outcomes, it remains unclear whether and how fast ISC progresses to liver cirrhosis. In our experience, end-stage liver disease is an uncommon complication in patients with ISC. Except for a single case of non-treated ISC showing early cirrhotic transformation, liver fibrosis was bridging fibrosis at worst in our cohort [58]. However, a previous study reported that four out of 53 patients with ISC eventually developed portal hypertension and cirrhosis within 5 years of the onset of initial symptoms [14]. Another unsolved question is whether ISC increases the risk of malignancy. Recent studies have suggested that the incidence of malignancy in patients with IgG4-RD including ISC is not significantly higher than that in age- and gender-matched control subjects in the first 3 years; however, a longer follow-up is required in order to determine whether a cumulative increase occurs in cancer risk in ISC [20, 92].

Pathophysiology

The pathogenetic process of IgG4-RD has been suggested to be multifactorial and similar across organ manifestations [17]. This section summarizes the immunological characteristics underlying clinicopathological features (Fig. 6). Similar to other immune-mediated conditions, a likely mechanism is that the disease develops in genetically susceptible individuals exposed to external or endogenous antigens [17].

Etiology

IgG4-RD including ISC was originally suspected to be an autoimmune disorder based on its frequent association with serological autoimmune abnormalities (e.g., ANA positivity) and steroid responsiveness [93, 94]. However, this possibility has been questioned. Unlike classic autoimmune disorders, patients with IgG4-RD are older (median age, 67 years) and 80 % are male. No disease-specific autoantibodies have been identified to date. Other suspected pathogenetic processes include allergic reactions, a lymphoproliferative nature, and immune-complex deposition disease; however, no conclusive data is available for any of these possibilities.

Genetic risks

Although the HLA serotypes DRB1*0405 and DQB1*0401 are known to increase susceptibility in Japanese populations [95], this association has not been proven in other ethnicities [96]. Five non-HLA genes, single-nucleotide polymorphisms (SNP) in which are associated with disease development and/or higher disease activity, are cytotoxic T lymphocyte-associated protein 4 (*CTLA4*), tumor necrosis factor (*TNF*), Fc receptor-like 3 (*FCRL3*), trypsin 1 (*PRSS1*), and cystic fibrosis transmembrane conductance regulator (*CFTR*) [97–101]. More comprehensive analyses such as genome-wide association studies (GSWAs) are needed in order to more fully understand the genetic risks of this condition.

IgG4 molecules

IgG4 is a key molecule in immunological reactions in ISC because massive infiltration by IgG4-positive plasma cells is a consistent histological hallmark of this condition. However, it remains unclear whether IgG4 molecules are induced in a pro- or anti-inflammatory manner. When IgG4 elevations were previously discovered in patients with type 1 AIP, many investigators suspected that IgG4 functioned as a tissue-destructive antibody. However, IgG4-type autoantibodies have never been confirmed in patients with IgG4-RD. A general view is that IgG4 is a non-inflammatory antibody because of its relative inability to fix complement and its poor capacity to bind to Fc receptors [102, 103]. Another unique feature of IgG4 molecules is "Fab-arm exchange", a process in which a pair of heavy and light chains of an IgG4 antibody is exchanged with those derived from another IgG4 [104]. Due to this structural change, IgG4 molecules become asymmetric, and eventually lose their antigen cross-linking ability, behave as monovalent antibodies, and become incapable of forming large immune complexes [17]. Due to the anti-inflammatory properties of IgG4, many investigators currently suspect that IgG4 may be secondarily induced to dampen extensive immune reactions in IgG4-RD.

T cell response

Two subsets of T-cells that are known to be up-regulated in ISC are T-helper (Th) 2 lymphocytes and regulatory T cells (Tregs) [105, 106]. A caveat is that Th1 lymphocytes are not completely suppressed because the number of Th1 lymphocytes and expression of Th1 cytokines are similar to those in PSC. In contrast, Th2 cytokines such as IL-4, IL-5, and IL-13 are significantly overexpressed [105]. Th2-dominant immune reactions in ISC seem to be reasonable because patients sometimes have serum eosinophilia and elevated IgE concentrations. Th2 cytokines produced in tissue may be involved in these systemic serological features [105, 106]. IL-21 was recently proven to be up-regulated in IgG4-related sialodacryoadenitis [107]. This cytokine, which is produced by Th2 and T follicular helper (Tfh) cells, leads to germinal center formation [108]. However, it is important to note that germinal center formation is less common in ISC than in IgG4-related

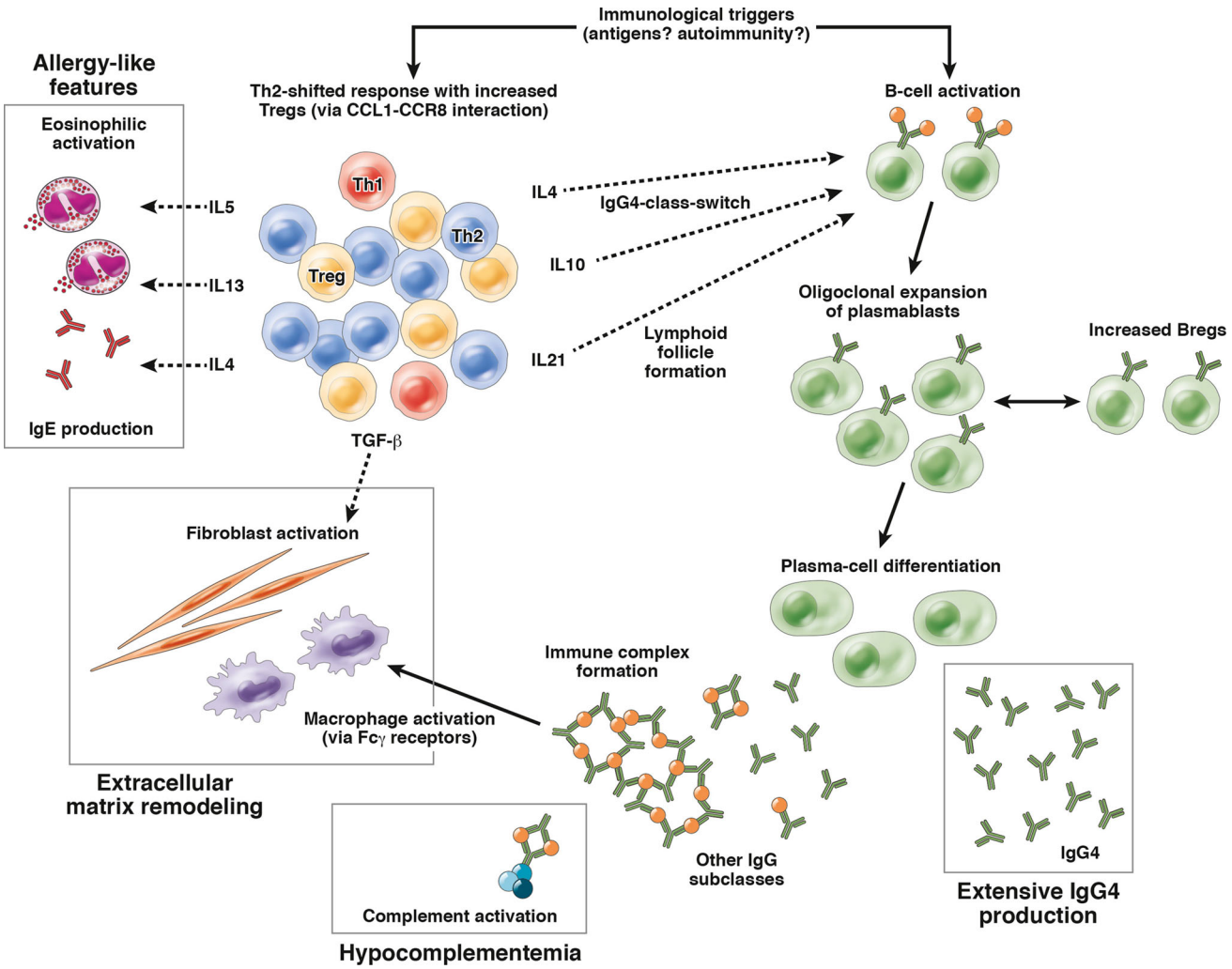


Fig. 6 Proposed immunological interactions in ISC. (2015 copyright by AGA Institute. Hart et al. [17]. Reprinted with permission from Elsevier Inc.)

sialodacryoadenitis [5]. A more recent study also demonstrated that the number of circulating Tfh2 cells was increased in patients with IgG4-RD, and these numbers correlated with plasmablast counts and the serum levels of IL-4 and IgG4 [109]. Since Tfh cells are a distinct subset of CD4+ T cells that expedite B-cell and plasma cell differentiation, Thf2 cells may play a crucial role in T-cell–B-cell interactions in IgG4-RD.

Tregs are also likely activated in ISC. This is another reason why ISC is considered to be a non-autoimmune disease because the functions of this subset of immune-suppressive T cells are generally decreased in classic autoimmune disorders [110, 111]. Histologically, a large number of FOXP3+ CD4+ CD25+ Tregs has been observed in bile duct tissue with ISC, along with the overexpression of two regulatory cytokines (IL-10 and TGF-β) [105, 112]. IL-10 is suspected to participate in an IgG4 class-switch in B cells. When IL-4 and IL-10 simultaneously act on B cells, the production of IgG4 is known to be selectively induced [113]. Therefore, Treg activation against the background of Th2-dominant immune reactions may provide a driving force toward an IgG4 class switch via IL-4 and IL-10. TGF-β is a strong fibrogenic cytokine, likely contributing to fibrosis in ISC [106].

Chemokines and chemokine receptors

The roles of chemotactic factors in the immunopathology of IgG4-RD are poorly understood, with only less than a dozen chemotactic factors known to be upregulated (e.g., CXCL13, CCL18, and CCR4) [114, 115]. A critical question is which chemotactic factors are involved in creating a milieu rich in Th2 and Tregs. We investigated the expression of Th2 chemokines and their receptors, and found that CCL1 and CCR8 were up-regulated in ISC

[116]. These two molecules are probably important because 50 % of Th2 lymphocytes and 60 % of FOXP3+ Tregs express CCR8 [117]. CCL1 is expressed in the ductal and glandular epithelia in ISC. CCR8-positive lymphocytes are also present around the bile ducts and peribiliary glands, suggesting CCL1-CCR8 interactions operating in these particular microscopic foci [116]. Another source of CCL1 in ISC is endothelial cells. The endothelium involved in obliterative phlebitis is positive for CCL1 and is infiltrated by CCR8-positive lymphocytes, suggesting that CCL1-CCR8 interactions may also cause obliterative phlebitis [116].

It currently remains unclear why the biliary epithelium is intact despite the expression of CCL1. Although there are CCR8-positive Th2 lymphocytes and Tregs around the ducts, intraepithelial lymphocytes are rare. One possible explanation is that Th2 lymphocytes and Tregs may not be strong enough to infiltrate the basement membrane. A previous study demonstrated that the bile duct epithelium is damaged at the molecular level despite its unremarkable morphological appearance. The biliary epithelium in ISC has impaired barrier function because of the abnormal expression of cell adhesion molecules such as claudins, which are supposedly induced by a direct interaction between Th2 cytokines and their receptors expressed on cholangiocytes [118].

Expansion of B-cell subsets

Recent studies have examined the B-cell aspects of IgG4-RD, and their findings have been reinforced by the clinical observation that B-cell depletion therapy with anti-CD20 antibodies is effective in patients with IgG4-RD [87, 90]. Two subsets of B cells (regulatory B cells [Bregs] and plasmablasts) are upregulated in IgG4-RD. Similar to Tregs, a subset of Bregs may be activated under these conditions [119]. A recent study suggested that IL-10-producing Bregs have a strong capacity to produce IgG4 [120]; however, their involvement in this particular condition remains to be examined. Molecular studies using a next-generation sequencing protocol have identified the oligoclonal expansion of IgG4-switched B cells and CD19+ CD20-CD27+ CD38+ plasmablasts in IgG4-RD [112, 121]. Circulating plasmablasts are largely IgG4-positive, and have undergone extensive somatic hypermutation [121, 122]. Recombinant IgG4 molecules derived from the most dominant IgG4-positive plasmablasts in a patient with IgG4-RD were also shown to react with human cells [121].

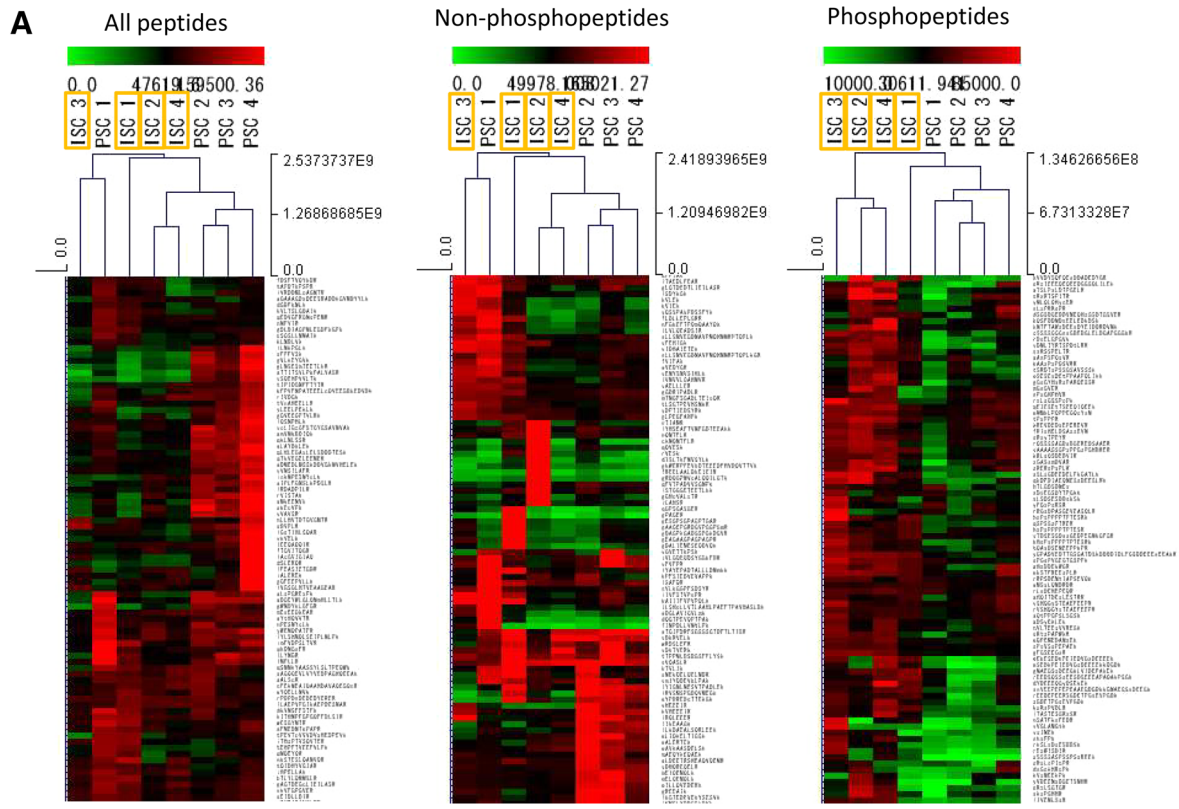
A recent global proteomic study on ISC and PSC also highlighted the involvement of B cells in the pathogenesis of ISC [123]. Protein profiles in the frozen bile duct tissue of ISC were compared with those of PSC. To the best of our knowledge, this was the first non-biased global tissue examination of ISC. A robust proteomic approach with phosphopeptide enrichment methods identified 23,373 peptides and 4870 proteins, including 4801 phosphopeptides and 1121 phosphoproteins [123]. The expression profiles of phosphopeptides discriminated ISC from PSC better than those of non-phosphopeptides, suggesting that the phosphorylation status of proteins better characterizes these conditions than their expression levels (Fig. 7a) [123]. In the pathway analysis based on strongly expressed or highly phosphorylated proteins, ISC was found to have 11 more activated signal cascades including three immunological pathways than PSC. Interestingly, the three immune cascades were all B-cell- or immunoglobulin-related. The most significantly modulated immunological pathway was Fc-gamma receptor-mediated phagocytosis (Fig. 7b) [123]. This is a signal cascade that is triggered by the interaction between IgG molecules and Fc-gamma receptors on the cell membrane. It is important to note here again that IgG4 has a poor capacity to bind to Fc receptors [102]. Therefore, it remains unclear whether IgG4 or other IgG subclasses activate this signaling pathway under this particular condition. The other two activated cascades were the B-cell receptor signaling pathway and Fc-epsilon receptor I signaling pathway [123]. Since no pathways directly related to T cells were significantly modulated between the two conditions, B-cell immune responses may better discriminate the immunological features of ISC and PSC. This may be one reason for why rituximab works well in patients with ISC.

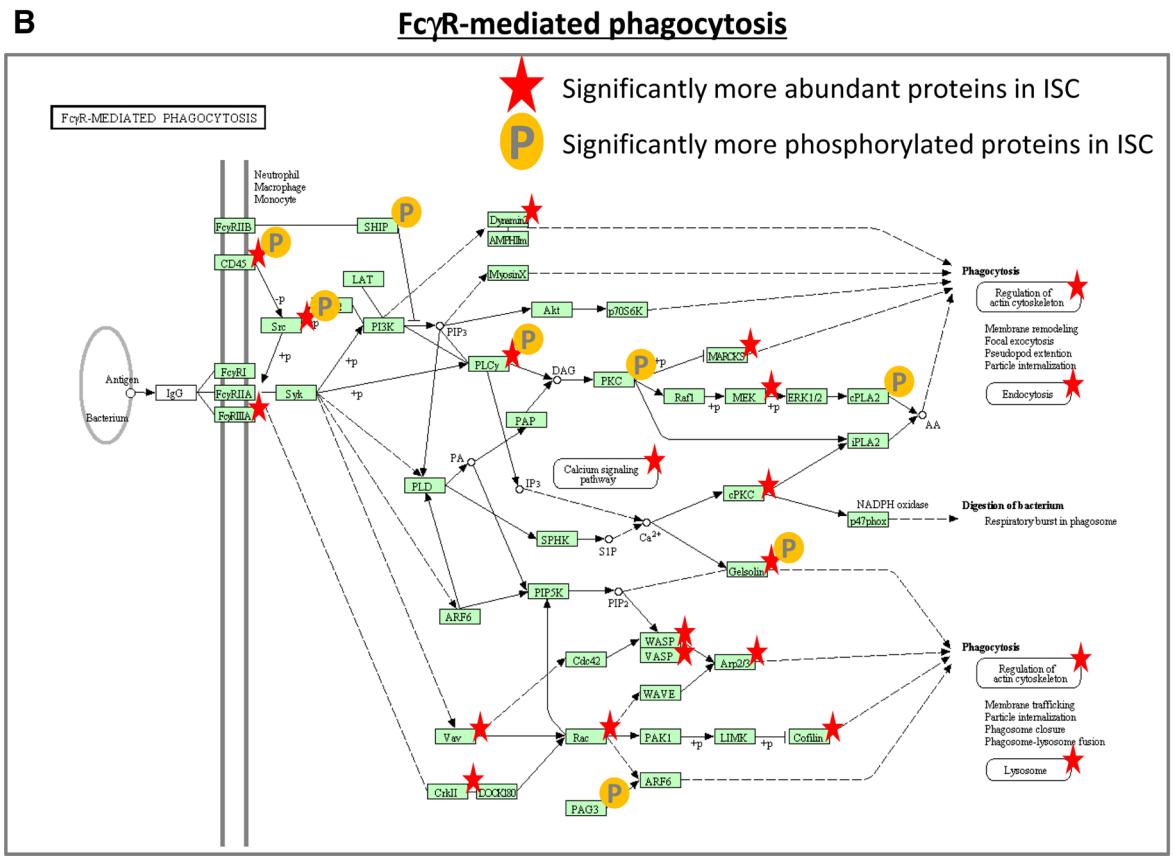
Macrophage activation

Macrophages are difficult to identify in ISC on H&E-stained sections or even using immunostaining for CD68, the most commonly used marker for macrophages. However, immunostaining for CD163, which is expressed on M2-type macrophages, shows that this subset of macrophages is abundant in bile duct tissue with ISC (Fig. 3f) [123, 124]. The signal cascade "Fc-gamma receptor-mediated phagocytosis", which was determined to be significantly activated in ISC by a proteomic study, also occurs inside macrophages. Macrophages, particularly the M2 type, may be involved in orchestral immune reactions as well as in extracellular matrix remodeling in ISC.

Future perspectives

In the last decade, as ISC has been increasingly recognized as a novel form of sclerosing cholangiopathy, our knowledge on this condition, particularly in terms of its diagnosis and systemic manifestations, has expanded. In the next


A
All peptides
Non-phosphopeptides
Phosphopeptides
ISC 3
PSC 1
ISC 1
ISC 2
ISC 4
PSC 2
PSC 3
PSC 4
2.5373737E9
1.26868685E9
0.0
2.41893965E9
1.20946982E9
1.34626656E8
6.7313328E7


B
FcγR-mediated phagocytosis
Significantly more abundant proteins in ISC
Significantly more phosphorylated proteins in ISC
FCγR-MEDIATED PHAGOCYTOSIS
Neutrophil
Macrophage
Monocyte
FcγRIIB
CD45
SHIP
LAT
Src
PI3K
Akt
p70S6K
Dynamin
AMPHIIm
MyosinX
PIP3
PLCγ
DAG
PKC
MARCKS
Raf1
MEK
ERK1/2
cPLA2
AA
iPLA2
Antigen
IgG
Bacterium
FcγRI
FcγRIIA
FcγRIIIA
Syk
PAP
PA
PLD
IP3
Calcium signaling pathway
cPKC
NADPH oxidase
p47phox
Digestion of bacterium
Respiratory burst in phagosome
SPHK
S1P
Ca2+
Gelsolin
PIP5K
PIP2
ARF6
Phagocytosis
Regulation of actin cytoskeleton
Membrane remodeling
Focal exocytosis
Pseudopod extention
Particle internalization
Endocytosis
WASP
VASP
Cdc42
Arp2/3
WAVE
Vav
Rac
PAK1
LIMK
Cofilin
CrkII
DOCK180
PAG3
Membrane trafficking
Particle internalization
Phagosome closure
Phagosome-lysosome fusion
Lysosome

◀**Fig. 7** Protein expression profiles in frozen bile duct samples of ISC. **a** Proteins extracted from frozen bile duct samples of ISC and PSC cases ($n = 4$ each) were examined in a global non-biased manner. Clustering analysis of ISC and PSC cases was performed based on the expression profiles of non-phosphopeptides, phosphopeptides, or both. The analysis based on phosphopeptides only showed better separation than the other two. *Each row* represents individual peptides identified by the proteomic analysis. Since whole heat maps are very long, only representative areas are shown. **b** The most significantly activated signaling pathways in ISC. Many proteins involved in these cascades were more abundant (marked with *red stars*) or more phosphorylated (marked with "*P*" *marks*) in ISC. (2015 copyright by John Wiley & Sons Ltd. Reprinted from Zen et al. [123]

decade, further efforts are needed in order to elucidate the long-term outcomes of and establish the best treatment strategy for patients with ISC. More studies are also required for obtaining a better understanding of its pathophysiology. It still remains unknown why IgG4 is selectively induced in this condition. Given the rarity of ISC, multi-institutional collaborations are necessary to answer these questions. Specialists in other fields (e.g., immunologists and molecular biologists) will also be welcomed to future developments in this field.

Compliances with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344(10):732–8 **(Epub 2001/03/10)**.
2. Zen Y, Inoue D, Kitao A, Onodera M, Abo H, Miyayama S, et al. IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. Am J Surg Pathol. 2009;33(12):1886–93.
3. Zen Y, Kitagawa S, Minato H, Kurumaya H, Katayanagi K, Masuda S, et al. IgG4-positive plasma cells in inflammatory pseudotumor (plasma cell granuloma) of the lung. Hum Pathol. 2005;36(7):710–7.
4. Zen Y, Sawazaki A, Miyayama S, Notsumata K, Tanaka N, Nakanuma Y. A case of retroperitoneal and mediastinal fibrosis exhibiting elevated levels of IgG4 in the absence of sclerosing pancreatitis (autoimmune pancreatitis). Hum Pathol. 2006;37(2):239–43.
5. Zen Y, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. Am J Surg Pathol. 2010;34(12):1812–9.
6. Zen Y, Kasashima S, Inoue D. Retroperitoneal and aortic manifestations of immunoglobulin G4-related disease. Semin Diagn Pathol. 2012;29(4):212–8.
7. Zen Y, Onodera M, Inoue D, Kitao A, Matsui O, Nohara T, et al. Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. Am J Surg Pathol. 2009;33(12):1833–9.
8. Kamisawa T, Funata N, Hayashi Y, Tsuruta K, Okamoto A, Amemiya K, et al. Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. Gut. 2003;52(5):683–7 **(Epub 2003/04/15)**.
9. Kitagawa S, Zen Y, Harada K, Sasaki M, Sato Y, Minato H, et al. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner's tumor). Am J Surg Pathol. 2005;29(6):783–91.
10. Kasashima S, Zen Y, Kawashima A, Konishi K, Sasaki H, Endo M, et al. Inflammatory abdominal aortic aneurysm: close relationship to IgG4-related periaortitis. Am J Surg Pathol. 2008;32(2):197–204.
11. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012;366(6):539–51.
12. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet. 2015;385:1460-71 **(Epub 2014/12/4)**.
13. Zen Y, Nakanuma Y. IgG4 Cholangiopathy. Int J Hepatol. 2012;2012:472376.
14. Ghazale A, Chari ST, Zhang L, Smyrk TC, Takahashi N, Levy MJ, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology. 2008;134(3):706–15 **(Epub 2008/01/29)**.
15. Bjornsson E, Chari ST, Smyrk TC, Lindor K. Immunoglobulin G4-associated cholangitis: description of an emerging clinical entity based on review of the literature. Hepatology (Baltimore, Md). 2007;45(6):1547–54 **(Epub 2007/06/01)**.
16. Stone JH, Khosroshahi A, Deshpande V, Chan JK, Heathcote JG, Aalberse R, et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis Rheum. 2012;64(10):3061–7.
17. Hart PA, Zen Y, Chari ST. Recent advances in autoimmune pancreatitis. Gastroenterology. 2015;149(1):39–51 **(Epub 2015/03/17)**.
18. Chari ST, Kloeppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T. Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu consensus document. Pancreas. 2010;39(5):549–54 **(Epub 2010/06/22)**.
19. Hamano H, Arakura N, Muraki T, Ozaki Y, Kiyosawa K, Kawa S. Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. J Gastroenterol. 2006;41(12):1197–205 **(Epub 2007/02/09)**.
20. Inoue D, Yoshida K, Yoneda N, Ozaki K, Matsubara T, Nagai K, et al. IgG4-related disease: dataset of 235 consecutive patients. Medicine. 2015;94(15):e680 **(Epub 2015/04/18)**.
21. Hirano K, Tada M, Isayama H, Koike K. Intrapancreatic biliary stricture in autoimmune pancreatitis should not be included in IgG4-related sclerosing cholangitis. Pancreas. 2014;43(7):1123 **(Epub 2014/09/11)**.
22. Park do H, Kim MH. Intrapancreatic common bile duct involvement of autoimmune pancreatitis: is it really IgG4-associated cholangitis? Gastroenterology. 2008;135(1):324–5 **(author reply 5. Epub 2008/06/17)**.
23. Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, et al. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol. 2004;28(9):1193–203 **Epub 2004/08/19**.
24. Zen Y, Bogdanos DP, Kawa S. Type 1 autoimmune pancreatitis. Orphanet J Rare Dis. 2011;6:82.
25. Kanno A, Masamune A, Okazaki K, Kamisawa T, Kawa S, Nishimori I, et al. Nationwide epidemiological survey of autoimmune pancreatitis in Japan in 2011. Pancreas. 2015;44(4):535–9 **(Epub 2015/03/31)**.
26. Komatsu K, Hamano H, Ochi Y, Takayama M, Muraki T, Yoshizawa K, et al. High prevalence of hypothyroidism in patients with autoimmune pancreatitis. Dig Dis Sci. 2005;50(6):1052–7 **(Epub 2005/07/01)**.
27. Okazaki K, Uchida K, Koyabu M, Miyoshi H, Ikeura T, Takaoka M. IgG4 cholangiopathy: current concept, diagnosis, and pathogenesis. J Hepatol. 2014;61(3):690–5 **(Epub 2014/04/29)**.

28. Oseini AM, Chaiteerakij R, Shire AM, Ghazale A, Kaiya J, Moser CD, et al. Utility of serum immunoglobulin G4 in distinguishing immunoglobulin G4-associated cholangitis from cholangiocarcinoma. Hepatology (Baltimore, Md). 2011;54(3):940–8 **(Epub 2011/06/16)**.
29. Mendes FD, Jorgensen R, Keach J, Katzmann JA, Smyrk T, Donlinger J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. Am J Gastroenterol. 2006;101(9):2070–5 **(Epub 2006/08/02)**.
30. Ngwa TN, Law R, Murray D, Chari ST. Serum immunoglobulin G4 level is a poor predictor of immunoglobulin G4-related disease. Pancreas. 2014;43(5):704–7 **(Epub 2014/03/19)**.
31. Boonstra K, Culver EL, de Buy Wenniger LM, van Heerde MJ, van Erpecum KJ, Poen AC, et al. Serum immunoglobulin G4 and immunoglobulin G1 for distinguishing immunoglobulin G4-associated cholangitis from primary sclerosing cholangitis. Hepatology (Baltimore, Md). 2014;59(5):1954–63 **(Epub 2014/01/01)**.
32. Okazaki K, Uchida K, Fukui T. Recent advances in autoimmune pancreatitis: concept, diagnosis, and pathogenesis. J Gastroenterol. 2008;43(6):409–18 **(Epub 2008/07/05)**.
33. Sah RP, Pannala R, Zhang L, Graham RP, Sugumar A, Chari ST. Eosinophilia and allergic disorders in autoimmune pancreatitis. Am J Gastroenterol. 2010;105(11):2485–91 **(Epub 2010/06/17)**.
34. Kamisawa T, Anjiki H, Egawa N, Kubota N. Allergic manifestations in autoimmune pancreatitis. Eur J Gastroenterol Hepatol. 2009;21(10):1136–9 **(Epub 2009/09/17)**.
35. Nakazawa T, Ohara H, Sano H, Aoki S, Kobayashi S, Okamoto T, et al. Cholangiography can discriminate sclerosing cholangitis with autoimmune pancreatitis from primary sclerosing cholangitis. Gastrointest Endosc. 2004;60(6):937–44 **(Epub 2004/12/18)**.
36. Nishino T, Oyama H, Hashimoto E, Toki F, Oi I, Kobayashi M, et al. Clinicopathological differentiation between sclerosing cholangitis with autoimmune pancreatitis and primary sclerosing cholangitis. J Gastroenterol. 2007;42(7):550–9 **(Epub 2007/07/27)**.
37. Darge K, Anupindi SA, Jaramillo D. MR imaging of the abdomen and pelvis in infants, children, and adolescents. Radiology. 2011;261(1):12–29.
38. Shanmugam V, Beattie GC, Yule SR, Reid W, Loudon MA. Is magnetic resonance cholangiopancreatography the new gold standard in biliary imaging. Gastrointest Endosc. 2005;62(3):360–6.
39. Sahani DV, Kalva SP, Farrell J, Maher MM, Saini S, Mueller PR, et al. Autoimmune pancreatitis: imaging features 1. Radiology. 2004;233(2):345–52.
40. Yang D, Kim K, Kim T, Park S, Kim S, Kim M, et al. Autoimmune pancreatitis: radiologic findings in 20 patients. Abdom Imaging. 2006;31(1):94–102.
41. Khalili K, Doyle DJ, Chawla TP, Hanbidge AE. Renal cortical lesions in patients with autoimmune pancreatitis: a clue to differentiation from pancreatic malignancy. Eur J Radiol. 2008;67(2):329–35.
42. Sohn J-H, Byun JH, Yoon SE, Choi EK, Park SH, Kim M-H, et al. Abdominal extrapancreatic lesions associated with autoimmune pancreatitis: radiological findings and changes after therapy. Eur J Radiol. 2008;67(3):497–507.
43. Takahashi N, Kawashima A, Fletcher JG, Chari ST. Renal involvement in patients with autoimmune pancreatitis: CT and MR imaging findings 1. Radiology. 2007;242(3):791–801.
44. Inoue D, Zen Y, Abo H, Gabata T, Demachi H, Yoshikawa J, et al. Immunoglobulin G4-related periaortitis and periarteritis: CT findings in 17 patients. Radiology. 2011;261(2):625–33 **(Epub 2011/08/02)**.
45. Matsubayashi H, Uesaka K, Sugiura T, Ohgi K, Sasaki K, Ono H. IgG4-related sclerosing cholangitis without obvious pancreatic lesion: difficulty in differential diagnosis. J Dig Dis. 2014;15(7):394–403.
46. Sivakumaran Y, Le Page PA, Becerril-Martinez G, Beasley WD, Anderson LA, Joseph DM, et al. IgG4-related sclerosing cholangitis: the cholangiocarcinoma mimic. ANZ J Surg. 2014;84(6):486–7.
47. Arikawa S, Uchida M, Kunou Y, Uozumi J, Abe T, Hayabuchi N, et al. Comparison of sclerosing cholangitis with autoimmune pancreatitis and infiltrative extrahepatic cholangiocarcinoma: multidetector-row computed tomography findings. Jpn J Radiol. 2010;28(3):205–13.
48. Itoh S, Nagasaka T, Suzuki K, Satake H, Ota T, Naganawa S. Lymphoplasmacytic sclerosing cholangitis: assessment of clinical, CT, and pathological findings. Clin Radiol. 2009;64(11):1104–14.
49. Kojima E, Kimura K, Noda Y, Kobayashi G, Itoh K, Fujita N. Autoimmune pancreatitis and multiple bile duct strictures treated effectively with steroid. J Gastroenterol. 2003;38(6):603–7.
50. Takahashi N, Fletcher JG, Fidler JL, Hough DM, Kawashima A, Chari ST. Dual-phase CT of autoimmune pancreatitis: a multireader study. Am J Roentgenol. 2008;190(2):280–6.
51. Kim JY, Lee JM, Han JK, Kim SH, Lee JY, Choi JY, et al. Contrast-enhanced MRI combined with MR cholangiopancreatography for the evaluation of patients with biliary strictures: differentiation of malignant from benign bile duct strictures. J Magn Reson Imaging. 2007;26(2):304–12.
52. Park M-S, Kim TK, Kim KW, Park SW, Lee JK, Kim J-S, et al. Differentiation of extrahepatic bile duct cholangiocarcinoma from benign stricture: findings at MRCP versus ERCP 1. Radiology. 2004;233(1):234–40.
53. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. J Gastroenterol. 2006;41(7):613–25.
54. Tokala A, Khalili K, Menezes R, Hirschfield G, Jhaveri KS. Comparative MRI analysis of morphologic patterns of bile duct disease in IgG4-related systemic disease versus primary sclerosing cholangitis. Am J Roentgenol. 2014;202(3):536–43.
55. Naitoh I, Nakazawa T, Ohara H, Ando T, Hayashi K, Tanaka H, et al. Endoscopic transpapillary intraductal ultrasonography and biopsy in the diagnosis of IgG4-related sclerosing cholangitis. J Gastroenterol. 2009;44(11):1147–55 **(Epub 2009/07/29)**.
56. Itoi T, Kamisawa T, Igarashi Y, Kawakami H, Yasuda I, Itokawa F, et al. The role of peroral video cholangioscopy in patients with IgG4-related sclerosing cholangitis. J Gastroenterol. 2013;48(4):504–14 **(Epub 2012/09/06)**.
57. Kawakami H, Kuwatani M, Etoh K, Haba S, Yamato H, Shinada K, et al. Endoscopic retrograde cholangiography versus peroral cholangioscopy to evaluate intraepithelial tumor spread in biliary cancer. Endoscopy. 2009;41(11):959–64 **(Epub 2009/10/06)**.
58. Zen Y, Nakanuma Y, Portmann B. Immunoglobulin G4-related sclerosing cholangitis: pathologic features and histologic mimics. Semin Diagn Pathol. 2012;29(4):205–11.
59. Zen Y, Fujii T, Sato Y, Masuda S, Nakanuma Y. Pathological classification of hepatic inflammatory pseudotumor with respect to IgG4-related disease. Mod Pathol. 2007;20(8):884–94.
60. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25(9):1181–92.
61. Umemura T, Zen Y, Hamano H, Kawa S, Nakanuma Y, Kiyosawa K. Immunoglobin G4-hepatopathy: association of immunoglobin G4-bearing plasma cells in liver with autoimmune pancreatitis. Hepatology (Baltimore, Md). 2007;46(2):463–71.
62. Naitoh I, Zen Y, Nakazawa T, Ando T, Hayashi K, Okumura F, et al. Small bile duct involvement in IgG4-related sclerosing

cholangitis: liver biopsy and cholangiography correlation. J Gastroenterol. 2011;46(2):269–76.
63. Deshpande V, Sainani NI, Chung RT, Pratt DS, Mentha G, Rubbia-Brandt L, et al. IgG4-associated cholangitis: a comparative histological and immunophenotypic study with primary sclerosing cholangitis on liver biopsy material. Mod Pathol. 2009;22(10):1287–95 **(Epub 2009/07/28)**.
64. Chari ST. Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORt criteria. J Gastroenterol. 2007;42(Suppl 18):39–41 **(Epub 2007/05/24)**.
65. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol. 2006;4(8):1010–6 **(quiz 934. Epub 2006/07/18)**.
66. Ohara H, Okazaki K, Tsubouchi H, Inui K, Kawa S, Kamisawa T, et al. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepato Biliary Pancreat Sci. 2012;19(5):536–42 **(Epub 2012/06/22)**.
67. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011;40(3):352–8 **(Epub 2011/03/18)**.
68. Kawakami H, Zen Y, Kuwatani M, Eto K, Haba S, Yamato H, et al. IgG4-related sclerosing cholangitis and autoimmune pancreatitis: histological assessment of biopsies from Vater's ampulla and the bile duct. J Gastroenterol Hepatol. 2010;25(10):1648–55.
69. Nakazawa T, Naitoh I, Hayashi K, Okumura F, Miyabe K, Yoshida M, et al. Diagnostic criteria for IgG4-related sclerosing cholangitis based on cholangiographic classification. J Gastroenterol. 2012;47(1):79–87 **(Epub 2011/09/29)**.
70. Zen Y, Quaglia A, Portmann B. Immunoglobulin G4-positive plasma cell infiltration in explanted livers for primary sclerosing cholangitis. Histopathology. 2011;58(3):414–22.
71. Zhang L, Lewis JT, Abraham SC, Smyrk TC, Leung S, Chari ST, et al. IgG4+ plasma cell infiltrates in liver explants with primary sclerosing cholangitis. Am J Surg Pathol. 2010;34(1):88–94 **(Epub 2009/12/26)**.
72. Portmann B, Zen Y. Inflammatory disease of the bile ducts-cholangiopathies: liver biopsy challenge and clinicopathological correlation. Histopathology. 2012;60(2):236–48.
73. Zen Y, Ishikawa A, Ogiso S, Heaton N, Portmann B. Follicular cholangitis and pancreatitis—clinicopathological features and differential diagnosis of an under-recognized entity. Histopathology. 2012;60(2):261–9 **(Epub 2012/01/04)**.
74. Lee JY, Lim JH, Lim HK. Follicular cholangitis mimicking hilar cholangiocarcinoma. Abdom Imaging. 2005;30(6):744–7 **(Epub 2005/09/01)**.
75. Fujita T, Kojima M, Kato Y, Gotohda N, Takahashi S, Konishi M, et al. Clinical and histopathological study of "follicular cholangitis": sclerosing cholangitis with prominent lymphocytic infiltration masquerading as hilar cholangiocarcinoma. Hepatol Res. 2010;40(12):1239–47 **(Epub 2010/10/01)**.
76. Aoki T, Kubota K, Oka T, Hasegawa K, Hirai I, Makuuchi M. Follicular cholangitis: another cause of benign biliary stricture. Hepatogastroenterology. 2003;50(51):639–42 **(Epub 2003/06/28)**.
77. Gupta RK, Xie BH, Patton KT, Lisovsky M, Burks E, Behrman SW, et al. Follicular pancreatitis: a distinct form of chronic pancreatitis-an additional mimic of pancreatic neoplasms. Hum Pathol. 2016;48:154-62 **(Epub 2015/10/3)**.
78. Zamboni G, Luttges J, Capelli P, Frulloni L, Cavallini G, Pederzoli P, et al. Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. Virchows Arch. 2004;445(6):552–63 **(Epub 2004/11/02)**.
79. Zhang L, Chari S, Smyrk TC, Deshpande V, Kloppel G, Kojima M, et al. Autoimmune pancreatitis (AIP) type 1 and type 2: an international consensus study on histopathologic diagnostic criteria. Pancreas. 2011;40(8):1172–9 **(Epub 2011/10/07)**.
80. Zen Y, Grammatikopoulos T, Heneghan MA, Vergani D, Mieli-Vergani G, Portmann BC. Sclerosing cholangitis with granulocytic epithelial lesion: a benign form of sclerosing cholangiopathy. Am J Surg Pathol. 2012;36(10):1555–61.
81. Zen Y, Fujii T, Nakanuma Y. Hepatic pseudolymphoma: a clinicopathological study of five cases and review of the literature. Mod Pathol. 2010;23(2):244–50 **(Epub 2009/11/17)**.
82. Kamisawa T, Okazaki K, Kawa S, Shimosegawa T, Tanaka M. Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP. J Gastroenterol. 2010;45(5):471–7 **(Epub 2010/03/10)**.
83. Kamisawa T, Chari ST, Giday SA, Kim MH, Chung JB, Lee KT, et al. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. Pancreas. 2011;40(6):809–14 **(Epub 2011/07/13)**.
84. Hart PA, Kamisawa T, Brugge WR, Chung JB, Culver EL, Czako L, et al. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. Gut. 2013;62(12):1771–6 **(Epub 2012/12/13)**.
85. Sandanayake NS, Church NI, Chapman MH, Johnson GJ, Dhar DK, Amin Z, et al. Presentation and management of post-treatment relapse in autoimmune pancreatitis/immunoglobulin G4-associated cholangitis. Clin Gastroenterol Hepatol. 2009;7(10):1089–96 **(Epub 2009/04/07)**.
86. Kamisawa T, Shimosegawa T, Okazaki K, Nishino T, Watanabe H, Kanno A, et al. Standard steroid treatment for autoimmune pancreatitis. Gut. 2009;58(11):1504–7 **(Epub 2009/04/29)**.
87. Hart PA, Topazian MD, Witzig TE, Clain JE, Gleeson FC, Klebig RR, et al. Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. Gut. 2013;62(11):1607–15 **(Epub 2012/09/01)**.
88. Topazian M, Witzig TE, Smyrk TC, Pulido JS, Levy MJ, Kamath PS, et al. Rituximab therapy for refractory biliary strictures in immunoglobulin G4-associated cholangitis. Clin Gastroenterol Hepatol. 2008;6(3):364–6 **(Epub 2008/03/11)**.
89. Khosroshahi A, Bloch DB, Deshpande V, Stone JH. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. Arthritis Rheum. 2010;62(6):1755–62 **(Epub 2010/03/02)**.
90. Khosroshahi A, Carruthers MN, Deshpande V, Unizony S, Bloch DB, Stone JH. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. Medicine. 2012;91(1):57–66 **(Epub 2012/01/03)**.
91. Carruthers MN, Topazian MD, Khosroshahi A, Witzig TE, Wallace ZS, Hart PA, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis. 2015;74(6):1171–7 **(Epub 2015/02/11)**.
92. Hart PA, Law RJ, Dierkhising RA, Smyrk TC, Takahashi N, Chari ST. Risk of cancer in autoimmune pancreatitis: a case-control study and review of the literature. Pancreas. 2014;43(3):417–21 **(Epub 2014/03/14)**.
93. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci. 1995;40(7):1561–8 **(Epub 1995/07/01)**.
94. Okazaki K, Uchida K, Ohana M, Nakase H, Uose S, Inai M, et al. Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2-type cellular immune response. Gastroenterology. 2000;118(3):573–81 **(Epub 2000/03/04)**.

95. Kawa S, Ota M, Yoshizawa K, Horiuchi A, Hamano H, Ochi Y, et al. HLA DRB10405-DQB10401 haplotype is associated with autoimmune pancreatitis in the Japanese population. Gastroenterology. 2002;122(5):1264–9 **(Epub 2002/05/02)**.
96. Park do H, Kim MH, Oh HB, Kwon OJ, Choi YJ, Lee SS, et al. Substitution of aspartic acid at position 57 of the DQbeta1 affects relapse of autoimmune pancreatitis. Gastroenterology. 2008;134(2):440–6 **(Epub 2007/12/25)**.
97. Chang MC, Jan IS, Liang PC, Jeng YM, Yang CY, Tien YW, et al. Cystic fibrosis transmembrane conductance regulator gene variants are associated with autoimmune pancreatitis and slow response to steroid treatment. J Cyst Fibros. 2015;14(5):661–7 **(Epub 2015/04/15)**.
98. Chang MC, Chang YT, Tien YW, Liang PC, Jan IS, Wei SC, et al. T-cell regulatory gene CTLA-4 polymorphism/haplotype association with autoimmune pancreatitis. Clin Chem. 2007;53(9):1700–5 **(Epub 2007/08/23)**.
99. Chang MC, Jan IS, Liang PC, Jeng YM, Yang CY, Tien YW, et al. Human cationic trypsinogen but not serine peptidase inhibitor, Kazal type 1 variants increase the risk of type 1 autoimmune pancreatitis. J Gastroenterol Hepatol. 2014;29(12):2038–42 **(Epub 2014/06/10)**.
100. Umemura T, Ota M, Hamano H, Katsuyama Y, Muraki T, Arakura N, et al. Association of autoimmune pancreatitis with cytotoxic T-lymphocyte antigen 4 gene polymorphisms in Japanese patients. Am J Gastroenterol. 2008;103(3):588–94 **(Epub 2008/03/18)**.
101. Umemura T, Ota M, Hamano H, Katsuyama Y, Kiyosawa K, Kawa S. Genetic association of Fc receptor-like 3 polymorphisms with autoimmune pancreatitis in Japanese patients. Gut. 2006;55(9):1367–8 **(Epub 2006/08/15)**.
102. Aalberse RC, Stapel SO, Schuurman J, Rispens T. Immunoglobulin G4: an odd antibody. Clin Exp Allergy. 2009;39(4):469–77 **(Epub 2009/02/19)**.
103. Nirula A, Glaser SM, Kalled SL, Taylor FR. What is IgG4? A review of the biology of a unique immunoglobulin subtype. Curr Opin Rheumatol. 2011;23(1):119–24 **(Epub 2010/12/03)**.
104. van der Neut Kolfschoten M, Schuurman J, Losen M, Bleeker WK, Martinez-Martinez P, Vermeulen E, et al. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. Science (New York, NY). 2007;317(5844):1554–7 **(Epub 2007/09/18)**.
105. Zen Y, Fujii T, Harada K, Kawano M, Yamada K, Takahira M, et al. Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. Hepatology (Baltimore, Md). 2007;45(6):1538–46.
106. Zen Y, Nakanuma Y. Pathogenesis of IgG4-related disease. Curr Opin Rheumatol. 2011;23(1):114–8.
107. Maehara T, Moriyama M, Nakashima H, Miyake K, Hayashida JN, Tanaka A, et al. Interleukin-21 contributes to germinal centre formation and immunoglobulin G4 production in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease. Ann Rheum Dis. 2012;71(12):2011–9 **(Epub 2012/07/04)**.
108. Ettinger R, Kuchen S, Lipsky PE. Interleukin 21 as a target of intervention in autoimmune disease. Ann Rheum Dis. 2008;67 Suppl 3:iii83–6 **(Epub 2008/12/17)**.
109. Akiyama M, Suzuki K, Yamaoka K, Yasuoka H, Takeshita M, Kaneko Y, et al. Number of circulating follicular helper 2 T cells correlates with IgG4 and interleukin-4 levels and plasmablast numbers in IgG4-related disease. Arthritis Rheumatol (Hoboken, NJ). 2015;67(9):2476–81 **(Epub 2015/05/20)**.
110. Kleinewietfeld M, Hafler DA. Regulatory T cells in autoimmune neuroinflammation. Immunol Rev. 2014;259(1):231–44 **(Epub 2014/04/10)**.
111. Grant CR, Liberal R, Mieli-Vergani G, Vergani D, Longhi MS. Regulatory T-cells in autoimmune diseases: challenges, controversies and–yet–unanswered questions. Autoimmun Rev. 2015;14(2):105–16 **(Epub 2014/12/03)**.
112. Koyabu M, Uchida K, Miyoshi H, Sakaguchi Y, Fukui T, Ikeda H, et al. Analysis of regulatory T cells and IgG4-positive plasma cells among patients of IgG4-related sclerosing cholangitis and autoimmune liver diseases. J Gastroenterol. 2010;45:732-41 **(Epub 2010/01/20)**.
113. Jeannin P, Lecoanet S, Delneste Y, Gauchat JF, Bonnefoy JY. IgE versus IgG4 production can be differentially regulated by IL-10. J Immunol (Baltimore, Md: 1950). 1998;160(7):3555–61 **(Epub 1998/04/08)**.
114. Esposito I, Born D, Bergmann F, Longerich T, Welsch T, Giese NA, et al. Autoimmune pancreatocholangitis, non-autoimmune pancreatitis and primary sclerosing cholangitis: a comparative morphological and immunological analysis. PloS one. 2008;3(7):e2539 **(Epub 2008/07/04)**.
115. Tsuboi H, Nakai Y, Iizuka M, Asashima H, Hagiya C, Tsuzuki S, et al. DNA microarray analysis of labial salivary glands in IgG4-related disease: comparison with Sjögren's syndrome. Arthritis Rheumatol (Hoboken, NJ). 2014;66(10):2892–9 **(Epub 2014/06/20)**.
116. Zen Y, Liberal R, Nakanuma Y, Heaton N, Portmann B. Possible involvement of CCL1-CCR8 interaction in lymphocytic recruitment in IgG4-related sclerosing cholangitis. J Hepatol. 2013;59(5):1059–64.
117. Soler D, Chapman TR, Poisson LR, Wang L, Cote-Sierra J, Ryan M, et al. CCR8 expression identifies CD4 memory T cells enriched for FOXP3+ regulatory and Th2 effector lymphocytes. J Immunol (Baltimore, Md: 1950). 2006;177(10):6940–51 **(Epub 2006/11/04)**.
118. Muller T, Beutler C, Pico AH, Otten M, Durr A, Al-Abadi H, et al. Increased T-helper 2 cytokines in bile from patients with IgG4-related cholangitis disrupt the tight junction-associated biliary epithelial cell barrier. Gastroenterology. 2013;144(5):1116–28 **(Epub 2013/02/09)**.
119. Sumimoto K, Uchida K, Kusuda T, Mitsuyama T, Sakaguchi Y, Fukui T, et al. The role of CD19+ CD24high CD38high and CD19+ CD24high CD27+ regulatory B cells in patients with type 1 autoimmune pancreatitis. Pancreatology. 2014;14(3):193–200 **(Epub 2014/05/24)**.
120. van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Sollner S, Akdis DG, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. J Allergy Clin Immunol. 2013;131(4):1204–12 **(Epub 2013/03/05)**.
121. Mattoo H, Mahajan VS, Della-Torre E, Sekigami Y, Carruthers M, Wallace ZS, et al. De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4-related disease. J Allergy Clin Immunol. 2014;134(3):679–87 **(Epub 2014/05/13)**.
122. Wallace ZS, Mattoo H, Carruthers M, Mahajan VS, Della Torre E, Lee H, et al. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. Ann Rheum Dis. 2015;74(1):190–5 **(Epub 2014/05/13)**.
123. Zen Y, Britton D, Mitra V, Pike I, Heaton N, Quaglia A. A global proteomic study identifies distinct pathological features of IgG4-related and primary sclerosing cholangitis. Histopathology. 2015. doi:10.1111/his.12813**(Epub ahead of print)**.
124. Furukawa S, Moriyama M, Tanaka A, Maehara T, Tsuboi H, Iizuka M, et al. Preferential M2 macrophages contribute to fibrosis in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease. Clin Immunol (Orlando, Fla). 2015;156(1):9–18 **(Epub 2014/12/03)**.