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REVIEW AND PERSPECTIVES

IgG4-related disease: with emphasis on the biopsy diagnosis of autoimmune pancreatitis and sclerosing cholangitis

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Abstract

In 2011, chronic fibroinflammatory processes occurring simultaneously or metachronously in various organs and associated with elevated IgG4 serum levels and/or tissue infiltration with IgG4-positive plasma cells have been recognized as manifestations of a systemic disorder called IgG4-related disease (IgG4-RD). The histologic key findings are lymphoplasmacytic infiltration rich in IgG4-positive plasma cells combined with storiform fibrosis and obliterative phlebitis. Among the organs mainly affected by IgG4-RD are the pancreas and the extrahepatic bile ducts. The pancreatic and biliary alterations have been described under the terms autoimmune pancreatitis (AIP) and sclerosing cholangitis, respectively. These diseases are currently more precisely called IgG4-related pancreatitis (or type 1 AIP to distinguish it from type 2 AIP that is unrelated to IgG4-RD) and IgG4-related sclerosing cholangitis (IgG4-related SC). Clinically and grossly, both diseases commonly imitate pancreatic and biliary adenocarcinoma, tumors that are well known for their dismal prognosis. As IgG4-RD responds to steroid treatment, making a resection of a suspected tumor unnecessary, a biopsy is often required to establish the preoperative diagnosis. This review discusses the morphologic spectrum of IgG4-related pancreatitis and IgG4-related SC and focuses on the biopsy relevant histologic features for the diagnosis and differential diagnosis of these diseases.

Keywords IgG4-related disease · Histology · Diagnosis · Autoimmune pancreatitis · Sclerosing cholangitis · Hepatopathy

Introduction

IgG4-related disease (IgG4-RD) is a chronic inflammatory process that involves many organ systems. Its exact cause is still not known, but it can be effectively treated with steroids. In 2003, Kamisawa et al. [1] reported on 21 pancreatitis patients whose disease was thought to be of autoimmune nature. These patients also had sclerosing cholangitis, retroperitoneal fibrosis, rheumatoid arthritis, and Sjögren's syndrome [1]. Based on this observation, Kamisawa introduced the term "IgG4-related systemic disease," hypothesizing that the various lesions may be organ manifestations of a systemic autoimmune disorder [1]. Since then, numerous reports have revealed that the disease can involve many more organs than was originally thought, notably the salivary glands, thyroid, lungs, liver, and kidney (Fig. 1) [2]. In 2011, a consensus meeting was held in Boston, which proposed the name "IgG4-RD" and highlighted three findings as histopathologic features: (1) lymphoplasmacytic infiltration containing abundant IgG4-positive plasma cells, (2) storiform fibrosis, and (3) obliterative phlebitis [3, 4].

The recent definition of IgG4-RD as a systemic inflammatory disorder somehow hides the fact that a number of its organ manifestations were already described some decades ago [3–6]. This concerns particularly the manifestations of IgG4-RD in the pancreas and the extrahepatic bile duct system. Pancreatitis cases showing the histopathologic criteria of IgG4-RD were reported from 1950 onwards [7–9]. In 1991 and 1997 followed the reports of Kawaguchi et al. [9] and Ectors et al. [12], which laid the basis for the detailed histopathology of the disease and its clear distinction from other types of pancreatitis such as alcoholic pancreatitis. In 1995, Yoshida et al. named the disease autoimmune pancreatitis (AIP) [7]. In 2003 and 2004, Notohara et al. [10] and

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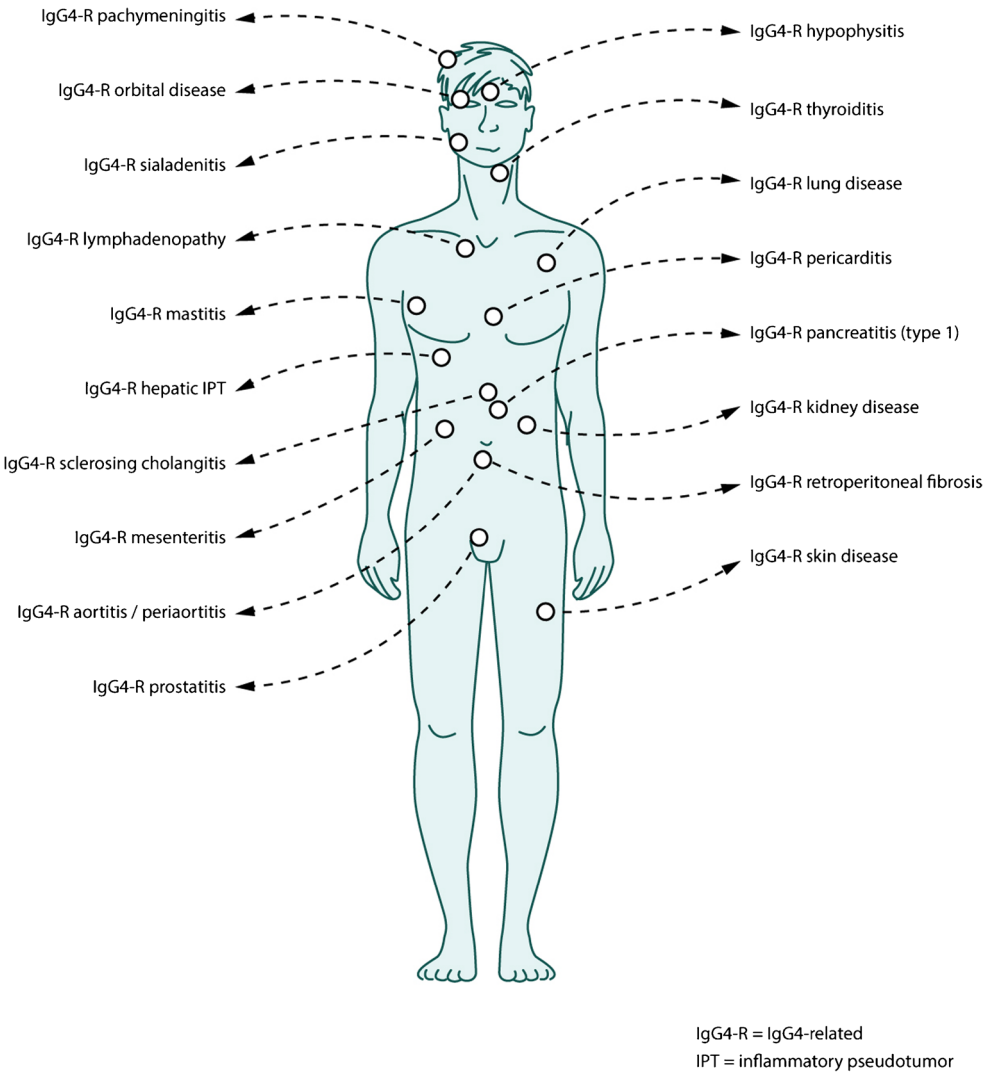

Fig. 1 Cartoon showing the main organ manifestations of IgG4-related disease (IgG4-RD)

Zamboni et al. [11] showed in their studies that AIP is a heterogeneous disease including two types: type 1 AIP, also called "lymphoplasmacytic sclerosing pancreatitis," and type 2 AIP, also called "idiopathic duct-centric pancreatitis" [9, 12]. Further analysis of the serological and clinical features of AIP patients soon revealed that type 1 AIP represents a manifestation of IgG4-RD, while type 2 AIP is unrelated to IgG4-RD [13–17].

Already in 1963, a special form of sclerosing cholangitis (SC) was described that, in retrospect, corresponds to a manifestation of IgG4-RD in the common bile duct. It was part of a multi-inflammatory syndrome encompassing also retroperitoneal fibrosis (RF) and Riedel's thyroiditis [6]. SC was also part of a systemic disease described by Comings et al. [5] in 1967 as multifocal fibrosclerosis. Two patients, brothers with consanguineous parents, had, in addition to SC, orbital inflammatory pseudotumor, RF, mediastinal fibrosis, and Riedel's thyroiditis [5]. In the ensuing decades, until the inclusion of lymphoplasmacytic SC into IgG4-RD as *IgG4-related SC*, it has become clear that IgG4-related SC involves the bile duct system in two ways. Most commonly, it affects the intrapancreatic section of the distal common bile duct in association with type 1 AIP. Rarely it diffusely affects the extrapancreatic biliary duct system or presents as solitary manifestation in the hilar bile ducts (with or without concomitant involvement of the intrahepatic bile ducts) or the gallbladder [13]. The term "IgG4-related hepatopathy" is used for portal liver changes in relation to IgG4-RD. Whether the recently described IgG4-positive subtype of autoimmune hepatitis (AIH) belongs to IgG4-RD has not yet been settled.

The serum half-life of IgG4 is around 23 days, and this marker can therefore be used to track response to treatment to some extent [18]. It can be roughly assumed that the sensitivity of serum IgG4 for type 1 AIP is around 66%, even though it varies between different regions and countries [14, 19–21]. Besides, the sensitivity and specificity are dependent on the cutoff value used. Using a cutoff of > 140 mg/dl, IgG4 had a sensitivity and specificity of 76 and 93%, respectively,

but using a cutoff of > 280 mg/dl, these values were 53 and 99%, respectively [22]. For differentiating IgG4-related SC from primary sclerosing cholangitis (PSC) and primary biliary cholangitis, the sensitivity of serum IgG4 is reported to be high, around 90%, with a specificity of 85% [23].

In this review, we outline the general histopathologic features of IgG4-RD and focus then on the pathology of the IgG4-RD lesions in the pancreas and the bile ducts. Particular emphasis is put on the discussion of the biopsy-relevant histologic features of IgG4-RD in the pancreas and the bile ducts, since these lesions are clinically notoriously difficult to distinguish from neoplastic disease. However, as IgG4-RD is responsive to steroids, a correct preoperative diagnosis that often requires a biopsy is of utmost importance to avoid resection.

General histopathologic features of IgG4-RD

The *Boston criteria* encompass the three histologic key findings: lymphoplasmacytic infiltration affecting the tissue either diffusely or patchy and focusing on ducts (Fig. 2a), storiform fibrosis composed of thick collagen bundles which form a characteristic "swirling" and focally cartwheel-like (e.g., storiform) pattern (Fig. 2b), and obliterative phlebitis characterized in its early stage by a mainly lymphocytic perivascular infiltrate and in its later stages by an intravascular infiltration that finally leads to fibroinflammatory obliteration (Fig. 2c) and may only be recognized in Elastica-Van Gieson or Verhoeff staining (Fig. 2d). However, it is noteworthy that the three criteria are not observed in all organ manifestations of the disease. For instance, storiform fibrosis and obliterative phlebitis may be insignificant or even absent in the lacrimal glands, salivary glands, lymph nodes, lung, or kidney [3]. Infiltration by eosinophilic granulocytes is another histologic finding that may be observed in association with IgG4-RD [3, 24], but has insufficient diagnostic sensitivity and specificity in the absence of the major features to serve as a cardinal feature for the disease [3, 24]. Findings that are not compatible with the diagnosis of IgG4-RD are neutrophilic microabscesses, granulomas, necrosis, and multinucleated giant cells [2, 3, 25].

The most important adjunct to the tissue diagnosis of IgG4-RD is immunostaining for IgG4-positive plasma cells [21]. It should be performed even in cases showing all three major histologic features—simply because it supports firmly the diagnosis [3]. Immunohistochemical *IgG4 positivity* means abundant tissue infiltration by IgG4-positive plasma cells (Fig. 3a) [26]. To avoid overdiagnosis of IgG4-RD, due to the fact that the mere infiltration with IgG4-positive cells can occur in many other diseases, especially diseases involving mucosal surfaces as in plasma cell mucositis, Crohn's disease and ulcerative colitis, or diseases such as multicentric

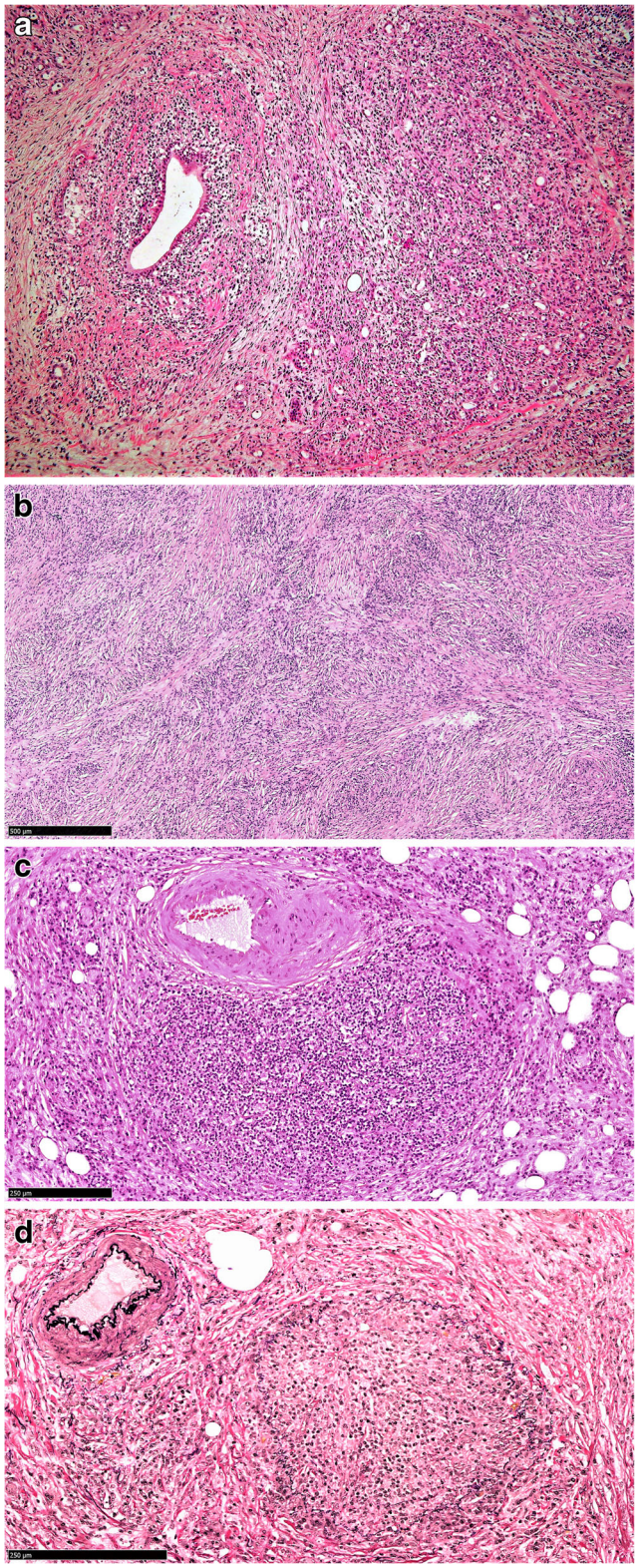

Fig. 2 Key histologic features of IgG4-RD in type 1 AIP. **a** Diffuse infiltration of pancreatic tissue by lymphocytes and plasma cells with periductal accentuation and fibrosis (H&E staining). **b** Diffuse storiform fibrosis replacing pancreatic tissue (H&E staining). Obliterative phlebitis with H&E staining (**c**) and Verhoeff elastin staining (**d**), highlighting the wall of the vein

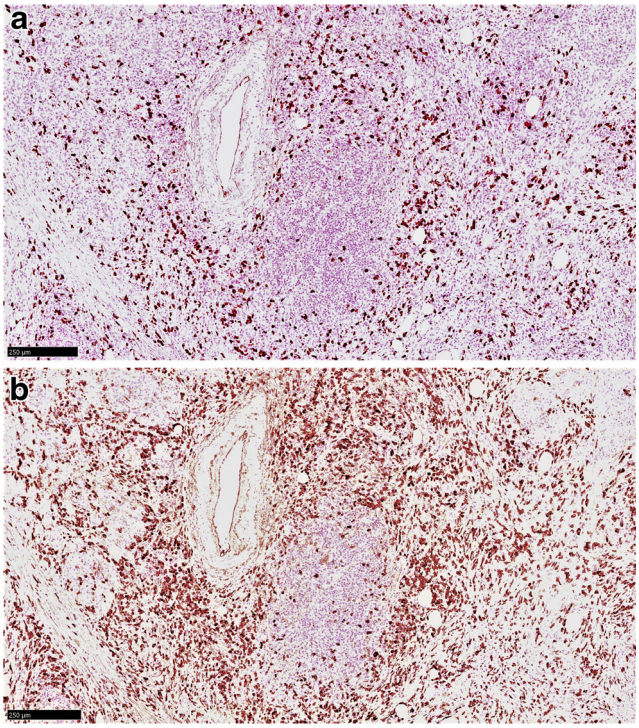

Fig. 3 IgG4-related type 1 AIP showing increased numbers of immunostained **a** IgG4- and **b** IgG-positive cells surrounding a vein and its corresponding artery. IgG4-positive cells are outnumbered by IgG-positive cells by a ratio of 0.48

Castleman disease and granulomatosis with polyangiitis, it is important to apply both a cutoff for the number of infiltrating IgG4-positive cells and a ratio of IgG4- over IgG-positive cells (Fig. 3) [27–29]. These ratios vary and are dependent on the affected organ and the focality of the disease [3]. However, a cutoff of 10 IgG4-positive cells/high-power field (HPF) in biopsy specimens and 50 IgG4-positive cells/HPF in resection specimens, both with an IgG4/IgG ratio of more than 40%, may be recommended as a general rule [3, 30, 31]. For special IgG4-RD manifestations such as the salivary glands or lymph nodes, organ-specific cutoff values for IgG4-positive cell infiltration and IgG4/IgG ratios have been recommended to avoid overdiagnosis [3].

Tissue diagnosis of IgG4-RD in the pancreas

IgG4-RD in the pancreas, called type 1 AIP, grossly imitates pancreatic ductal adenocarcinoma (PDAC), because it commonly forms a firm tumor-like mass in the pancreatic head, narrowing the intrapancreatic common bile duct and the main pancreatic duct [32–35]. In a surgical series of European AIP patients, the disease affected the pancreatic head region in 76% of the patients, while it rarely occurred in the body (6%) or tail (14%) or occupied the entire pancreas (3%) [13]. The striking focality of AIP, noted in this study but also in other studies based on pancreatic resection specimens, may be, however, overestimated, since if not only surgical patients but also conservatively treated patients are considered, about 40% of type 1 AIP patients appear to have whole-organ involvement [36]. Pseudocysts or calculi, features of early and late alcoholic chronic pancreatitis, are usually not seen in type 1 AIP [10–12].

Histologically, the lymphoplasmacytic infiltration and the storiform and swirling fibrosis (Fig. 2b) are often diffuse but change in intensity in the involved area. In addition, most medium-sized ducts are typically surrounded and often narrowed by a collar-like lymphoplasmacytic infiltrate (Fig. 2a). Obliterative phlebitis affects particularly medium-sized veins next to arteries and may be so pronounced that it obscures the involved vessel (Fig. 2c, d). Immunostaining of the infiltrating inflammatory cells reveals abundant CD3- and CD4-positive lymphocytes and, to a lesser extent, CD8-positive lymphocytes [37]. Next in frequency are plasma cells (including IgG4-positive cells), CD68-positive macrophages, and myofibroblasts [11, 37, 38]. Rarely the infiltrate contains significant numbers of eosinophils as the dominating inflammatory cell type, giving a reason to the diagnosis of eosinophilic pancreatitis [39].

In a few cases of type 1 AIP, the inflammatory process presents as an IgG4-related inflammatory pseudotumor (IgG4-related IPT) [40]. These IgG4-related IPTs that are rare in the pancreas and more often seen in the liver, lung, orbit, or kidney are histologically dominated by storiform cellular fibrosis with increased numbers of IgG4-positive cells [40].

After steroid therapy, the pancreas normalizes in size or may even shrink [41, 42]. Data regarding the histologic changes in post-steroid pancreatic tissue are sparse. Two papers describing three AIP patients (probably type 1 AIP, as granulocytic epithelial lesions (GELs) were lacking) in whom biopsies were taken before and after steroid therapy noted that the degree of lymphoplasmacytic infiltration and fibrosis appeared to be decreased after therapy [41, 42]. However, it has also been reported that the pancreas still may show fibrosis with some degree of inflammation, even though the patient clinically may show signs of good response [43].

Type 1 AIP has to be distinguished from type 2 AIP because of the biologic diversity of the two diseases, although both respond equally well to steroid treatment. Clinically, type 1 AIP is commonly (20–50% of the cases) associated with other manifestations of IgG4-RD, is more prevalent in men (75%) than in women, and has its peak incidence between 60 and 70 years [13–17]. Type 2 AIP, in contrast, is associated with inflammatory bowel disease, with frequencies between 10 and 48%, and affects both genders equally and typically in their 40s [11, 13, 15, 36]. Macroscopically, both types of AIP look alike. Histologically, however, type 2 AIP is distinguished from type 1 AIP by a finding called GEL (Fig. 4). GELs are characterized by neutrophilic granulocyte penetration through the duct epithelium, resulting in rupture of the

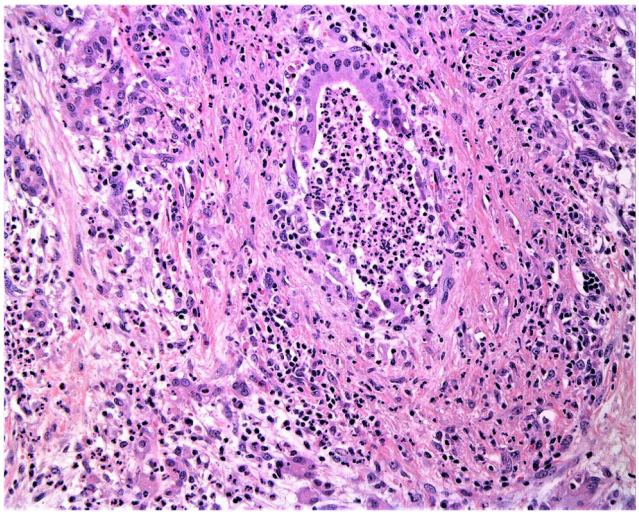

Fig. 4 Type 2 AIP. Small duct with a granulocytic epithelial lesion (GEL). Destruction of the duct epithelium and intraductal accumulation of neutrophilic granulocytes (H&E staining)

epithelium and luminal microabscesses [11]. GELs may be rare or may occur in many large and small ducts and even in acini [11, 44]. In addition, there are lymphoplasmacytic infiltrates, swirling perilobular fibrosis, and obliterative phlebitis, but usually to a lesser extent and more patchy than in type 1 AIP. Particularly, the lymphoplasmacytic infiltration may sometimes be scarce and concentrated to the periductal (*ductocentric*) regions.

Biopsy diagnosis of IgG4-RD in the pancreas

The main indications for a biopsy of the pancreas in a patient with suspected AIP is the histologic proof of the disease, the exclusion of a carcinoma, and the distinction of type 1 AIP from type 2 AIP. For the diagnosis of AIP in core needle biopsy specimens, all the key features of IgG4-RD in the pancreas (see above) are relevant. However, due to the limited sample size in core needle biopsies, difficulties in establishing the diagnosis may be encountered. If at least two of the three key features such as lymphoplasmacytic infiltration and storiform fibrosis are present (Fig. 2a, b) and a significant increase in IgG4-positive cells (Fig. 3a) and an increased IgG4/IgG ratio (Fig. 3) are demonstrated, the diagnosis of IgG4-RD is *highly suggestive* (Table 1). If not all of these criteria are met, the diagnosis of IgG4-RD is *probable* but needs additional evidence such as increased serum IgG4 levels, imaging findings, and/or involvement of other organs [45]. Recently, it was reported that also increased numbers of circulating plasmablasts can support the diagnosis of IgG4-RD, independent of the serum IgG4 value [46].

The distinction of AIP from PDAC may be easy or difficult. It is easy if either all criteria of AIP are present or if neoplastic duct structures are unequivocally recognized (Fig. 5a). Difficulties arise in biopsy specimens that show an

Table 1 Histologic features relevant for the biopsy diagnosis and differential diagnosis in patients with suspected type 1 (IgG4-related) autoimmune pancreatitis (AIP)

Disease	Main microscopic findings	Inconsistent microscopic findings
Type 1 (IgG4-related) AIP	• Marked lymphocytic and plasmacytic infiltration • Cellular perilobular fibrosis, typically with storiform and undulating pattern • Obliterative phlebitis • > 10 IgG4-positive plasma cells/HPF (biopsy)	• Eosinophils
Type 2 AIP	• Lymphoplasmacytic infiltration and scattered granulocytic infiltrates • Granulocytic epithelial duct and/or acinar lesions • Perilobular fibrosis, rarely with a typical storiform and undulating pattern	• No or single scattered IgG4-positive plasma cells
Follicular pancreatitis	• Inflammation with numerous lymphoid follicles (sometimes with prominent germinal centers)	
Ductal adenocarcinoma	• Neoplastic duct-like glands of variable size, disorderly distributed and embedded in dense fibrotic tissue • Angular and irregular gland contours • "Ruptured ducts" • Small lymphocytic infiltrates • Perineural or vascular invasion	• Single IgG4-positive plasma cells
Obstructive chronic pancreatitis (OCP)	• Groups of acini and scattered tubular complexes and small ducts, embedded in fibrous tissue • Macrophages and lymphocytes • Aggregation of normal islets of Langerhans	• Single scattered IgG4-positive plasma cells

unspecific type of chronic pancreatitis that could be caused by a PDAC in the near vicinity that obstructs the draining ducts (see the obstructive chronic pancreatitis in Table 1 and Fig. 5b, c). In such biopsies, there is no conclusive diagnosis possible, as neither AIP can be demonstrated nor a tumor can safely be excluded [47, 48]. The likelihood that a patient with AIP has also, or develops, a PDAC is small. There are, to date, only few case reports on PDACs that were found synchronously or developed metachronously together with AIP. Moreover, there are controversial data on the question whether there is an increased incidence in the total number of malignancies in patients with IgG4-RD compared to the general population [13, 20, 49, 50].

The distinction of type 1 from type 2 AIP is easy in resection specimens but can be difficult in core needle or

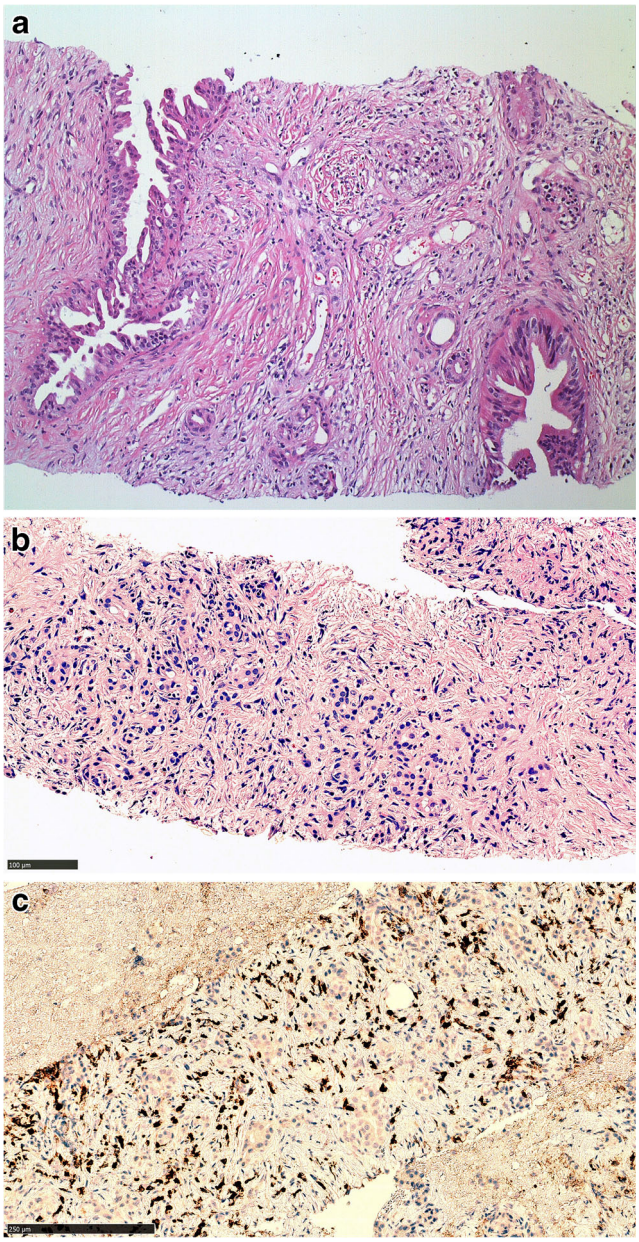

Fig. 5 Pancreatic core needle biopsy (CNB) and EUS-guided fine needle biopsy (FNB) in pancreatic ductal adenocarcinoma (**a**) and peritumoral pancreatitis (**b**, **c**). **a** CNB with neoplastic duct-like glands of variable size embedded in dense fibrotic tissue (H&E staining). **b** EUS-guided FNB showing peritumoral pancreatitis with ductular complexes surrounded by lymphocytes (H&E staining). **c** Most lymphocytes stain for CD3 (CD3 immunostaining)

histological fine needle biopsies, which are needed in patients in whom typical features of type 1 AIP such as diffuse "sausage-like" enlargement of the pancreas at imaging, extrapancreatic organ involvement, or an elevated serum IgG4 are lacking. In a study including 26 patients with AIP, it was possible to distinguish type 1 AIP from type 2 AIP by using the abovementioned criteria. Forty-five percent of the patients showed GELs indicative of type 2 AIP (Fig. 4), while 38% of the patients had infiltration with IgG4-positive cells indicative of type 1 AIP [24].

Follicular pancreatitis is a rare type of chronic pancreatitis that shares lymphoplasmacytic infiltration with AIP. However, in contrast to AIP, follicular pancreatitis shows numerous lymphoid follicles, often with activated germinal centers, as the dominating feature and lacks storiform fibrosis, obliterative phlebitis, and intense infiltration by IgG4-positive cells [24]. Other types of pancreatitis such as alcoholic chronic pancreatitis do usually play no role in the differential diagnosis of AIP, since alcoholic chronic pancreatitis is mostly already recognized by imaging, revealing pseudocystic and necrotic changes and/or calculi in distorted ducts and dense but patchy fibrosis [51, 52].

While ultrasound-guided core needle (trucut) biopsies mostly provide satisfactory results for the histodiagnosis of AIP and allow a distinction of type 2 from type 1 AIP, fine needle aspiration (FNA) cytology usually lacks the specificity necessary for a diagnosis of AIP [20, 24, 26, 53, 54]. Only if the FNA material, as was observed in some endoscopic ultrasound (EUS)-guided FNA biopsies, contained small tissue fragments enabling the search for the histological features typical for IgG4-RD, satisfactory results were reported [55, 56]. Therefore, new types of EUS-guided needles such as the ProCore or SharkCore needle have been developed. So far, published data on the use of ProCore or SharkCore fine needle biopsies (FNBs) in AIP patients are limited to small series and case reports [20, 57–59]. However, in our institution, the increased use of EUS-guided FNB obtained with the SharkCore needle (Fig. 6) has resulted in a low rate of inconclusive diagnoses [60]. In the work up of a biopsy, we cut 13 serial sections upfront from the tissue block. Sections 1 and 13 are stained with hematoxylin and eosin and section 2 with alcian blue periodic acid-Schiff. The remaining sections are initially left unstained and only used if supplementary stains are needed for establishing the diagnosis. Stains that may aid in the diagnosis of IgG4-RD, particularly when the EUS-guided FNB specimen (Fig. 6) is small or shows crush artifacts, are Verhoeff elastin, IgG4 (Fig. 6c), IgG, CD3, and CD38. If malignancy is suspected, also tumor markers are applied such as carcinoembryonic antigen (CEA), maspin, MUC5AC, or SMAD4.

Tissue diagnosis of IgG4-related SC

Type 1 AIP is usually located in the pancreatic head and therefore also involves the distal common bile duct. If this is considered as IgG4-related SC, it is the most frequent extrapancreatic manifestation of IgG4-RD [13, 15]. However, if only the isolated extrapancreatic involvement of the large bile ducts is recognized as IgG4-related SC, it

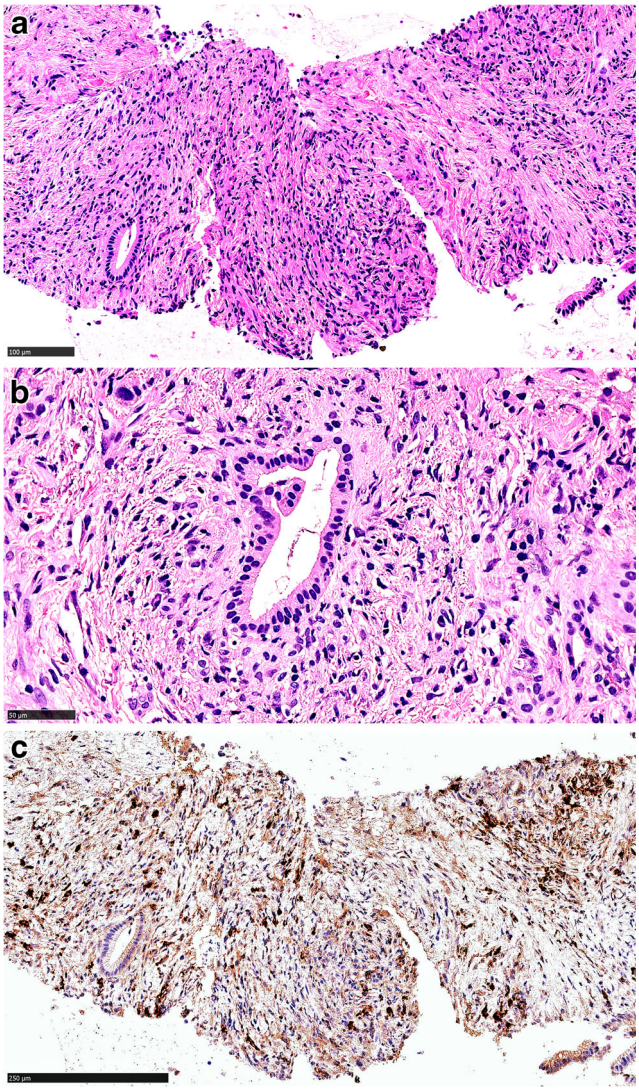

Fig. 6 EUS-guided fine needle biopsy (FNB) in type 1 AIP. Diffuse (**a**) and periductal (**b**) lymphoplasmacytic infiltration, fibrosis, and **c** IgG4-positive plasma cells

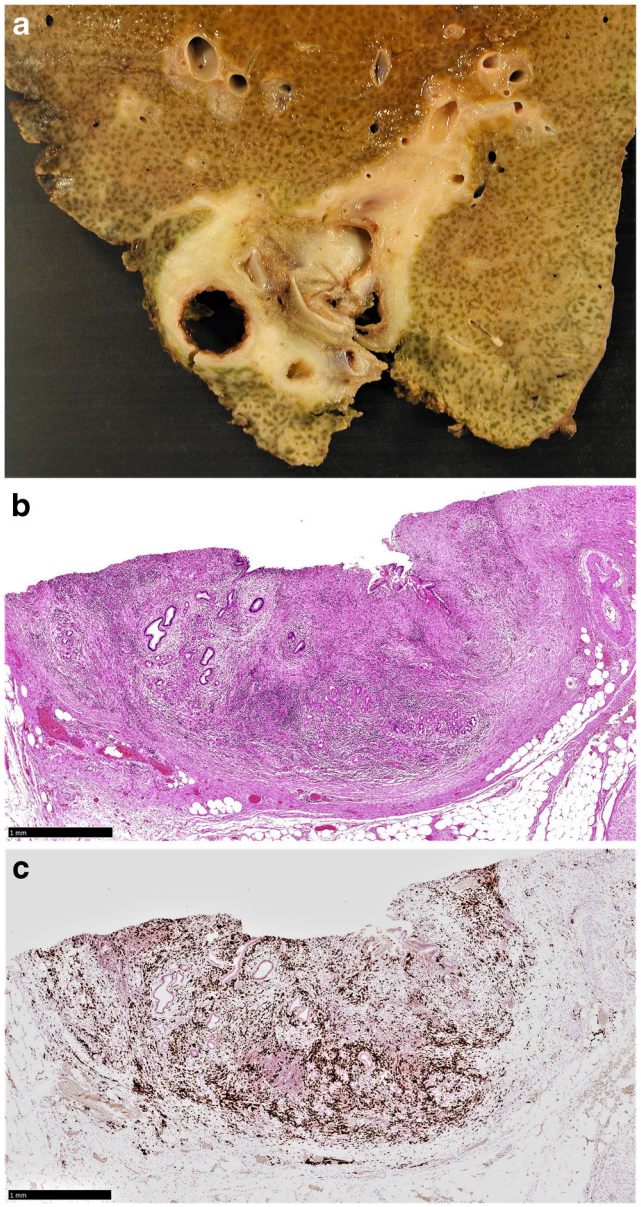

Fig. 7 IgG4-related sclerosing cholangitis (IgG4-related SC). **a** Cut section through the liver hilus showing a tumor-like thickening of the wall of the right prestenotic hepatic bile duct (courtesy of Dr. Dankoweit-Timpe, Hannover, Germany). **b** Bile duct wall showing fibroinflammatory thickening (H&E staining). **c** Immunostaining for CD38 reveals high numbers of plasma cells

is rare and was only the sixth most common manifestation of IgG4-RD in a consecutive series of 235 IgG4-RD patients [61]. Isolated distal (intrapancreatic) IgG4-related SC is extremely uncommon [43].

Grossly, IgG4-related SC presents in most cases as a tumorous thickening of the wall of the common hepatic duct at the hilar region, resulting in a bile duct stricture. It may also manifest as a mass-forming, tumor-like lesion at the liver hilus (Fig. 7a). The extrahepatic changes can be associated with involvement of the intrahepatic bile ducts, leading to various patterns of strictures and dilatations that are best recognized and classified in cholangiograms [62]. Histologically, it shows the characteristic features of IgG4-RD, even though storiform fibrosis and obliterative phlebitis may not be as prominent as in type 1 AIP (Table 2) [63]. In typical cases, a transmural lymphoplasmacytic infiltrate (Fig. 7b, c) rich in IgG4-positive plasma cells (> 50 cells per HPF in resection specimens and > 10 cells per HPF in biopsies), often also containing eosinophilic granulocytes, leads to diffuse and circumferential thickening of the duct wall. The mucosa is intact, and granulomas, abscesses, multinucleated giant cells, and excess of neutrophils are usually not seen [64]. Mucosal erosion and infiltration by neutrophils are usually due to stenting of the narrowed bile duct.

Table 2 Histologic features relevant for the biopsy diagnosis and differential diagnosis in patients with suspected IgG4-related sclerosing cholangitis (IgG4-related SC)

Disease	Main microscopic findings	Inconsistent microscopic findings
IgG4-related sclerosing cholangitis (IgG4-related SC)	• Fibrotic thickening of the bile duct wall • Lymphoplasmacytic infiltration • Storiform fibrosis • Obliterative phlebitis • > 10 IgG4-positive plasma cells/HPF	• Prominent infiltration with eosinophils
Primary sclerosing cholangitis (PSC)	• Mucosal ulceration • Subepithelial stromal fibrosis • Xanthogranulomatous inflammation • Fibrous obliteration of the peribiliary ducts	• Lymphocytic infiltration • Single IgG4-positive plasma cells
Follicular cholangitis (FC)	• Inflammation with lymphoid follicles (sometimes with prominent germinal centers)	
Bile duct adenocarcinoma	• Neoplastic duct-like structures, haphazardly arranged and with irregular contours • Single poorly differentiated tumor cells, sometimes forming small clusters	• One or several of the features characterizing IgG4-related SC, PSC, or FC may be observed

Liver changes in IgG4-RD, characterized by inflammatory portal tract infiltrates containing increased numbers of IgG4-positive plasma cells, have been termed IgG4-related hepatopathy. An IgG4-positive subtype of AIH has also been described, but when using the strict criteria put forward by Umemura et al. including elevated serum IgG4 levels, fulfillment of diagnostic criteria for classical AIH, and detection of at least 10 IgG4-positive cells per HPF in portal tracts on liver biopsy, only three unequivocal cases are identified in the recent literature [65, 66].

Isolated tumorous manifestations of IgG4-RD in the liver were reported as IgG4-related IPT [4, 67]. They have to be distinguished from *fibrohistiocytic IPTs*, which, in contrast to IgG4-related IPTs, occur more often in the liver periphery than in the hilar region [68]. Even though obliterative phlebitis and venous occlusion may occasionally be seen, this type of IPT seems not to be related to IgG4-RD [68].

In the differential diagnosis of IgG4-related SC from PSC, the following histological findings are important. PSC usually involves the luminal part of the bile ducts, particularly the mucosa, where ulceration and xanthogranulomatous inflammation and/or sclerosis may be observed and the key findings of IgG4-related SC are missing [43]. Other features that contribute very much to the separation of PSC from IgG4-related SC are imaging and clinical data. PSC affects often patients below the age of 40 and sometimes even children, and these patients have commonly associated inflammatory bowel disease and p-ANCA antibodies [69]. Only those PSC patients may be difficult to separate from IgG4-related SC patients, in whom the sclerosis particularly involves the extrahepatic bile ducts and/or is associated with elevated serum IgG4 levels, which, however, often are below two times of the upper normal limit.

Recently, Zen et al. described a *sclerosing cholangitis with GELs*, mainly in liver core needle biopsies from children who otherwise had features of PSC [70]. This may be a possible biliary counterpart to type 2 AIP. Apart from GELs, the other histological findings in these cases were similar to PSC, including onion-skin periductal sclerosis. It remains to be elucidated if a similar *GEL-positive, IgG4-negative* type of large-duct SC exists.

Another, though very rare, type of chronic cholangitis that has to be distinguished from IgG4-related SC is *follicular cholangitis*. Like *follicular pancreatitis*, it shows numerous lymphoid follicles and dense infiltration with lymphocytes and plasma cells [71]. Obliterative phlebitis and a storiform type of fibrosis as well as IgG4 positivity in the tissue are not observed.

Biopsy diagnosis of IgG4-related SC

Good cytological brushings and biopsies from extrahepatic biliary strictures are notoriously difficult to obtain. If bile duct brushings contain epithelial cells, they often have an atypical appearance. Such cells have to be interpreted with great caution, particularly if they are observed on a background of inflammation, as they are most likely reactive and unspecific in nature. Therefore, these brushings are usually unable to safely exclude a hilar carcinoma. Moreover, they fail to establish the diagnosis of IgG4-related SC or its differential diagnosis, PSC (Table 2) [69, 72–74]. If histologic biopsy material is available, the diagnosis can be straightforward, in case adenocarcinoma cells are identified without any doubt (Fig. 8a). To support a diagnosis of low-grade adenocarcinoma of the bile duct over reactive changes, immunohistochemistry showing overexpression of maspin (Fig. 8b) and CEA or loss of SMAD4 can be helpful.

However, in many cases, the diagnosis is hampered by the fact that stenting (which often precedes the biopsy because of a bile duct stenosis) usually leads to reactive epithelial changes that may mimic neoplastic alterations and could result in the wrong diagnosis of

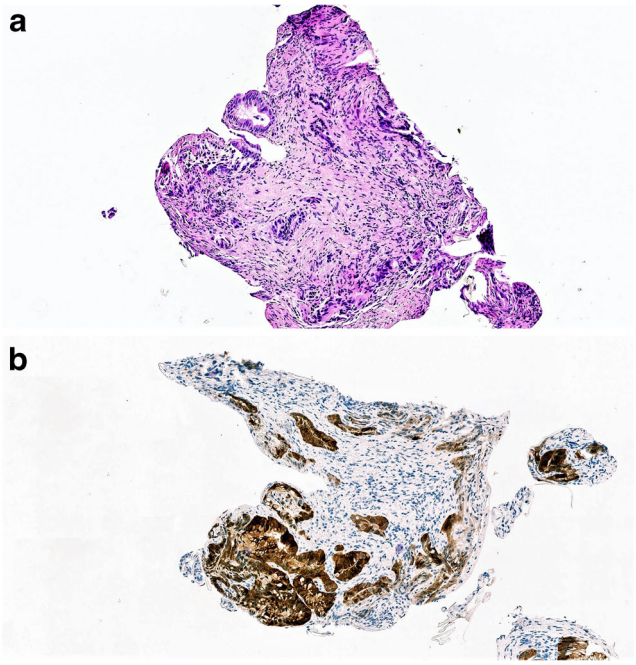

Fig. 8 Endoscopic bile duct biopsy. **a** Neoplastic duct-like glands with angular and irregular contours, indicative of bile duct adenocarcinoma (H&E staining). **b** The neoplastic glands show immunohistochemical overexpression of maspin

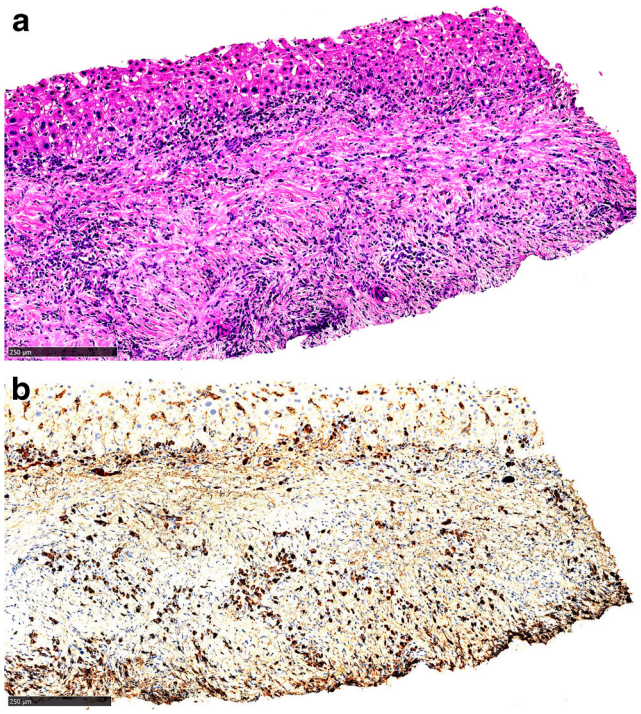

Fig. 9 Liver core needle biopsy showing **a** fibroinflammatory expansion of a portal tract, a so-called "inflammatory nodule," and **b** infiltration by IgG4-positive cells

adenocarcinoma. Also, the proper diagnosis of IgG4-related SC is severely limited. The tiny subepithelial connective tissue that is usually found in the biopsies is not sufficient enough to reveal key findings of IgG4-related SC, such as obliterative phlebitis and storiform fibrosis. If the subepithelial tissue contains small lymphoplasmacytic infiltrates showing some IgG4 positivity, these findings have also to be interpreted with caution, since they are unfortunately also frequently encountered in bile duct carcinomas [75, 76]. The diagnostic value of an additional liver core needle biopsy is often limited, since in most instances, only secondary obstructive changes are found. Only in 26% of IgG4-related SC patients, particularly in those with intrahepatic cholangiographic strictures, the disease was found to extend along the portal tracts and involve the intrahepatic small bile ducts [77]. In these instances, an inflammatory fibrosis (so-called "inflammatory nodule") expanding the portal tracts (Fig. 9a) and showing a lymphoplasmacytic infiltrate with high numbers of IgG4-positive cells (Fig. 9b) and sometimes also eosinophils may be found, and is then highly suggestive of IgG4-related SC [64]. The neutrophilic infiltration, which may also be observed in these biopsies, accompanies reactive bile ductules around the portal tracts and is an unspecific finding [43]. It is important to note that, at present, isolated intrahepatic small-duct IgG4-related SC has not been reported [77].

Because of the diagnostic difficulties so often encountered in bile duct biopsies, biopsies from the ampulla of Vater have been recommended. They may show increased IgG4-positive cells and IgG4/IgG ratios [72, 78]. However, in our experience and in the experience of others, the sensitivity and specificity of this approach is often low and only rarely useful in the diagnosis of IgG4-related SC [79]. Ampullary biopsies are of greatest value in patients with suspected AIP and showing a pathologically enlarged papilla.

Conclusion

Among the various organ manifestations of IgG4-RD, the pancreas and the common bile duct represent some of the most important sites because of the disease's difficult distinction from pancreatic and bile duct carcinoma, respectively. The histologic features of IgG4-RD in the pancreas and the bile duct are easily recognized in resection specimens. In biopsies, however, changes representative of the disease may be difficult to identify. Therefore, it is important to correlate the biopsy findings with clinical, imaging, and serological data, in close collaboration with the gastroenterologist, radiologist, and surgeon. Future prospective studies are needed to evaluate whether new histologic

biopsy needles guided by endoscopic ultrasound (pancreas) or cholangioscopy (bile ducts) can improve the tissue yield and the diagnostic sensitivity and specificity.

Author contribution Both authors contributed substantially to the conception, design, drafting, and final approval of this work. Both authors are accountable for all aspects of this work.

Compliance with ethical standards

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

References

1. Kamisawa T, Egawa N, Nakajima H (2003) Autoimmune pancreatitis is a systemic autoimmune disease. Am J Gastroenterol 98(12): 2811–2812. https://doi.org/10.1111/j.1572-0241.2003.08758.x
2. Zen Y, Nakanuma Y (2010) IgG4-related disease: a cross-sectional study of 114 cases. Am J Surg Pathol 34(12):1812–1819. https://doi.org/10.1097/PAS.0b013e3181f7266b
3. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T et al (2012) Consensus statement on the pathology of IgG4-related disease. Mod Pathol 25(9):1181–1192. https://doi.org/10.1038/modpathol.2012.72
4. Stone JH, Khosroshahi A, Deshpande V, Chan JK, Heathcote JG, Aalberse R et al (2012) Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis Rheum 64(10):3061–3067. https://doi.org/10.1002/art.34593
5. Comings DE, Skubi KB, Van EJ, Motulsky AG (1967) Familial multifocal fibrosclerosis. Findings suggesting that retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and pseudotumor of the orbit may be different manifestations of a single disease. Ann Intern Med 66(5):884–892. https://doi.org/10.7326/0003-4819-66-5-884
6. Bartholomew LG, Cain JC, Woolner LB, Utz DC, Ferris DO (1963) Sclerosing cholangitis: its possible association with Riedel's struma and fibrous retroperitonitis. Report of two cases. N Engl J Med 269(1):8–12. https://doi.org/10.1056/NEJM196307042690102
7. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N (1995) Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci 40(7):1561–1568. https://doi.org/10.1007/BF02285209
8. Sarles H, Sarles JC, Muratore R, Guien C (1961) Chronic inflammatory sclerosis of the pancreas—an autonomous pancreatic disease? Am J Dig Dis 6(7):688–698. https://doi.org/10.1007/BF02232341
9. Kawaguchi K, Koike M, Tsuruta K, Okamoto A, Tabata I, Fujita N (1991) Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. Hum Pathol 22(4):387–395. https://doi.org/10.1016/0046-8177(91)90087-6
10. Notohara K, Burgart LJ, Yadav D, Chari S, Smyrk TC (2003) Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. Am J Surg Pathol 27(8):1119–1127. https://doi.org/10.1097/00000478-200308000-00009
11. Zamboni G, Lüttges J, Capelli P, Frulloni L, Cavallini G, Pederzoli P, Leins A, Longnecker D, Klöppel G (2004) Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. Virchows Arch 445(6):552–563. https://doi.org/10.1007/s00428-004-1140-z
12. Ectors N, Maillet B, Aerts R, Geboes K, Donner A, Borchard F, Lankisch P, Stolte M, Luttges J, Kremer B, Kloppel G (1997) Non-alcoholic duct destructive chronic pancreatitis. Gut 41(2):263–268. https://doi.org/10.1136/gut.41.2.263
13. Detlefsen S, Zamboni G, Frulloni L, Feyerabend B, Braun F, Gerke O, Schlitter AM, Esposito I, Klöppel G (2012) Clinical features and relapse rates after surgery in type 1 autoimmune pancreatitis differ from type 2: a study of 114 surgically treated European patients. Pancreatology 12(3):276–283. https://doi.org/10.1016/j.pan.2012.03.055
14. Maire F, Le BY, Rebours V, Vullierme MP, Couvelard A, Voitot H et al (2011) Outcome of patients with type 1 or 2 autoimmune pancreatitis. Am J Gastroenterol 106(1):151–156. https://doi.org/10.1038/ajg.2010.314
15. Sah RP, Chari ST, Pannala R, Sugumar A, Clain JE, Levy MJ, Pearson RK, Smyrk TC, Petersen BT, Topazian MD, Takahashi N, Farnell MB, Vege SS (2010) Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis. Gastroenterology 139(1):140–148. https://doi.org/10.1053/j.gastro.2010.03.054
16. Chari ST, Longnecker DS, Klöppel G (2009) The diagnosis of autoimmune pancreatitis: a Western perspective. Pancreas 38(8): 846–848. https://doi.org/10.1097/MPA.0b013e3181bba281
17. Chari ST, Klöppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T (2010) Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu consensus document. Pancreas 39(5):549–554. https://doi.org/10.1097/MPA.0b013e3181e4d9e5
18. Saxena A, Wu D (2016) Advances in therapeutic Fc engineering—modulation of IgG-associated effector functions and serum half-life. Front Immunol 7:580. https://doi.org/10.3389/fimmu.2016.00580
19. Hart PA, Krishna SG, Okazaki K (2017) Diagnosis and management of autoimmune pancreatitis. Curr Treat Options Gastroenterol 15:538–547
20. Detlefsen S, Mortensen MB, Pless TK, Cribe AS, de Muckadell OB (2015) Laparoscopic and percutaneous core needle biopsy plays a central role for the diagnosis of autoimmune pancreatitis in a single-center study from Denmark. Pancreas 44(6):845–858. https://doi.org/10.1097/MPA.0000000000000312
21. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K (2001) High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 344(10):732–738. https://doi.org/10.1056/NEJM200103083441005
22. Ghazale A, Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Clain JE, Pearson RK, Pelaez-Luna M, Petersen BT, Vege SS, Farnell MB (2007) Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. Am J Gastroenterol 102(8):1646–1653. https://doi.org/10.1111/j.1572-0241.2007.01264.x
23. Boonstra K, Culver EL, de Buy Wenniger LM, van Heerde MJ, van Erpecum KJ, Poen AC, van Nieuwkerk KMJ, Spanier BWM, Witteman BJM, Tuynman HARE, van Geloven N, van Buuren H, Chapman RW, Barnes E, Beuers U, Ponsioen CY (2014) Serum immunoglobulin G4 and immunoglobulin G1 for distinguishing immunoglobulin G4-associated cholangitis from primary sclerosing cholangitis. Hepatology 59(5):1954–1963. https://doi.org/10.1002/hep.26977
24. Detlefsen S, Drewes AM, Vyberg M, Klöppel G (2009) Diagnosis of autoimmune pancreatitis by core needle biopsy: application of six microscopic criteria. Virchows Arch 454(5):531–539. https://doi.org/10.1007/s00428-009-0747-5

25. Deshpande V, Gupta R, Sainani N, Sahani DV, Virk R, Ferrone C, Khosroshahi A, Stone JH, Lauwers GY (2011) Subclassification of autoimmune pancreatitis: a histologic classification with clinical significance. Am J Surg Pathol 35(1):26–35. https://doi.org/10.1097/PAS.0b013e3182027717
26. Deshpande V, Mino-Kenudson M, Brugge W, Lauwers GY (2005) Autoimmune pancreatitis: more than just a pancreatic disease? A contemporary review of its pathology. Arch Pathol Lab Med 129(9):1148–1154. https://doi.org/10.1043/1543-2165(2005)129[1148:APMTJA]2.0.CO;2
27. Bateman AC, Culver EL (2017) IgG4-related disease-experience of 100 consecutive cases from a specialist centre. Histopathology 70(5):798–813. https://doi.org/10.1111/his.13136
28. Strehl JD, Hartmann A, Agaimy A (2011) Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. J Clin Pathol 64(3):237–243. https://doi.org/10.1136/jcp.2010.085613
29. Chang SY, Keogh KA, Lewis JE, Ryu JH, Cornell LD, Garrity JA, Yi ES (2013) IgG4-positive plasma cells in granulomatosis with polyangiitis (Wegener's): a clinicopathologic and immunohistochemical study on 43 granulomatosis with polyangiitis and 20 control cases. Hum Pathol 44(11):2432–2437. https://doi.org/10.1016/j.humpath.2013.05.023
30. Okazaki K, Uchida K, Koyabu M, Miyoshi H, Takaoka M (2011) Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. J Gastroenterol 46(3):277–288. https://doi.org/10.1007/s00535-011-0386-x
31. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S, Hamano H, Kamisawa T, Shimosegawa T, Shimatsu A, Nakamura S, Ito T, Notohara K, Sumida T, Tanaka Y, Mimori T, Chiba T, Mishima M, Hibi T, Tsubouchi H, Inui K, Ohara H (2012) Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol 22(1):21–30. https://doi.org/10.3109/s10165-011-0571-z
32. Klöppel G, Sipos B, Zamboni G, Kojima M, Morohoshi T (2007) Autoimmune pancreatitis: histo- and immunopathological features. J Gastroenterol 42(Suppl 18):28–31. https://doi.org/10.1007/s00535-007-2048-6
33. Esposito I, Born D, Bergmann F, Longerich T, Welsch T, Giese NA, Büchler MW, Kleeff J, Friess H, Schirmacher P (2008) Autoimmune pancreatocholangitis, non-autoimmune pancreatitis and primary sclerosing cholangitis: a comparative morphological and immunological analysis. PLoS One 3(7):e2539. https://doi.org/10.1371/journal.pone.0002539
34. Zamboni G, Capelli P, Pesci A, Beghelli S, Lüttges J, Klöppel G (2000) Pancreatic head mass: what can be done? Classification: the pathological point of view. JOP : J Pancreas 1(3 Suppl):77–84
35. Zamboni G, Capelli P, Scarpa A, Bogina G, Pesci A, Brunello E, Klöppel G (2009) Nonneoplastic mimickers of pancreatic neoplasms. Arch Pathol Lab Med 133(3):439–453. https://doi.org/10.1043/1543-2165-133.3.439
36. Kamisawa T, Chari ST, Giday SA, Kim MH, Chung JB, Lee KT, Werner J, Bergmann F, Lerch MM, Mayerle J, Pickartz T, Lohr M, Schneider A, Frulloni L, Webster GJM, Reddy DN, Liao WC, Wang HP, Okazaki K, Shimosegawa T, Kloeppel G, Go VLW (2011) Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. Pancreas 40(6):809–814. https://doi.org/10.1097/MPA.0b013e3182258a15
37. Kojima M, Sipos B, Klapper W, Frahm O, Knuth HC, Yanagisawa A, Zamboni G, Morohoshi T, Klöppel G (2007) Autoimmune pancreatitis: frequency, IgG4 expression, and clonality of T and B cells. Am J Surg Pathol 31(4):521–528. https://doi.org/10.1097/01.pas.0000213390.55536.47
38. Detlefsen S, Sipos B, Zhao J, Drewes AM, Klöppel G (2008) Autoimmune pancreatitis: expression and cellular source of profibrotic cytokines and their receptors. Am J Surg Pathol 32(7):986–995. https://doi.org/10.1097/PAS.0b013e31815d2583
39. Abraham SC, Leach S, Yeo CJ, Cameron JL, Murakata LA, Boitnott JK, Albores-Saavedra J, Hruban RH (2003) Eosinophilic pancreatitis and increased eosinophils in the pancreas. Am J Surg Pathol 27(3):334–342. https://doi.org/10.1097/00000478-200303000-00006
40. Chougule A, Bal A (2017) IgG4-related inflammatory pseudotumor: a systematic review of histopathological features of reported cases. Mod Rheumatol 27(2):320–325. https://doi.org/10.1080/14397595.2016.1206241
41. Saito T, Tanaka S, Yoshida H, Imamura T, Ukegawa J, Seki T, Ikegami A, Yamamura F, Mikami T, Aoyagi Y, Niikawa J, Mitamura K (2002) A case of autoimmune pancreatitis responding to steroid therapy. Evidence of histologic recovery. Pancreatology 2(6):550–556. https://doi.org/10.1159/000066092
42. Song MH, Kim MH, Lee SK, Seo DW, Lee SS, Han J, Kim KP, Min YI, Song DE, Yu E, Jang SJ (2005) Regression of pancreatic fibrosis after steroid therapy in patients with autoimmune chronic pancreatitis. Pancreas 30(1):83–86
43. Zen Y, Kawakami H, Kim JH (2016) IgG4-related sclerosing cholangitis: all we need to know. J Gastroenterol 51(4):295–312. https://doi.org/10.1007/s00535-016-1163-7
44. Klöppel G, Detlefsen S, Chari ST, Longnecker DS, Zamboni G (2010) Autoimmune pancreatitis: the clinicopathological characteristics of the subtype with granulocytic epithelial lesions. J Gastroenterol 45(8):787–793. https://doi.org/10.1007/s00535-010-0265-x
45. Stone JH, Brito-Zeron P, Bosch X, Ramos-Casals M (2015) Diagnostic approach to the complexity of IgG4-related disease. Mayo Clin Proc 90(7):927–939. https://doi.org/10.1016/j.mayocp.2015.03.020
46. Wallace ZS, Mattoo H, Carruthers M, Mahajan VS, Della TE, Lee H et al (2015) Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. Ann Rheum Dis 74(1):190–195. https://doi.org/10.1136/annrheumdis-2014-205233
47. Klöppel G, Detlefsen S, Feyerabend B (2004) Fibrosis of the pancreas: the initial tissue damage and the resulting pattern. Virchows Arch 445(1):1–8. https://doi.org/10.1007/s00428-004-1021-5
48. Klöppel G (2007) Chronic pancreatitis, pseudotumors and other tumor-like lesions. Mod Pathol 20(Suppl 1):S113–S131. https://doi.org/10.1038/modpathol.3800690
49. Asano J, Watanabe T, Oguchi T, Kanai K, Maruyama M, Ito T, Muraki T, Hamano H, Arakura N, Matsumoto A, Kawa S (2015) Association between immunoglobulin G4-related disease and malignancy within 12 years after diagnosis: an analysis after longterm followup. J Rheumatol 42(11):2135–2142. https://doi.org/10.3899/jrheum.150436
50. Yamamoto M, Takahashi H, Tabeya T, Suzuki C, Naishiro Y, Ishigami K, Yajima H, Shimizu Y, Obara M, Yamamoto H, Himi T, Imai K, Shinomura Y (2012) Risk of malignancies in IgG4-related disease. Mod Rheumatol 22(3):414–418. https://doi.org/10.3109/s10165-011-0520-x
51. Detlefsen S, Sipos B, Feyerabend B, Klöppel G (2006) Fibrogenesis in alcoholic chronic pancreatitis: the role of tissue necrosis, macrophages, myofibroblasts and cytokines. Mod Pathol 19(8):1019–1026. https://doi.org/10.1038/modpathol.3800613
52. Klöppel G, Maillet B (1993) Pathology of acute and chronic pancreatitis. Pancreas 8(6):659–670. https://doi.org/10.1097/00006676-199311000-00001
53. Levy MJ, Reddy RP, Wiersema MJ, Smyrk TC, Clain JE, Harewood GC, Pearson RK, Rajan E, Topazian MD, Yusuf TE, Chari ST, Petersen BT (2005) EUS-guided trucut biopsy in

establishing autoimmune pancreatitis as the cause of obstructive jaundice. Gastrointest Endosc 61(3):467–472. https://doi.org/10.1016/S0016-5107(04)02802-0
54. Levy MJ, Smyrk TC, Takahashi N, Zhang L, Chari ST (2011) Idiopathic duct-centric pancreatitis: disease description and endoscopic ultrasonography-guided trucut biopsy diagnosis. Pancreatology 11(1):76–80. https://doi.org/10.1159/000324189
55. Mizuno N, Bhatia V, Hosoda W, Sawaki A, Hoki N, Hara K, Takagi T, Ko SBH, Yatabe Y, Goto H, Yamao K (2009) Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy: a comparison study with EUS-FNA. J Gastroenterol 44(7):742–750. https://doi.org/10.1007/s00535-009-0062-6
56. Kanno A, Masamune A, Fujishima F, Iwashita T, Kodama Y, Katanuma A, Ohara H, Kitano M, Inoue H, Itoi T, Mizuno N, Miyakawa H, Mikata R, Irisawa A, Sato S, Notohara K, Shimosegawa T (2016) Diagnosis of autoimmune pancreatitis by EUS-guided FNA using a 22-gauge needle: a prospective multicenter study. Gastrointest Endosc 84(5):797–804. https://doi.org/10.1016/j.gie.2016.03.1511
57. Samarasena J, Kaye S, Jalali F, Lee JG, Chang K (2013) Autoimmune pancreatitis diagnosed using endoscopic ultrasound and a novel 19-gauge histology needle. J Interv Gastroenterol 3:147–148
58. Kerdsirichairat T, Saini SD, Chamberlain PR, Prabhu A (2017) Autoimmune pancreatitis diagnosed with core biopsy obtained from a novel fork-tip EUS needle. ACG Case Rep J 4:e7. 10.14309/crj.2017.7
59. Detlefsen S, Joergensen MT, Mortensen MB (2017) Microscopic findings in EUS-guided fine needle (SharkCore) biopsies with type 1 and type 2 autoimmune pancreatitis. Pathol Int 67(10):514–520. https://doi.org/10.1111/pin.12563
60. Larsen MH, Fristrup CW, Detlefsen S, Mortensen MB (2017) Prospective evaluation of EUS-guided fine needle biopsy in pancreatic mass lesions. Endosc Int Open in press
61. Inoue D, Yoshida K, Yoneda N, Ozaki K, Matsubara T, Nagai K, Okumura K, Toshima F, Toyama J, Minami T, Matsui O, Gabata T, Zen Y (2015) IgG4-related disease: dataset of 235 consecutive patients. Medicine (Baltimore) 94(15):e680. https://doi.org/10.1097/MD.0000000000000680
62. Culver EL, Chapman RW (2016) IgG4-related hepatobiliary disease: an overview. Nat Rev Gastroenterol Hepatol 13:601–612
63. Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, Kurumaya H, Katayanagi K, Masuda S, Niwa H, Morimoto H, Miwa A, Uchiyama A, Portmann BC, Nakanuma Y (2004) 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 28(9):1193–1203. https://doi.org/10.1097/01.pas.0000136449.37936.6c
64. Deshpande V, Sainani NI, Chung RT, Pratt DS, Mentha G, Rubbia-Brandt L, Lauwers GY (2009) IgG4-associated cholangitis: a comparative histological and immunophenotypic study with primary sclerosing cholangitis on liver biopsy material. Mod Pathol 22(10):1287–1295. https://doi.org/10.1038/modpathol.2009.94
65. Umemura T, Zen Y, Hamano H, Kawa S, Nakanuma Y, Kiyosawa K (2007) Immunoglobin G4-hepatopathy: association of immunoglobin G4-bearing plasma cells in liver with autoimmune pancreatitis. Hepatology 46(2):463–471. https://doi.org/10.1002/hep.21700
66. Umemura T, Zen Y, Hamano H, Joshita S, Ichijo T, Yoshizawa K, Kiyosawa K, Ota M, Kawa S, Nakanuma Y, Tanaka E (2011) Clinical significance of immunoglobulin G4-associated autoimmune hepatitis. J Gastroenterol 46(Suppl 1):48–55. https://doi.org/10.1007/s00535-010-0323-4
67. Umemura T, Zen Y, Hamano H, Ichijo T, Kawa S, Nakanuma Y, Kiyosawa K (2007) IgG4 associated autoimmune hepatitis: a differential diagnosis for classical autoimmune hepatitis. Gut 56(10):1471–1472. https://doi.org/10.1136/gut.2007.122283
68. Zen Y, Fujii T, Sato Y, Masuda S, Nakanuma Y (2007) Pathological classification of hepatic inflammatory pseudotumor with respect to IgG4-related disease. Mod Pathol 20(8):884–894. https://doi.org/10.1038/modpathol.3800836
69. Mendes F, Lindor KD (2010) Primary sclerosing cholangitis: overview and update. Nat Rev Gastroenterol Hepatol 7(11):611–619. https://doi.org/10.1038/nrgastro.2010.155
70. Zen Y, Grammatikopoulos T, Heneghan MA, Vergani D, Mieli-Vergani G, Portmann BC (2012) Sclerosing cholangitis with granulocytic epithelial lesion: a benign form of sclerosing cholangiopathy. Am J Surg Pathol 36(10):1555–1561. https://doi.org/10.1097/PAS.0b013e31825faae0
71. Zen Y, Ishikawa A, Ogiso S, Heaton N, Portmann B (2012) Follicular cholangitis and pancreatitis—clinicopathological features and differential diagnosis of an under-recognized entity. Histopathology 60(2):261–269. https://doi.org/10.1111/j.1365-2559.2011.04078.x
72. Kawakami H, Zen Y, Kuwatani M, Eto K, Haba S, Yamato H, Shinada K, Kubota K, Asaka M (2010) IgG4-related sclerosing cholangitis and autoimmune pancreatitis: histological assessment of biopsies from Vater's ampulla and the bile duct. J Gastroenterol Hepatol 25(10):1648–1655. https://doi.org/10.1111/j.1440-1746.2010.06346.x
73. Horiguchi S, Ikeda F, Shiraha H, Yamamoto N, Sakakihara I, Noma Y, Tsutsumi K, Kato H, Hagihara H, Yasunaka T, Nakamura S, Kobashi H, Kawamoto H, Yamamoto K (2012) Diagnostic usefulness of precise examinations with intraductal ultrasonography, peroral cholangioscopy and laparoscopy of immunoglobulin G4-related sclerosing cholangitis. Dig Endosc 24(5):370–373. https://doi.org/10.1111/j.1443-1661.2012.01300.x
74. Ohara H, Okazaki K, Tsubouchi H, Inui K, Kawa S, Kamisawa T, Tazuma S, Uchida K, Hirano K, Yoshida H, Nishino T, Ko SB, Mizuno N, Hamano H, Kanno A, Notohara K, Hasebe O, Nakazawa T, Nakanuma Y, Takikawa H, Research Committee of IgG4-related Diseases, Research Committee of Intractable Diseases of Liver and Biliary Tract, Ministry of Health, Labor and Welfare, Japan, Japan Biliary Association (2012) Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci 19(5):536–542. https://doi.org/10.1007/s00534-012-0521-y
75. Kimura Y, Harada K, Nakanuma Y (2012) Pathologic significance of immunoglobulin G4-positive plasma cells in extrahepatic cholangiocarcinoma. Hum Pathol 43(12):2149–2156. https://doi.org/10.1016/j.humpath.2012.03.001
76. Deshpande V (2015) IgG4-related disease of the gastrointestinal tract: a 21st century chameleon. Arch Pathol Lab Med 139(6):742–749. https://doi.org/10.5858/arpa.2014-0181-RA
77. Naitoh I, Zen Y, Nakazawa T, Ando T, Hayashi K, Okumura F, Miyabe K, Yoshida M, Nojiri S, Kanematsu T, Ohara H, Joh T (2011) Small bile duct involvement in IgG4-related sclerosing cholangitis: liver biopsy and cholangiography correlation. J Gastroenterol 46(2):269–276. https://doi.org/10.1007/s00535-010-0319-0
78. Moon SH, Kim MH, Park DH, Song TJ, Eum J, Lee SS, Seo DW, Lee SK (2010) IgG4 immunostaining of duodenal papillary biopsy specimens may be useful for supporting a diagnosis of autoimmune pancreatitis. Gastrointest Endosc 71(6):960–966. https://doi.org/10.1016/j.gie.2009.12.004
79. Cebe KM, Swanson PE, Upton MP, Westerhoff M (2013) Increased IgG4+ cells in duodenal biopsies are not specific for autoimmune pancreatitis. Am J Clin Pathol 139(3):323–329. https://doi.org/10.1309/AJCPT00NHQHXAHDS