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Review

Endoscopic approaches for the diagnosis of autoimmune pancreatitis

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Autoimmune pancreatitis (AIP) is characterized by diffuse pancreatic enlargement and irregular narrowing of the main pancreatic duct (MPD). Immunoglobulin (Ig)G4-related sclerosing cholangitis (IgG4-SC) associated with AIP frequently appears as a bile duct stricture. Therefore, it is important to differentiate AIP and IgG4-SC from pancreatic cancer and cholangiocarcinoma or primary sclerosing cholangitis, respectively. Endoscopy plays a central role in the diagnosis of AIP and IgG4-SC because it provides imaging of the MPD and bile duct strictures as well as the ability to obtain tissue samples for histological evaluations. Diffuse irregular narrowing of MPD on endoscopic retrograde cholangiopancreatography (ERCP) is rather specific to AIP, but localized narrowing of the MPD is often difficult to differentiate from MPD stenosis caused by pancreatic cancer. A long stricture (>1/3 the length of the MPD) and lack of upstream dilatation from the stricture (<5 mm) might be key features of AIP on ERCP. Some cholangiographic features, such as segmental strictures, strictures of the lower bile duct, and long strictures with prestenotic dilatation, are more common in IgG4-SC than in cholangiocarcinoma. Endoscopic ultrasonography (EUS) reveals diffuse hypoechoic pancreatic enlargement, sometimes with hypoechoic inclusions, in patients with AIP. In addition, EUS-elastography and contrast-enhanced harmonic EUS have been developed with promising results. The usefulness of EUS-guided fine-needle aspiration has been increasingly recognized for obtaining adequate tissue samples for the histological diagnosis of AIP. Further improvement of endoscopic procedures and devices will contribute to more accurate diagnosis of AIP and IgG4-SC.

Key words: endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), EUS-guided fine-needle aspiration (EUS-FNA), immunoglobulin (Ig)G4-related disease, IgG4-related sclerosing cholangitis

INTRODUCTION

AUTOIMMUNE PANCREATITIS (AIP) has been increasingly recognized as a distinctive type of pancreatitis with a presumed autoimmune etiology. In 1995, Yoshida *et al.*[1] first proposed the concept of AIP as a disease entity. They summarized the clinical features as follows: increased serum γ-globulin or immunoglobulin (Ig) G levels and the presence of autoantibodies; diffuse and irregular narrowing of the main pancreatic duct (MPD) and enlargement of the pancreas; occasional association with stenosis of the lower bile duct and other autoimmune diseases; mild symptoms, usually without acute attacks of pancreatitis; effectiveness of steroid therapy; and histological findings of lymphoplasmacytic sclerosing pancreatitis (LPSP).[2] Thereafter, cases of AIP have been reported worldwide including from Japan, Korea, Europe and the USA. Importantly, the histopathological features of AIP other than LPSP were reported in Western countries.[3–5] This type of pancreatitis was also defined as idiopathic duct-centric chronic pancreatitis (IDCP) or granulocytic epithelial lesion (GEL), which is histologically characterized by the infiltration of neutrophils in the pancreatic duct epithelium, and associated with destruction of the pancreatic duct epithelium and the accumulation of neutrophils in the pancreatic duct.[3–5] AIP with the histological findings of either LPSP or IDCP (AIP with GEL) has been categorized as type 1 or type 2 AIP, respectively.[6,7] Patients with type 1 AIP often develop other organ involvement (OOI), such as sclerosing cholangitis and sclerosing sialoadenitis, suggesting that type 1 AIP is a systemic disorder.[8] Over the decade, several diagnostic criteria for AIP have been proposed and revised, and the endoscopic findings have been incorporated in them. In the present article, we

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will review the role and future perspectives of endoscopy in the diagnosis of AIP.

HISTORY OF DIAGNOSTIC CRITERIA FOR AIP

SARLES *ET AL.*[9] FIRST REPORTED a form of idiopathic chronic pancreatitis possibly caused by an autoimmune mechanism in 1961. In 1995, Yoshida *et al.*[1] proposed AIP as a new clinical entity from Japan. Thereafter, cases of AIP have been extensively reported worldwide. With the accumulation of similar cases in Japan, the Japan Pancreas Society (JPS) proposed the world's first clinical diagnostic criteria for AIP in 2002 (JPS2002).[10] The JPS2002 criteria consisted of three items: (i) specific imaging findings (a mandatory requirement); (ii) serological; and/or (iii) pathological evidence. A diagnosis of AIP is made when more than two items, including the essential imaging findings, are observed. In the criteria, the length of MPD narrowing on endoscopic retrograde pancreatography (ERP) was defined as more than one-third the length of the entire pancreas, because the differential diagnosis of AIP from pancreatic cancer was very difficult in cases of localized MPD narrowing. As a result, the 2002 criteria were diagnostic for typical diffuse-type AIP, but were unable to diagnose atypical localized/segmental-type AIP, which shows focal or segmental swelling of the pancreas and MPD narrowing in less than one-third of the entire pancreas.

The JPS2002 were revised in 2006 by the JPS and Research Committee for Intractable Pancreatic Disease supported by the Ministry of Health, Labour and Welfare of Japan (RCIPD) (JPS2006).[11] Major revisions included elimination of the dependency on the length of MPD narrowing and the incorporation of IgG4 as a serology criterion.[12] In addition, several AIP diagnostic criteria were proposed from other countries such as Korea,[13] the USA,[14] Italy,[15] and Germany.[16] Therefore, it was necessary to create an international consensus for the diagnosis, clinicopathological understanding, and treatment of AIP. In 2012, the international consensus diagnostic criteria for AIP (ICDC) were proposed based on the opinions of experts in each country.[17] According to the ICDC, AIP has been classified into two subtypes: type 1 related with IgG4 (LPSP) and type 2 with GEL (IDCP). The ICDC used a combination of five cardinal features of AIP: (i) pancreatic imaging (parenchyma [P] and duct [D]); (ii) serology (S); (iii) OOI; (iv) histology (H); and (v) steroid responsiveness (Rt). The ICDC can be applied worldwide and contribute to avoiding the misdiagnosis of pancreatic cancer. Because these criteria might be complicated for general use and because type 2 AIP is extremely rare in Japan, the JPS and RCIPD revised the Japanese diagnostic criteria for AIP, focusing on type 1 AIP in 2011 (JPS2011).[18,19]

ROLE OF ENDOSCOPY IN THE DIAGNOSIS OF AIP

Endoscopic retrograde cholangiopancreatography

Endoscopic pancreatogram

Typical AIP exhibits diffuse irregular narrowing of the MPD with a diffusely enlarged pancreas.[1] Narrowing of the MPD is usually determined based on ERP images. Diffuse irregular MPD narrowing is rather specific to AIP (Figs 1,2), and long (>1/3 length of the MPD), or multiple strictures without marked upstream dilatation are adopted as level 1 findings in the ICDC.[17] The narrowing of the MPD is different from obstruction or stenosis, as the narrowing extends and the diameter is narrower than normal, but with some irregularities.[20] It is not easy to differentiate localized MPD narrowing from MPD stenosis as a result of pancreatic cancer (Fig. 3). ERP findings were adopted as mandatory criteria in the definitive diagnosis of focal/segmental-type AIP according to the ICDC[17] and JPS2011.[18,19] There have been several studies reporting the features of ERP findings in patients with AIP and pancreatic cancer.[21–23] Wakabayashi *et al.*[21] compared the pancreatograms of nine patients with focal-type AIP and 80 patients with pancreatic cancer. They

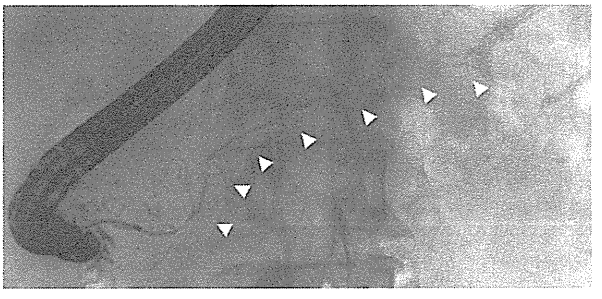

Figure 1 Endoscopic retrograde pancreatography reveals diffuse irregular narrowing of the main pancreatic duct (arrowheads).

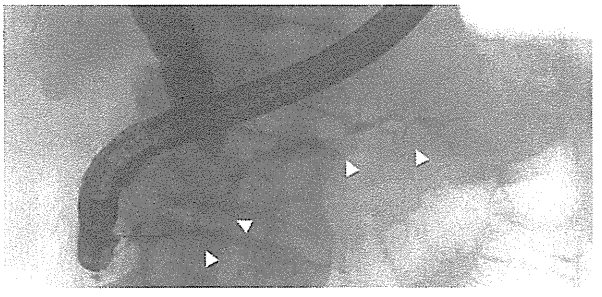

Figure 2 Endoscopic retrograde pancreatography shows skipped stenosis of the main pancreatic duct (arrowheads).

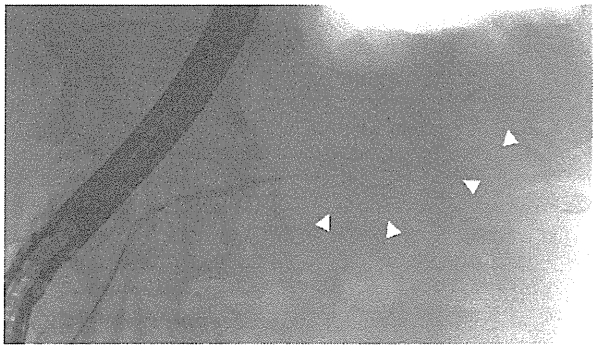

Figure 3 Endoscopic retrograde pancreatography shows focal stenosis in the pancreatic tail (arrowheads).

showed that MPD obstruction was less frequent in AIP than in pancreatic cancer (11% in AIP *vs* 60% in pancreatic cancer). A narrowed MPD portion of ≥3 cm in length (100% in AIP *vs* 22% in pancreatic cancer) and a maximal upstream MPD diameter of <4 mm (67% in AIP *vs* 4% in pancreatic cancer) were more common in AIP. They concluded that ERP findings showing longer stenosis of the MPD and a thinner MPD upstream from the stricture might be useful for the differential diagnosis of AIP from pancreatic cancer. Similarly, Takuma *et al.*[22] showed that skipped MPD lesions, a side branch derivation from a narrowed MPD, a narrowing of the MPD longer than 3 cm, and an upstream MPD dilatation of <5 mm were more frequent in AIP. In a multicenter, international study that addressed the role of ERP in AIP, Sugumar *et al.*[23] reported that the ability to diagnose AIP on the basis of ERP features alone was limited. The overall sensitivity, specificity, and interobserver agreement of ERP alone in the diagnosis of AIP were 44%, 92%, and 0.23, respectively. Importantly, they identified key features of AIP including long stricture (>1/3 the length of the MPD), lack of upstream dilatation from the stricture (<5 mm), multiple strictures, and side branches arising from strictured segments. Collectively, the ability to diagnose AIP could be improved with knowledge of the characteristic features on ERP.

Endoscopic cholangiogram

In addition to pancreatitis, AIP patients often develop extrapancreatic lesions such as biliary lesions, sialoadenitis, retroperitoneal fibrosis, enlarged hilar lymph nodes, and intestinal nephritis,[8] suggesting that AIP may be a systemic disorder or part of the so-called IgG4-related disease.[24] In the nationwide epidemiological survey of 2007, sclerosing cholangitis was the leading extrapancreatic lesion and was found in 53.4% of the patients.[25] Lesions of the biliary tract were specifically defined as IgG4-related sclerosing cholangitis (IgG4-SC).[26,27] IgG4-SC is a characteristic type of sclerosing cholangitis with an unknown pathogenic mechanism. Patients with IgG4-SC often present increased levels of

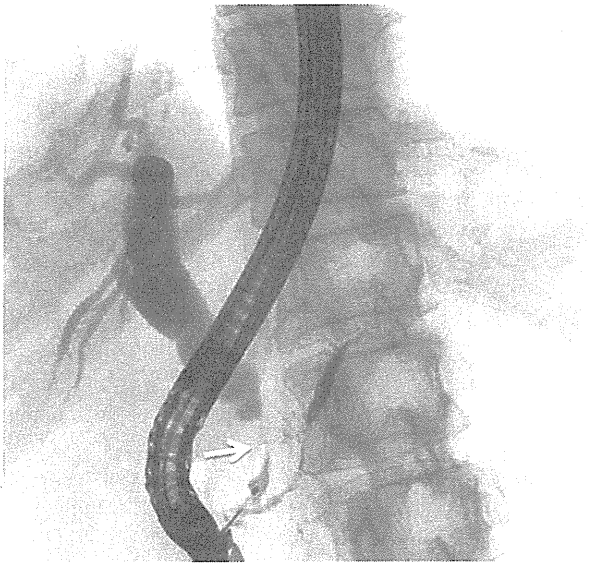

Figure 4 Endoscopic retrograde cholangiography reveals stenosis of the lower bile duct (arrow).

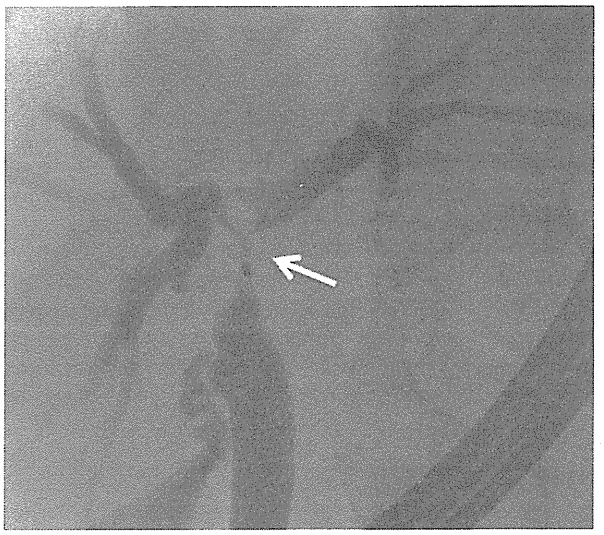

Figure 5 Endoscopic retrograde cholangiography shows stenosis of the hilar bile duct (arrow).

serum IgG4 and a dense infiltration of lymphocytes and plasma cells into the bile duct wall. Obstructive jaundice is frequently observed in IgG4-SC. The most common finding of IgG4-SC is intrapancreatic common bile duct involvement (Fig. 4), but biliary strictures can be observed anywhere in the biliary tree, including the hilar and intrahepatic bile ducts (Fig. 5). Differentiation of IgG4-SC from primary sclerosing cholangitis (PSC) and neoplastic lesions such as pancreatic and biliary cancers is very important.

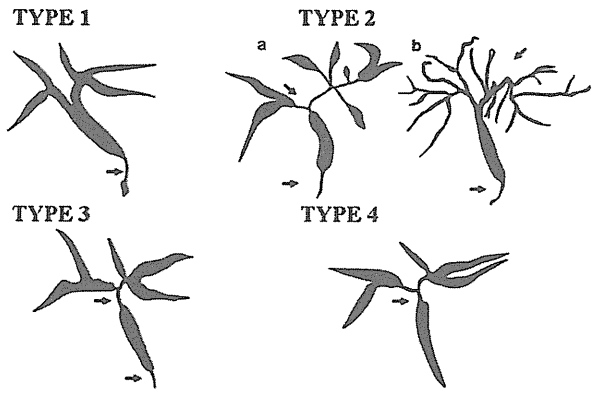

Figure 6 Schematic classification of cholangiographic findings in immunoglobulin (Ig)G4-related sclerosing cholangitis (IgG4-SC) (cited from Nakazawa *et al.* [28]). Type 1 IgG4-SC reveals stenosis in the intrapancreatic bile duct. Stenosis of the bile duct in type 2 IgG4-SC is located in the intrahepatic bile duct. Stenosis of the bile duct in type 3 IgG4-SC is shown in both hilar hepatic lesions and in the intrapancreatic bile duct. Type 4 IgG4-SC indicates stenosis in the hilar bile duct only.

Nakazawa *et al.*[28] reported the classification of IgG4-SC into four types based on the region of strictures revealed by cholangiography (Fig. 6). The endoscopic retrograde cholangiography (ERC) findings in type 1 might be similar to those in pancreatic head cancer, those of type 2 look like those in PSC, and those in types 3 and 4 are similar to those in cholangiocarcinoma. There are several cholangiographic findings that might be useful to differentiate IgG4-SC from PSC.[28,29] A beaded or 'pruned tree' appearance, band-like strictures, and diverticulum-like outpouchings are more frequent in PSC cases. Segmental strictures, long strictures with prestenotic dilatation, and strictures of the lower bile duct might suggest IgG4-SC. In addition to these differences on cholangiography, the clinical presentation might be different between IgG4-SC and PSC. PSC is often progressive and involves both the intra- and extrahepatic bile ducts, resulting in liver cirrhosis. IgG4-SC occasionally improves spontaneously and responds well to steroid therapy.[26] Serum IgG4 levels are increased in 74–90% of patients with IgG4-SC.[26,30] Importantly, an elevation of serum IgG4 levels is not specific to IgG4-SC. However, usually mild elevations of serum IgG4 were found in 12–22% of patients with PSC and in 8% of those with cholangiocarcinoma.[30,31] Therefore, increased IgG4 levels might be suggestive, but alone are not sufficient to differentiate IgG4-SC from other diseases. IgG4-SC should be carefully diagnosed on the basis of a combination of characteristic clinical, serological, and morphological features based on the cholangiographic classification, and after excluding similarly appearing diseases. Interestingly, Vosskuhl *et al.*[32] reported that IgG4 levels in bile juice were increased in patients with IgG4-SC, but not in those with PSC or cholangiocarcinoma. Measurement of bile IgG4 might be a new approach to distinguish IgG4-SC from other biliary diseases.

Biopsy from bile duct and duodenal papilla

The gold standard for the diagnosis of IgG4-SC is based on histology.[27] Endobiliary biopsy for bile duct strictures may be carried out on ERCP for the diagnosis and to relieve biliary stenosis in cases of suspected IgG4-SC. However, it is often difficult to obtain adequate tissue specimens of the bile duct for histological evaluation by a forceps biopsy. Biopsy specimens from the bile duct often contain clusters of epithelial cells alone without stroma.[33] Immunostaining for IgG4 may contribute to the diagnosis of IgG4-SC. Ghazale *et al.*[26] reported that histological diagnosis of IgG4-SC could not be made on any of 16 biopsy specimens obtained, although in all specimens there was adequate epithelial tissue. IgG4 immunostaining showed more than 10 IgG4-positive cells per high-power field in 14 out of 16 samples.[26] Obviously, diagnostic ability is affected by the amount of histological specimens acquired when using biopsy forceps. Improved biopsy forceps are needed to acquire adequate bile duct specimens for the diagnosis of IgG4-SC.

Usefulness of IgG4 immunostaining of biopsy specimens obtained from the major papilla has been reported.[34,37] For the diagnosis of IgG4-SC, a biopsy of the duodenal papilla is safer, easier, and more reliable than obtaining a histological sample from the bile duct. Sensitivity and specificity for differentiation between IgG4-SC and PSC or biliary duct cancer were 52–80% and 89–100%, respectively.[34,37] Kubota *et al.*[35] reported that the characteristic duodenal endoscopic papillary features observed in patients with IgG4-SC, such as swollen papillae, may be helpful for discriminating IgG4-SC from PSC. Narrow-band imaging of the duodenal papilla might be useful for the differential diagnosis of these disorders.[38] In the ICDC,[17] endoscopic biopsy of the duodenal papilla is described as a useful adjunctive method.

Intraductal ultrasonography

Endoscopic transpapillary intraductal ultrasonography (IDUS) carried out after ERC is useful for the evaluation of bile duct wall thickening.[39,40] IDUS provides high-resolution images of the bile duct wall, which normally has inner hypoechoic and outer hyperechoic layers.[39,40] The characteristic IDUS findings in IgG4-SC are circular-symmetric wall thickness, a smooth outer margin, a smooth inner margin, and a homogeneous internal echo in the stricture of the bile duct (Fig. 7). IDUS findings regarding cholangiocarcinoma are a circular-asymmetric wall thickening, a notched outer margin, a rigid papillary inner margin, and a heterogeneous internal echo in the stricture. Naitoh *et al.*[41] reported that wall thickness in the non-stricture area of a cholangiogram was a useful parameter for differentiating IgG4-SC from cholangiocarcinoma, with an optimal cut-off value of

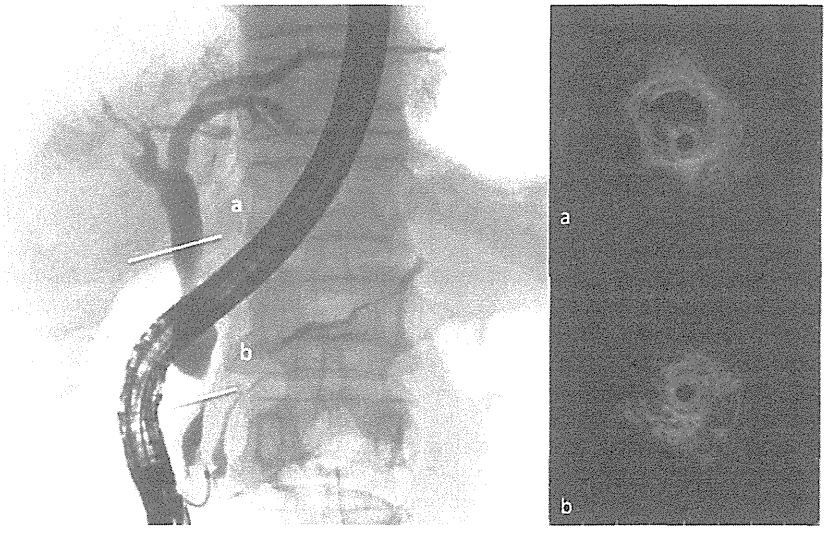

Figure 7 Intraductal ultrasonography (IDUS) findings. (a) In the non-stenotic portions where the cholangiogram result was normal, IDUS findings reveal wall thickening of the bile duct. (b) In the stenosis of the lower bile duct, IDUS findings also reveal wall thickening.

0.8 mm. IDUS combined with ERCP would give us valuable information for diagnosing IgG4-SC.

Peroral cholangioscopy

Peroral cholangioscopy has been developed over the past three decades to enable direct endoscopic diagnosis of bile duct lesions and targeted biopsies.[42,43] Itoi *et al.*[43] reported that dilated and tortuous vessels or partially enlarged vessels suggested IgG4-SC rather than PSC or cholangiocarcinoma. Further study is required to establish the role of peroral cholangioscopy in the diagnosis of IgG4-SC.

Endoscopic ultrasonography

Conventional imaging

Endoscopic ultrasonography (EUS) has become a routine modality for the evaluation of pancreatic masses because it provides fine imaging of the tumor and staging information. The compatible EUS finding for AIP is diffuse hypoechoic pancreatic mass lesion mimicking pancreatic cancer.[40,44,45] Some studies have tried to distinguish AIP from pancreatic cancer using conventional EUS images (Fig. 8). Hoki *et al.*[44] reported the conventional EUS features of AIP. With conventional EUS, diffuse hypoechoic areas, diffuse enlargement, bile duct wall thickening, and perihypoechoic margins are more frequent in AIP than in pancreatic cancer. However, it may be difficult to differentiate AIP from pancreatic cancer using conventional EUS imaging alone.

Contrast-enhanced harmonic EUS

An ultrasonographic contrast procedure was recently developed, and it made contrast-enhanced harmonic imaging of the pancreas using EUS possible.[46] Several studies have shown that contrast-enhanced harmonic EUS (CEH-EUS) could increase the accuracy of pancreatic cancer diagnosis by providing information about vascular patterns such as hypo-, hyper-, or isoenhancement (Fig. 9).[47–49] Imazu *et al.*[49] described the usefulness of CEH-EUS for differentiating AIP from pancreatic cancer by analyzing the perfusion quantitatively using a time-intensity curve.

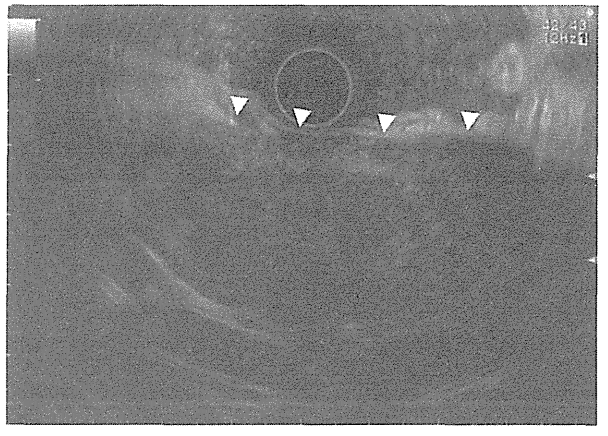

Figure 8 Endoscopic ultrasonography (EUS). Conventional EUS findings show diffuse pancreatic enlargement with a heterogeneous hypoechoic pattern (arrowheads).

Elastography

EUS-elastography can now be used as a technique to distinguish between benign and malignant pancreatic masses.[50–52] The diagnostic ability of EUS-elastography to differentiate AIP from pancreatic cancer is still questionable.

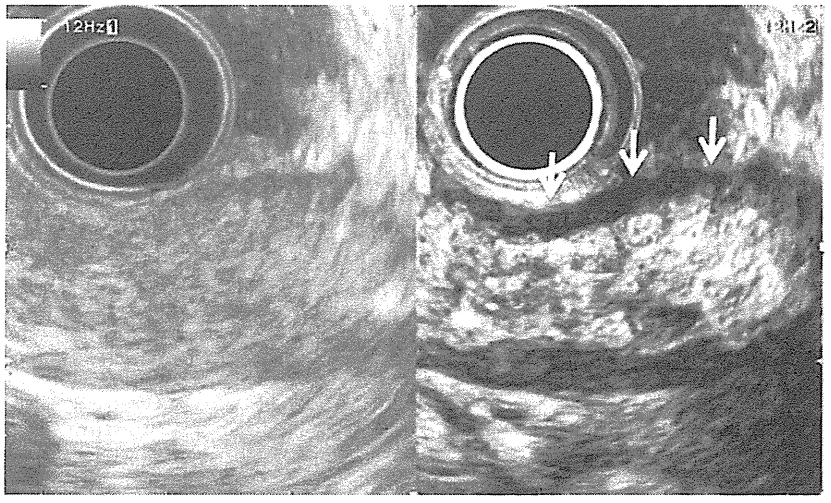

Figure 9 Contrast enhanced harmonic EUS (CEH-EUS). CEH-EUS findings reveal hypervascular pancreatic enlargement surrounded by hypovascular lesions (capsule-like rim) (arrows).

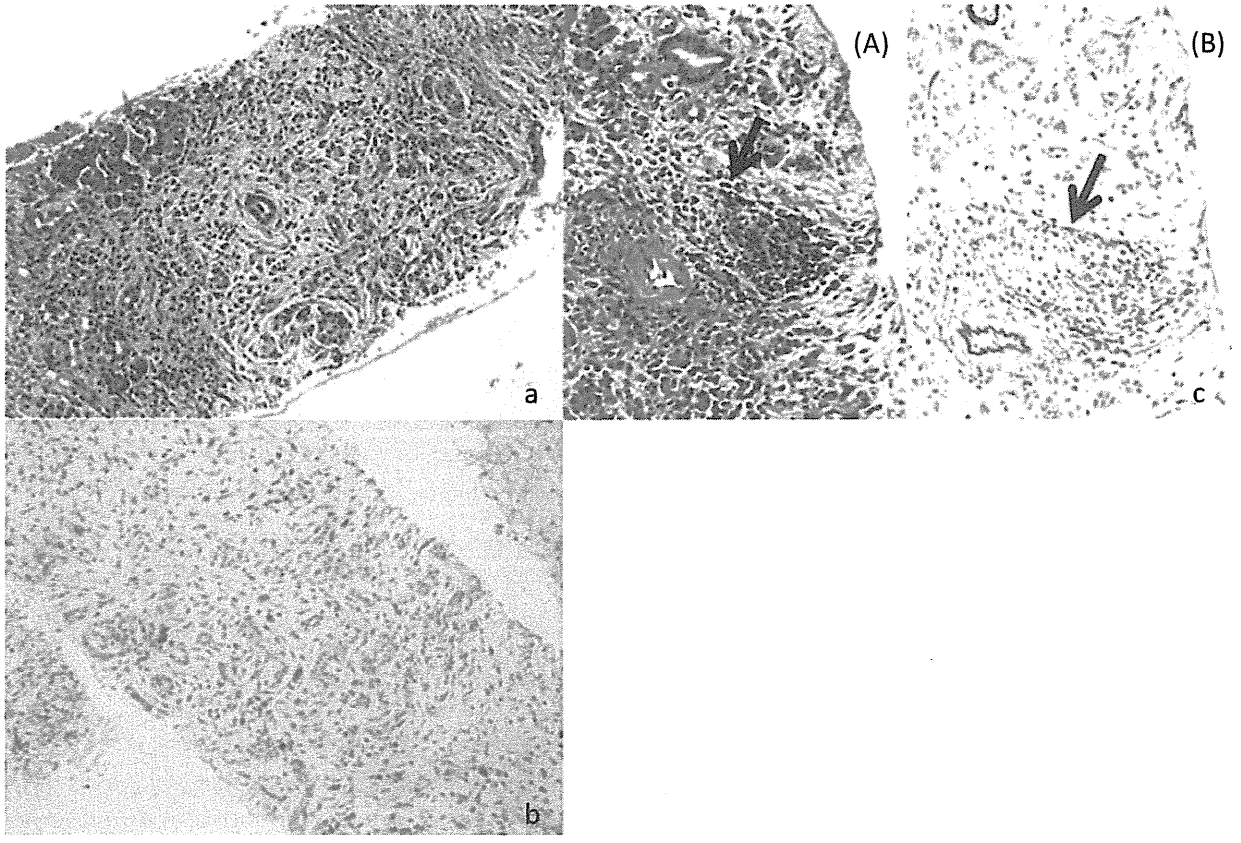

Figure 10 (a) High-power-field findings (400×) show lymphoplasmacytic infiltration and storiform fibrosis. (b) Immunohistochemical staining for immunoglobulin (Ig)G4. Abundant IgG4-positive plasma cells were found in the high-power field. (c) Obliterative phlebitis (arrow). (A) hematoxylin-eosin staining. (B) Elastica–Masson (EM) staining. The finding of obliterative phlebitis is clear in the EM staining.

Dietrich *et al.*[50] evaluated the usefulness of EUS-elastography in the diagnosis of AIP. EUS-elastography revealed a characteristic elastographic pattern of stiffness not only in the mass lesion but also in the surrounding pancreatic tissue. Mei *et al.*[52] reported a meta-analysis that evaluated EUS-elastography for the diagnosis of solid pancreatic masses. The sensitivity, specificity, and diagnostic odds ratio of EUS-elastography for the differentiation of benign from malignant solid pancreatic masses were 0.95 (95% confidence interval [CI], 0.94–0.97), 0.67 (95% CI, 0.61–0.73), and 42.28 (95% CI, 26.90–66.46). EUS-elastography is a promising diagnostic tool for the diagnosis of pancreatic masses; however, accuracy for the diagnosis of AIP or other pancreatic masses will need further improvement.

EUS-guided fine-needle aspiration and Trucut biopsy

The ICDC emphasize the importance of histological examinations in the diagnosis of AIP.[17] In the latest nationwide epidemiological survey of AIP patients who had visited hospitals in Japan in 2011, pancreatic tissues were obtained in 409 of 901 patients (45.4%) (Kanno A. *et al.*, unpubl. obs, 2014). Tissue samples were obtained by EUS-guided fine-needle aspiration (EUS-FNA) in 261 (63.8%) and by pancreatectomy in 65 patients (15.9%). In the ICDC, only tissue samples obtained by EUS-Trucut biopsy (TCB) or resection are considered suitable for histopathological diagnosis of AIP.[17,53] EUS-FNA using a 19-gauge (G) needle might be useful,[54] but these procedures have a potential risk of complications and require skill.[55] The reliability of EUS-FNA with a 22-G needle for the histological diagnosis of AIP has been recently reported.[56,57] Ishikawa *et al.*[56] reported that this procedure provides adequate histological samples for the diagnosis and differentiation of type 1 and 2 AIP, particularly seronegative cases. Kanno *et al.*[57] reported that the histological diagnosis of AIP could be made in 20 of 25 patients (80%) according to the ICDC (Fig. 10). To obtain sufficient histological samples, the authors emphasized the importance of careful sample processing after collection and rapid motion of the FNA needles. Because the speed with which the needle can be moved manually is limited, Kanno *et al.*[57] recommended the use of a spring-loaded biopsy needle. These new EUS-FNA needles improved the quality and quantity of the histological samples. Thus, EUS-FNA would provide new opportunities to diagnose AIP histologically.

FUTURE PERSPECTIVES OF ENDOSCOPY FOR THE DIAGNOSIS OF AIP AND IgG4-SC

THE ICDC WERE proposed to demonstrate a diagnostic algorithm and to provide flexibility in the diagnostic approach by considering the advantages and limitations of endoscopy.[17] When computed tomography (CT) or magnetic resonance imaging (MRI) findings are typical for AIP, diagnostic ERCP is not required. If pancreatic imaging yields indeterminate findings (segmental or focal enlargement) and localized narrowing of MPD, ERCP is basically required to make a diagnosis of definitive AIP. When a patient with a focal/segmental swelling of the pancreas does not fulfill two or more Level 1 criteria of the ICDC for type 1 AIP, pancreatic core biopsy is recommended for diagnosing AIP and differentiating it from pancreatic cancer. Moon and Kim[40] proposed an endoscopic strategy to distinguish AIP from pancreatobiliary malignancies; however, ERP has no role in the AIP diagnosis in this strategy. In cases of suspected AIP with obstructive jaundice associated with biliary strictures, we recommended an endobiliary biopsy to exclude malignancy at the time of carrying out ERCP for biliary decompression. Based on these guidelines, we propose an endoscopic strategy for diagnosing AIP (Fig. 11). Further studies will be required to assess the diagnostic abilities of several endoscopic tools, such as ERP and EUS-FNA.

CONCLUSIONS

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY and EUS play important roles in the differential diagnosis between AIP or IgG4-SC and pancreatobiliary malignancies. Various endoscopic devices have been developed for ERCP and EUS procedures and have improved the diagnostic capabilities of pancreatobiliary diseases. Because the gold standard for the diagnosis of AIP and IgG4-SC is based on histology, further improvements are required to obtain pancreatic tissues efficiently and safely.

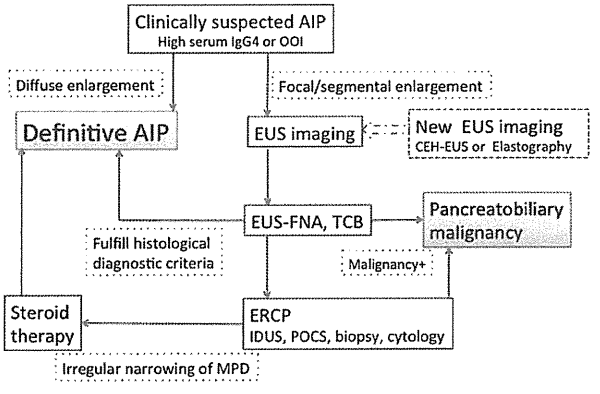

Figure 11 Endoscopic strategy for diagnosing autoimmune pancreatitis (AIP). CEH-EUS, contrast enhanced harmonic endoscopic ultrasonography; ERCP, endoscopic retrograde cholangiopancreatography; EUS-FNA, EUS-guided fine-needle aspiration; IDUS, intraductal ultrasonography; IgG4, immunoglobulin G4; MPD, main pancreatic duct; OOI, other organ involvement; POCS, peroral cholangioscopy; TCB, Trucut biopsy.

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CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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IgG4-related disease

Terumi Kamisawa, Yoh Zen, Shiv Pillai, John H Stone

IgG4-related disease is a protean condition that mimics many malignant, infectious, and inflammatory disorders. This multi-organ immune-mediated condition links many disorders previously regarded as isolated, single-organ diseases without any known underlying systemic condition. It was recognised as a unified entity only 10 years ago. Histopathology is the key to diagnosis. The three central pathology features of IgG4-related disease are lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis. The extent of fibrosis is an important determinant of responsiveness to immunosuppressive therapies. IgG4-related disease generally responds to glucocorticoids in its inflammatory stage, but recurrent or refractory cases are common. Important mechanistic insights have been derived from studies of patients treated by B-cell depletion. Greater awareness of this disease is needed to ensure earlier diagnoses, which can prevent severe organ damage, disabling tissue fibrosis, and even death. Identification of specific antigens and T-cell clones that drive the disease will be the first steps to elucidate the pathogenesis of IgG4-related disease.

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Introduction

IgG4-related disease is a multi-organ immune-mediated condition that mimics many malignant, infectious, and inflammatory disorders.[1–3] The diagnosis links many conditions once regarded as isolated, single-organ diseases without any known underlying systemic condition (panel 1). IgG4-related disease, unrecognised as a unified disease for well over a century, has been likened to a "black crow flying through the dark night".[4] The disease has many similarities to sarcoidosis and some forms of systemic vasculitis, other protean diseases in which the histopathological findings are consistent across a wide range of organ systems.

Two introductory points deserve emphasis. First, awareness of IgG4-related disease is essential because the disorder is treatable. The therapeutic approaches contrast starkly with those of some of the disorders in the differential diagnosis (panel 2), especially malignant disorders but also autoimmune diseases, such as Sjögren's syndrome, granulomatosis with polyangiitis, and membranous nephropathy. Second, knowledge of the immune dysregulation associated with IgG4-related disease explains much about the human immune system. Progress in elucidation of the basis of IgG4-related disease has been swift.

Epidemiology

Understanding of the epidemiology of IgG4-related disease is hampered by insufficient awareness of the diagnosis, because the disease did not appear in medical publications until 2003.[5,6] Definitive diagnosis generally necessitates a biopsy, insightful interpretation of the pathology, and rigorous clinicopathological correlation. Although the overall prevalence of type 1 (IgG4-related) autoimmune pancreatitis in Japan has been estimated as 2·2 cases per 100 000 population,[7] the pancreas is only one of more than a dozen organs affected by IgG4-related disease. Therefore, this is surely a substantial underestimate of the true prevalence, especially because the study from which this estimate was derived was done early in the development of knowledge about IgG4-related disease. The prevalence of various organ manifestations also remains unclear, but autoimmune pancreatitis, sialadenitis (particularly of the submandibular gland), dacryoadenitis, and IgG4-related retroperitoneal fibrosis are the most common disease features.

The typical patient with IgG4-related disease is a middle-aged to elderly man.[7,8] For autoimmune pancreatitis, the mean age at diagnosis is 67 years and the male to female ratio is three to one.[7] The male predilection contrasts strikingly with classic autoimmune diseases, for which female patients can outnumber male cases by nine to one. For organs of the head and neck, however—the orbits, salivary glands, and sinuses—the proportions of male and female patients are roughly equal.[9] The reasons for differential organ expression in the two sexes are unclear.

We know of no reports of familial cases of IgG4-related disease. More extensive studies of patients from several ethnic backgrounds are needed before any conclusions can be drawn about genetic susceptibility.[10–13]

Pathology

Histology features

Histopathology is the key to diagnosis of IgG4-related disease. Three central pathology features are lymphoplasmacytic infiltration, obliterative phlebitis, and storiform fibrosis (figure 1).[14] The lymphocytes and plasma cells are polyclonal. Eosinophils are also commonly present and extreme examples can resemble eosinophilic organopathy, but neutrophilic infiltration is

Search strategy and selection criteria

Data for this Review were identified by searches of Medline, PubMed, and references from relevant articles with the search terms "IgG4", "IgG4-related", and "autoimmune pancreatitis". We focused on publications since the year 2000, since the multiorgan nature of IgG4-related disease was not recognised until 2003. We also cited other important publications from earlier years pertaining to conditions now recognised as part of the IgG4-related disease spectrum.

Panel 1: Conditions once regarded as individual disorders now recognised to be part of IgG4-related disease

- Autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis)
- Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
- Fibrosing mediastinitis
- Hypertrophic pachymeningitis
- Idiopathic hypocomplementaemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
- Inflammatory pseudotumour (affecting the orbits, lungs, kidneys, and other organs)
- Küttner's tumour (affecting the submandibular glands)
- Mikulicz's disease (affecting the salivary and lacrimal glands)
- Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
- Periaortitis and periarteritis
- Inflammatory aortic aneurysm
- Retroperitoneal fibrosis (Ormond's disease)
- Riedel's thyroiditis
- Sclerosing mesenteritis

rare in IgG4-related disease. Necrosis, discrete granulomata, and xanthogranulomatous changes are atypical and, when present, suggest other diagnoses.[9,14]

Fibrosis is a histological prerequisite for the diagnosis. Some fibrosis is present in all cases, even in patients who present shortly after symptom onset. Storiform fibrosis, characterised by radially arranged collagen fibres that seem to weave through the tissue, typifies the unique pattern associated with IgG4-related disease (figure 1).[9,14] Because of its typically patchy distribution, however, storiform fibrosis sometimes escapes detection through sampling error, especially if the tissue is obtained by needle biopsy. Acellular, keloidal fibrosis is not characteristic of IgG4-related disease.

The characteristic venous lesion, obliterative phlebitis, is defined as the partial or complete obliteration of medium-sized veins.[9,14] This finding should be distinguished from fibrous venous occlusion with no inflammation, which is known to occur in other conditions (eg, primary sclerosing cholangitis). Obliterated veins commonly appear as an inflammatory nodule next to a patent artery (figure 1) and sometimes can be identified as veins only through elastin staining (figure 1).

See Online for appendix

The histological appearance is similar for all organs. Some more organ-specific changes, however, are noteworthy. Both obliterative arteritis and focal neutrophilic infiltration, rare in other organs, can occur in the lungs. Obliterative arteritis lacks the vascular-wall necrosis typical of many systemic vasculitides. The neutrophilic infiltration in IgG4-related pulmonary disease is typically seen in alveolar spaces.[15] Other minor pathological differences between organs include the absence of storiform fibrosis within lacrimal glands and lymph nodes, and the lower frequency of obliterative phlebitis in salivary glands, lacrimal glands, lymph nodes, and kidneys.[9,14] The rarity of fibrosis in lymph nodes means that the diagnosis of IgG4-related disease is difficult on the basis of lymph-node pathology alone.

Immunostaining

High numbers of IgG4-positive plasma cells at tissue sites are a disease hallmark, even when serum IgG4 concentrations are normal. The finding of IgG4-positive plasma cells is helpful in differentiating IgG4-related disease from other plasma-cell-rich disorders, such as primary sclerosing cholangitis and multicentric Castleman's disease.[16,17]

In interpretation of tissue IgG4 stains, several caveats must be borne in mind.[14] First, IgG4-positive plasma cells are generally present diffusely throughout lesions of IgG4-related disease. Focal aggregations of IgG4-positive cells are atypical. Second, the absolute number of IgG4-positive plasma cells must be interpreted according to the specific tissue. An international pathology consensus statement proposed, for example, that for sialadenitis the cutoff value should be at least 100 cells per high-power field, but that in the pancreas more than 50 cells per high-power field is compatible with a diagnosis of autoimmune pancreatitis.[14] Third, the ratio of IgG4 to IgG-positive plasma cells must be at least 40% (it is typically 70% or higher) (figure 1). Finally, and most importantly, IgG4-related disease cannot be diagnosed on the basis of infiltration by IgG4-positive cells alone, because these plasma cells can be present in other inflammatory and neoplastic disorders.[18]

Fibrosis commonly predominates over a long disease course, and the histological features can become less specific in patients with longstanding disease. Thus, some undiagnosed or untreated cases of IgG4-related disease are consigned to categories such as so-called idiopathic end-stage diseases—for example, chronic pancreatitis, cryptogenic cirrhosis, or honeycomb lung. Review of biopsy samples taken earlier in the course, however, could document the progression of IgG4-related disease from a lymphoplasmacytic infiltrate to one characterised mainly by fibrosis.

Morphological change of affected organs

Transformations in the gross pathology of affected organs occur. The pancreas and kidneys become diffusely enlarged (appendix). By contrast, ductal organs (eg, bile duct, bronchus) assume the appearance of a pipe stem, with diffuse wall-thickening (figure 1).[19] In IgG4-related disease, discrete small nodules within an otherwise unremarkable organ are seen occasionally, indicating site-selective immune reactions. The background tissue is histologically not inflamed, even though its tissue constituents are the same as those of affected regions (figure 1). This feature contrasts with those of classic autoimmune disorders such as autoimmune hepatitis and Graves' disease, in which the organs are diffusely inflamed and the cells targeted are injured non-selectively.

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Panel 2: **Differential diagnosis of IgG4-related disease, by organ system**

Orbits and periorbital tissues
- Lymphoma
- Graves' orbitopathy
- Granulomatosis with polyangiitis
- Sarcoidosis

Ears, nose, and sinuses
- Allergic disease
- Churg-Strauss syndrome
- Granulomatosis with polyangiitis
- Sarcoma
- Chronic infection

Salivary glands
- Lymphoma
- Sjögren's syndrome
- Sarcoidosis
- Sialodocholithiasis

Meninges
- Idiopathic hypertrophic pachymeningitis
- Inflammatory myofibroblastic tumour
- Lymphoma
- Granulomatosis with polyangiitis
- Giant-cell arteritis
- Langerhans-cell histiocytosis
- Sarcoidosis

Pituitary
- Neoplasms
- Histiocytosis
- Primary hypophysitis
- Secondary hypophysitis (sarcoidosis, ipilimumab-induced)

Lymph nodes
- Multicentric Castleman's disease
- Lymphoma
- Sarcoidosis
- Systemic lupus erythematosus

Thyroid gland
- Thyroid lymphoma
- Differentiated thyroid carcinoma (papillary variant)
- Other malignant disease

Lungs
- Malignancy (adenocarcinoma or bronchioloalveolar carcinoma)
- Inflammatory myofibroblastic tumour
- Sarcoidosis
- Granulomatosis with polyangiitis
- Castleman's disease
- Lymphomatoid granulomatosis
- Idiopathic interstitial pneumonitis
- Erdheim-Chester disease

Aorta
- Primary large-vessel vasculitis (giant-cell or Takayasu's arteritis)
- Sarcoidosis
- Erdheim-Chester disease
- Histiocytosis
- Lymphoma
- Infectious aortitis

Retroperitoneum
- Lymphoma
- Sarcoma
- Methysergide-induced retroperitoneal fibrosis
- Idiopathic retroperitoneal fibrosis

Kidney
- Lymphoma
- Renal-cell carcinoma
- Drug-induced tubulointerstitial nephritis
- Idiopathic membranous glomerulonephritis
- Pauci-immune, necrotising glomerulonephritis
- Sarcoidosis
- Sjögren's syndrome
- Systemic lupus erythematosus (membranous nephropathy)

Pancreas
- Pancreatic cancer

Biliary tree
- Pancreatic cancer
- Cholangiocarcinoma
- Primary sclerosing cholangitis

Liver
- Cholangiocarcinoma
- Hepatocellular carcinoma
- Primary sclerosing cholangitis

Prostate
- Benign prostatic hypertrophy

Skin
- Cutaneous lymphoma

Pathophysiology

Two parallel processes could underlie the observed pathological features in IgG4-related disease. The first is the induction of a polarised CD4-positive T-cell population, yet to be conclusively characterised, which activates innate immune cells, including macrophages, myofibroblasts, and fibroblasts to drive fibrosis. This process could involve the collaboration of activated B-lineage cells, possibly expanded plasmablasts that enter the damaged tissue along with activated CD4-positive T cells. The second is a feedback negative regulatory process, which might involve the generation of IgG4-secreting plasmablasts, plasma cells, and IgG4 antibodies.

Several reasons lead us to believe that IgG4 itself is not a driver of pathogenesis. IgG4 antibodies undergo a

process called Fab-arm exchange within the endosomal compartment of endothelial cells.[20] In this process, the heavy-chain dimers of an IgG4 molecule dissociate and each hemi-molecule associates with another, different, hemi-IgG4 protein. Most secreted IgG4 is therefore functionally monovalent and cannot crosslink antigens to form the lattice structure found in immune complexes. As a result, IgG4 antibodies do not directly fix complement, they bind poorly to activating Fc receptors, and they are generally thought to be non-inflammatory. IgG4 concentrations are also known to rise after IgE concentrations decline in allergic disorders. For these reasons, one possible view of IgG4 is that it perhaps evolved as a non-inflammatory antigen sink that is largely monovalent, the purpose of which is to mop up antigen in an attempt to attenuate inflammatory processes. In theory, however, IgG4 could be pathogenic and could perhaps collaborate with circulating lectins to activate complement in disease lesions. However, no evidence to support such a view is available.

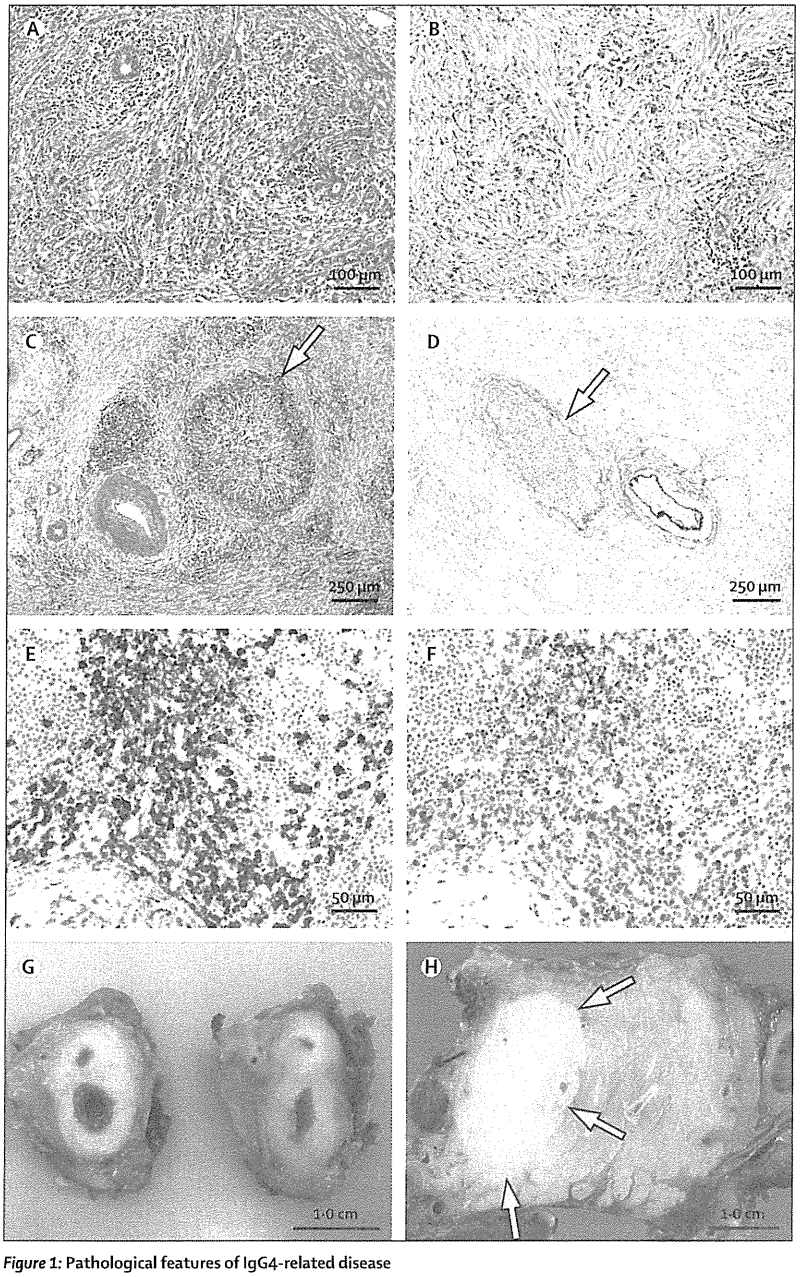

Figure 1: **Pathological features of IgG4-related disease**
(A) Submandibular gland affected by a fibroinflammatory process; the inflammatory-cell infiltrate consists mainly of lymphocytes and plasma cells, and whorls of fibrosis are evident throughout the tissue. (B) Storiform fibrosis is apparent in a sclerotic area of the bile duct in this patient with IgG4-related sclerosing cholangitis. (C) In obliterative phlebitis, an obliterated vein creates an inflammatory nodule (arrow) next to a patent artery (from a patient with type 1 [IgG4-related] autoimmune pancreatitis). (D) Van Gieson stain (for elastin) shows obliterative phlebitis (arrow); the adjacent artery is intact. (E) and (F): Immunostaining for IgG4 shows many IgG4-positive plasma cells in (E) a lacrimal-gland biopsy sample; (F) the IgG-stained section shows that the ratio of IgG4 to IgG-positive plasma cells is above 80%. (G) Transection of the bile duct with IgG4-related sclerosing cholangitis shows diffuse wall thickening. (H) A well circumscribed nodule (arrows) is formed in the pancreatic head of this patient with type 1 (IgG4-related) autoimmune pancreatitis; the background pancreas is unremarkable.

T cells are implicated in the disease pathogenesis for several reasons, the most obvious of which is the observation that many CD4-positive T cells are present at sites of inflammation in IgG4-related disease. The finding of a linkage to HLA class II in a Japanese population indirectly supports a role for CD4-positive T cells.[12] Although Th2 cells that secrete interleukins 4, 5, and 13 are commonly implicated in the pathogenesis of fibrosis, many diseases, including tuberculosis and Crohn's disease, have a more dominant Th1 phenotype that is linked to fibrosis. Indeed, in IgG4-related disease, conflicting reports have implicated Th1 cells and Th2 cells in disease pathophysiology.[21,22] Studies published this year suggest that circulating Th2 memory cells do accumulate in a proportion of people with IgG4-related disease but only if they have concomitant atopic disease.[23,24] The precise nature of the disease-causing CD4-positive T cells remains to be resolved.

The molecular mechanisms that drive the IgG4 class switch remain unknown, but roles for interleukins 4 and 10 have been suggested.[25] Although a link between Th2 cells and both the IgG4 class switch and the disease process is tempting, our understanding of the role of T cells in isotype switching has evolved. Class switching to IgE is driven by T-follicular helper cells that make interleukin 4, not by Th2 cells themselves.[26] Therefore, some polarised T cells, perhaps Th1 or Th2 cells or those of a yet to be identified phenotype, could drive the storiform fibrosis and obliterative phlebitis. A separate T-follicular helper cell response might bring about generation of the IgG4 phenotype that helps define the disease.

One plausible model of pathogenesis is that in genetically susceptible individuals, generally older men, some environmental insult, possibly an encounter with a specific microbe, triggers tissue damage and a break in immunological tolerance. A self-antigen-driven, polarised CD4-positive T-helper response would induce a fibrotic pathological process at one or several sites. The reasons for the targeting of particular organs remain unclear. Within these organs, increased CD4-positive T cells would

activate innate immune cells that secrete other cytokines and drive the pathology. The memory CD4-positive T cells that orchestrate the disease are presumably sustained by antigen-presenting B cells, which would explain the clinical improvement after B-cell depletion.[27,28] Either the same antigen or some event triggered by fibrosis could trigger a parallel T-follicular helper response that would induce the development of germinal centres within lymph nodes and the generation of IgG4-secreting plasmablasts and long-lived plasma cells. The existence of these cells can be inferred because rituximab does not completely attenuate IgG4 concentrations in treated patients.

Diagnosis

Tissue biopsy is the gold standard for diagnosis in most settings. Review of archived pathology samples can confirm the diagnosis of IgG4-related disease on histological findings alone, if large specimens such as submandibular gland resections are available. Even with supporting histopathological evidence, however, clinicopathological correlation is needed to confirm the diagnosis.

Imaging is an important part of the diagnostic approach in many organs. Under some circumstances, the imaging findings in autoimmune pancreatitis (appendix) can be regarded as diagnostic, provided that the clinical presentation is also straightforward. Because imaging findings elsewhere in the body are less specific, tissue diagnosis is important for patients with no pancreatic involvement. Several samples or repeat biopsy procedures might be needed. PET can help to define the extent of organ involvement and can also be helpful in monitoring disease activity after treatment.[29]

Differentiation of IgG4-related disease from malignant tumours is crucial. Common mimics of multi-organ IgG4-related disease are Sjögren's syndrome, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome), sarcoidosis, and multicentric Castleman's disease. Single-organ diseases such as primary sclerosing cholangitis must also be excluded (table).

Four sets of diagnostic criteria for specific organs have been devised.[30–33] Comprehensive diagnostic criteria for IgG4-related disease have been proposed for practical use by non-specialists.[34]

Serology

High serum IgG4 concentrations are neither sufficiently sensitive nor specific for diagnosis. Serum IgG4 concentrations are useful for screening but are unreliable as a single diagnostic marker. About 20% of patients with type 1 autoimmune pancreatitis have normal serum IgG4 concentrations at presentation.[35,36] The proportion with normal concentrations can be somewhat lower among patients with multi-organ disease,[37] but many diagnoses can be associated with high serum IgG4 concentrations. In one study, 22% of patients who did not have IgG4-related disease had serum IgG4 concentrations higher than twice normal.[37] Other studies have shown that 4–10% of both healthy and disease controls, including patients with pancreatic cancer, have high serum IgG4 concentrations.[36,38,39] Increased ratios of IgG4 to total IgG (>10%) or IgG1 (>24%) increase diagnostic specificity, especially when IgG4 concentrations are only slightly raised.[40] The identification of high numbers of plasmablasts within blood by flow cytometry is more sensitive than serum IgG4 concentrations,[41,42] but such assays are not yet widely available.

Monitoring of serum IgG4 concentrations seems useful in assessment of disease activity in some patients, but this measurement should never be used as the sole determinant in treatment decisions. The serum IgG4 concentration declines substantially after glucocorticoid treatment in most patients, but in one study did not return to the normal range in 115 (63%) of 182 patients.[43] Clinical relapses occurred in 10% of patients who had persistently normal IgG4 concentrations.[43]

Nephelometry assays for IgG4 are prone to error in the presence of large antigen excess, potentially leading to gross underestimates of the serum IgG4 concentration because flocculation does not occur. This effect, known as the prozone phenomenon, can lead to false reports of normal serum IgG4 concentrations and has been observed frequently in patients with IgG4-related disease with serum IgG4 concentrations many times higher than the upper limit of normal.[44] Appropriate dilution of the serum sample during the assay process prevents the prozone effect.

Organ involvement

Constitutional and musculoskeletal symptoms

The presentation of IgG4-related disease is typically subacute, with symptoms and organ dysfunction evident for months or even years before diagnosis. Disease can progress haltingly, with occasional spontaneous improvements (generally temporary) or long plateaus of disease quiescence in a specific organ. In such cases, disease recurrence in an organ known to be affected or the emergence of new organ involvement can lead to diagnosis.

Weight loss of 5–10 kg can occur over months, but fevers and hectic presentations are unusual. Fatigue commonly accompanies IgG4-related disease, especially when the disease affects several organ systems. We have observed a diffuse array of musculoskeletal symptoms, including arthralgias and enthesopathy (inflammation in the site at which a tendon inserts into a bone). To date, however, no histopathological abnormalities of synovium or tenosynovium have been confirmed.

Orbits

The typical ophthalmic presentation involves swelling within the ocular region or frank proptosis, generally

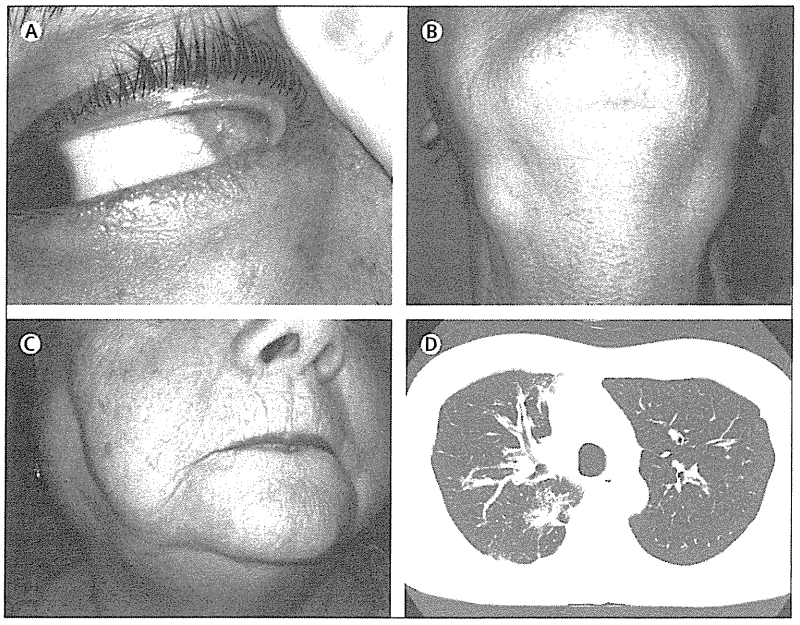

Figure 2: **Clinical features**
(A) Dacryoadenitis; the typical ophthalmic presentation of IgG4-related disease involves some swelling within the ocular region or proptosis, generally caused by lacrimal-gland enlargement. (B) Submandibular gland enlargement in a patient who had previously undergone a Whipple procedure for presumed pancreatic adenocarcinoma that was shown by histopathology to be type 1 (IgG4-related) autoimmune pancreatitis. (C) Parotid disease in a 70-year-old woman who had a classic case of what used to be called Mikulicz disease, the triad of parotid, lacrimal, and submandibular gland enlargement. (D) Chest CT shows thickening of the bronchovascular bundle in the right lung as well as a posterior ground-glass infiltrate.

caused by lacrimal-gland enlargement (dacryoadenitis; figure 2).[45] Proptosis can also result from orbital pseudotumours that do not affect the lacrimal gland, from involvement of extraocular muscles (orbital myositis), and from combinations of these abnormalities. Less common ophthalmic manifestations of IgG4-related disease are scleritis, disease of the nasolacrimal duct (obstruction), and compression of peripheral nerves in the area of the orbit, particularly the trigeminal and infra-orbital nerves.[46–49]

Salivary glands

Both major and minor salivary glands can be affected by IgG4-related disease.[50–52] A disorder known for more than 100 years as Mikulicz's disease, consisting of dacryoadenitis and enlargement of the parotid and submandibular glands, is now recognised as a classic IgG4-related condition.[53,54] Isolated enlargement of the submandibular glands (figure 2) is a common finding in IgG4-related disease. By contrast, in Sjögren's syndrome parotid enlargement predominates. Parotid disease in IgG4-related disease can also be extensive, however (figure 2), as can sublingual-gland enlargement. Xerostomia commonly accompanies IgG4-related disease, but it is generally less severe than in Sjögren's syndrome and, in contrast to Sjögren's syndrome, can improve with immunosuppression.

Ears, nose, and throat

Allergic features occur in a substantial subset of patients with IgG4-related disease and in many cases are most prominent in the ears, nose, and throat (eg, allergic rhinitis, nasal polyps, chronic sinusitis, nasal obstruction, and rhinorrhea). Many patients have longstanding histories of allergy (rhinitis, nasal polyps, asthma, mild eosinophilia) before the full IgG4-related disease phenotype emerges. Mild to moderate peripheral eosinophilia, sometimes up to 20% or more of the leucocyte count, is common. High serum IgE concentrations, sometimes higher than ten times the upper limit of normal, are also common. However, most patients with IgG4-related disease are not atopic.[24] A subset of non-atopic individuals has peripheral-blood eosinophilia and high concentrations of IgE, which suggests that processes inherent to IgG4-related disease itself rather than atopy contribute to the eosinophilia and high IgE concentrations.

IgG4-related disease can lead to diffuse inflammation in the pharynx, hypopharynx, and Waldeyer's ring, frequently associated with mass lesions.[55] Tracheal inflammation and vocal-cord involvement have also been described. Further studies are needed of the potential relation between IgG4-related disease and so-called idiopathic subglottic stenosis or isolated tracheal inflammation. Mass lesions can occur in the sinuses, and destructive lesions in the middle ear and facial bones have been reported.[56,57]

Thyroid gland

Riedel's thyroiditis (appendix) has been linked convincingly to IgG4-related disease.[58] Fibrosing Hashimoto's thyroiditis also seems to be in the range of IgG4-related disease pathology.[59,60] More controversial is the assertion that a substantial proportion of patients with Hashimoto's thyroiditis also have an IgG4-related disorder. A form of thyroid disease referred to as IgG4-related thyroiditis, distinct from Hashimoto's thyroiditis, is purported,[61] but further study is needed.

Lymphadenopathy

The lymphadenopathy associated with IgG4-related disease is typically either generalised or localised disease adjacent to an affected organ.[62] The affected lymph nodes are generally 1–3 cm in diameter and non-tender. Involvement of the cervical, supraclavicular, submandibular, axillary, hilar, mediastinal, para-aortic, retroperitoneal, and inguinal nodes has been described. Diagnosis of IgG4-related disease through lymph-node biopsy is difficult because lymph nodes are unlikely to show the degree of fibrosis seen in other organs.

Thoracic aorta, branches of the aorta, and coronary lesions

IgG4-related aortitis can lead to aneurysms or dissections in the thoracic aorta.[63–65] This feature, commonly an incidental radiological finding, is also sometimes an unexpected finding at surgery. In contrast to giant-cell and

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Takayasu's arteritis, which mainly affect the primary aortic branches, especially the subclavian arteries, IgG4-related disease tends to spare these vessels, at least in terms of clinical manifestations. No definitive histopathological investigations of primary aortic branch vessels have been undertaken, but small case series substantiate the concept that medium-sized blood vessels can also be affected by IgG4-related disease.[66,67] Coronary artery lesions in IgG4-related disease are rare but documented.[68]

Chronic periaortitis and retroperitoneal fibrosis

So-called idiopathic retroperitoneal fibrosis, known for decades as Ormond's disease,[69] is now classified within a larger disease grouping known as chronic periaortitis (appendix). The three major components of chronic periaortitis are IgG4-related retroperitoneal fibrosis, IgG4-related abdominal aortitis, and IgG4-related perianeurysmal fibrosis.[65,70]

The presentations of IgG4-related chronic periaortitis can be subtle and non-specific, leading to diagnostic delay. Common presentations are: a poorly localised pain in the back, flanks, lower abdomen, or thighs; leg oedema; and hydronephrosis from ureteral involvement. The disease targets three sites: periaortic/arterial regions, involving connective tissue around the abdominal aorta or its first branches (appendix); periureteral areas, tending to cause ureteral obstruction and hydronephrosis; and a plaque-like mass that broadly involves the retroperitoneum.

IgG4-related disease is the cause of up to two-thirds of cases of idiopathic retroperitoneal fibrosis.[69,70] In advanced disease, the ratio of IgG4-positive plasma cells to the total number of plasma cells in tissue can be more helpful diagnostically than the overall number of IgG4-positive plasma cells per high-power field. Even if the classic lymphoplasmacytic infiltrate is not evident in longstanding cases, both storiform fibrosis and obliterative phlebitis are commonly identified (appendix)

Lungs

The greatest diversity of clinical and radiological presentations is seen in the lungs.[71] Thickening of the bronchovascular bundle, best shown by CT, is a characteristic lesion (figure 2); it shows the tendency of IgG4-related disease to track along bronchi and blood vessels, which course together.[15] Other radiological features of IgG4-related disease include pulmonary nodules, ground-glass opacities, pleural thickening, and interstitial lung disease. The last of these, which mimics non-specific interstitial pneumonitis and other forms of interstitial fibrosis, emphasises the fibrotic tendencies of IgG4-related disease.

Kidneys

The most characteristic form of IgG4-related renal disease is tubulointerstitial nephritis, which has the same histopathology as in other organs: lymphoplasmacytic infiltrate with IgG4 predominance among plasma cells; storiform fibrosis; and moderate tissue eosinophilia (figure 3).[72] IgG4-related tubulointerstitial nephritis is distinguished from many other forms of organ involvement by profoundly low concentrations of complement. The basis of this feature remains poorly understood but is unlikely to be explained by IgG4 itself, because this molecule does not bind complement effectively. One plausible explanation is that hypocomplementaemia in IgG4-related disease results from the formation of immune complexes that contain IgG1 or IgG3, subclasses that are raised to a lesser degree in many cases and bind complement more effectively.

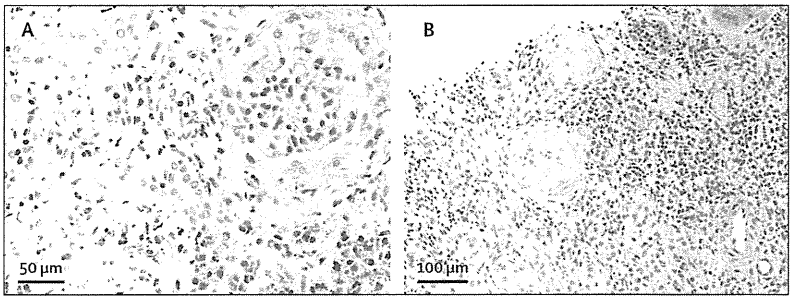

Figure 3: **IgG4-related disease in the kidney**
(A) Tubulointerstitial nephritis in the setting of IgG4-related disease shows the histopathology found in other organs: a lymphoplasmacytic infiltrate (with an IgG4 predominance among plasma cells), storiform fibrosis, and moderate tissue eosinophilia. (B) Obsolescent glomeruli.

Many patients with IgG4-related tubulointerstitial nephritis have substantial enlargements of the kidney and hypodense lesions evident on CT (appendix). Patients with this disorder can experience advanced renal dysfunction and even end-stage renal disease. Substantial proteinuria can develop, but concentrations are generally subnephrotic. Kidneys affected by IgG4-related disease can undergo atrophy, even in the setting of good clinical responses to therapy.[73]

Membranous glomerulonephropathy also occurs in IgG4-related disease.[74] Although the antibody to PLA2 receptor linked to idiopathic membranous glomerulonephritis is primarily of the IgG4 subclass,[75] this specific antibody is not associated with IgG4-related membranous glomerulonephropathy.[76]

Pancreas

The pancreas was the first organ recognised to be associated with high serum IgG4 concentrations.[5,6,77] Two subtypes of autoimmune pancreatitis are known, only one of which (type 1) is associated with IgG4-related disease.[3,78] Type 1 autoimmune pancreatitis, the more common form worldwide, is characterised by the classic histopathological findings of lymphoplasmacytic sclerosing pancreatitis. Type 2, by contrast, has no relation to IgG4-related disease and is identified on the basis of histological features of neutrophilic infiltration into the epithelium of the pancreatic duct.[79–81]

The most common clinical presentation of autoimmune pancreatitis is obstructive jaundice, induced by

concomitant IgG4-related sclerosing cholangitis. Secondary diabetes mellitus occurs in about half of cases, which makes treatment with glucocorticoids difficult in many patients. Differentiation of autoimmune pancreatitis from pancreatic cancer is crucial to avoid unnecessary surgery. The nearly diagnostic CT features of autoimmune pancreatitis include diffuse pancreatic enlargement with delayed enhancement and a capsule-like low-density rim (appendix).[80,81] Diffuse, irregular narrowing of the main pancreatic duct on endoscopic retrograde and magnetic resonance cholangiopancreatography is also highly specific for autoimmune pancreatitis. In cases of segmental autoimmune pancreatitis, skipped narrowed lesions, side-branch derivation from the narrowed portion, and relatively less upstream dilatation on pancreatography suggest autoimmune pancreatitis rather than pancreatic cancer (appendix).[81,82] In PET studies, uptake of fluorodeoxyglucose in organs other than the pancreas known to be affected by IgG4-related disease suggests autoimmune pancreatitis.[29,83]

International consensus diagnostic criteria for autoimmune pancreatitis were proposed in 2011.[30] Under these criteria, the diagnosis can be made by a combination of parenchymal and ductal imaging, serum IgG4 concentrations, pancreatic histology, extrapancreatic disease, and glucocorticoid responsiveness. Endoscopic ultrasonography-guided fine-needle aspiration is a useful diagnostic approach to exclude pancreatic cancer and should be attempted before any empirical trial of glucocorticoid treatment is undertaken. Several cases of pancreatic cancer have been reported in patients with type 1 autoimmune pancreatitis.[84,85] Pancreatic stones occur with increased frequency among these patients.[79,86]

IgG4-related sclerosing cholangitis and cholecystitis

Type 1 autoimmune pancreatitis is commonly accompanied by IgG4-related sclerosing cholangitis.[19] Whether the limited intrapancreatic bile-duct stricture associated with autoimmune pancreatitis should be regarded as a biliary manifestation of IgG4-related disease is controversial, because such stenoses can be induced by compression from the swollen pancreas.[87] The histology of IgG4-related sclerosing cholangitis includes obliterative phlebitis and transmural fibrosis with dense infiltration of IgG4-positive plasma cells and T cells.

IgG4-related sclerosing cholangitis must be differentiated from both primary sclerosing cholangitis and hilar cholangiocarcinoma. Neither serum IgG4 concentrations nor cholangiographic or cholangioscopic findings differentiate these disorders clearly.[88–91] Thus, endoscopic transpapillary biopsy is generally needed. Although cholangiocarcinoma can be excluded by endoscopic biopsy, the superficial nature of samples obtained by this procedure limits their usefulness for diagnosis of IgG4-related sclerosing cholangitis.[92]

IgG4-related cholecystitis can occur with sclerosing cholangitis. Thickening of the gallbladder wall is detected on imaging, but it is asymptomatic in most cases.[81]

Other organs

IgG4-related disease seldom, if ever, affects the brain parenchyma but it is one of the most common causes of hypertrophic pachymeningitis.[93] IgG4-related disease is also an unheralded cause of hypophysitis. IgG4-related hypophysitis can lead to hormone deficiencies from both the anterior and posterior pituitary.[94] MRI shows sellar enlargement and thickening of the pituitary stalk.

Sclerosing lesions of both the mediastinum and mesentery have been described.[95,96] In fibrosing mediastinitis, compression of vital mediastinal structures can result from proliferation of invasive fibrous tissue within the mediastinum. A review of 15 patients with fibrosing mediastinitis showed that a substantial proportion of cases are within the IgG4-related disease spectrum.[95] The relation between these cases and antecedent infections with histoplasma, if any, remains unclear.

The inflammatory process in sclerosing mesenteritis seems to originate at the mesenteric root.[96] The ensuing process merges imperceptibly with retroperitoneal fibrosis and can evolve in a devastating manner, encasing vital organs and obviating any attempt at surgical resection.

Several clinical presentations of IgG4-related skin disease have been reported. The most common is the presence of erythematous papules. These lesions typically affect the head and neck but have also been described on the trunk and limbs.[97] Among individuals with darkly pigmented skin, hyperpigmented lesions have been observed. Peripheral-nerve lesions typically consist of perineural masses, up to 3 cm in diameter. These are commonly seen on MRI in the absence of overt clinical manifestations.[48]

The diagnosis of IgG4-related prostate disease is commonly made presumptively when the initiation of treatment for IgG4-related disease in other organs mediates abrupt symptomatic relief of apparently benign prostatic hypertrophy. Both radiological demonstration of prostatic enlargement and biopsy-proven IgG4-related prostatic disease have been reported.[98]

Treatment

Glucocorticoids

Most clinical manifestations of IgG4-related disease respond to glucocorticoids. These agents are the first-line, standard-of-care approach for most patients.[43,99] However, no randomised treatment trials have been done, and few large retrospective examinations have been reported. One treatment approach uses a starting prednisolone dose of 0·6–1·0 mg/kg daily.[30,43] After 2–4 weeks, the dose is tapered by 5 mg every 1–2 weeks according to clinical responses (eg, clinical manifestations, blood tests, and follow-up imaging studies).

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Practice varies as to whether the prednisolone is discontinued entirely after 2 or 3 months or maintained at a low dose. A single-group trial of prednisolone in Japan showed complete remissions in only 61% of patients at 1 year despite continuation of maintenance doses of prednisone in all patients.[100]

Clinical improvement after the start of glucocorticoid therapy is rapid, and a follow-up serological assessment should be done about 2 weeks after treatment initiation. Follow-up radiological assessment is also appropriate for some types of organ involvement, such as the pancreas, biliary tree, lungs, and kidneys. PET with fluorodeoxyglucose is useful to assess treatment response.[29] A swift response to glucocorticoids is reassuring and provides further diagnostic confirmation if a tissue diagnosis was not possible before the start of therapy. A poor response to glucocorticoids, however, should raise the possibility of other diagnoses, particularly cancer.

The response to glucocorticoids varies according to the affected organs and the degree of fibrosis.[8] Both endocrine and exocrine pancreatic function can improve in autoimmune pancreatitis, and salivary secretion in IgG4-related sialadenitis is more likely to improve after glucocorticoid therapy than is the glandular function of Sjögren's syndrome.[100–103] By contrast, retroperitoneal fibrosis, sclerosing mesenteritis, and fibrosing mediastinitis are less amenable to therapy with glucocorticoids, underscoring the importance of early diagnosis and treatment.[104]

Conventional steroid-sparing agents

Drugs such as azathioprine, mycophenolate mofetil, and methotrexate, all used widely in gastroenterology, rheumatology, and transplant medicine as means of achieving additional immunosuppression and sparing patients the effects of long-term glucocorticoids, are commonly chosen for this purpose in IgG4-related disease.[79,105] However, none has been tested in prospective, controlled studies, and evidence for their efficacy beyond that offered by concomitant glucocorticoid therapy is scarce. Rigorous assessment of these treatments in IgG4-related disease is needed.

B-cell depletion

Rituximab was used initially in patients who did not respond to glucocorticoids, conventional steroid-sparing agents, or both, under the assumption that B-cell depletion might ameliorate the condition putatively mediated by high serum concentrations of IgG4.[27,48,106] The fundamental assumption underlying this approach now seems incorrect or at least not entirely true, but careful mechanistic studies of patients with IgG4-related disease treated with rituximab have led to several important observations and novel insights about the pathophysiology of this disorder. First, B-cell depletion targets the subset of plasma cells that produce IgG4 in IgG4-related disease.[27,28] They seem to achieve this action by depleting all circulating CD20-positive cells (ie, B cells), which interferes in turn with the repletion of short-lived plasma cells making IgG4. In other words, the plasma cells generating IgG4 in IgG4-related disease are mainly of the short-lived type that naturally undergo apoptosis within weeks. Once these cells disappear as programmed, they cannot be repleted after rituximab administration because their precursors—CD20-positive B cells—are not available.

Second, IgG4-positive plasmablasts (positive for IgG4, CD38, CD37, and CD19lo cells) seem to be a good biomarker for IgG4-related disease and are probably superior to serum IgG4 concentrations for diagnosis and monitoring of disease activity.[41,42] We have seen patients with substantially raised numbers of IgG4-positive plasmablasts whose serum IgG4 concentrations were normal in the setting of active disease. These plasmablasts decline quickly after B-cell depletion and can be useful in identifying when to readminister rituximab in some patients, but this question needs further study.

Future perspectives

In only 10 years since the recognition of extrapancreatic features in patients with autoimmune pancreatitis signalled a systemic, multi-organ disease, substantial progress has been achieved in IgG4-related disease. The disease has been identified in nearly every organ system and most of its clinical features have been mapped. Nomenclature has been standardised, and a consensus has been achieved about the major and minor pathological manifestations.[3,14] Effective treatments have been identified and important advances have been made in understanding of disease pathophysiology through mechanistic studies of B-cell depletion. Greater awareness in the medical community of this protean disease is needed to ensure earlier diagnoses, which can prevent severe organ damage, disabling tissue fibrosis, and death. The epidemiology of IgG4-related disease remains poorly understood, mainly because of challenges in recognition and differentiation from the many disorders it mimics. Blood-based diagnostic tests through serology or flow cytometry would be a step forward in case identification. Greater understanding of the immunopathology of IgG4-related disease promises new insights into human immunology and interactions between various T-cell pathways, as well as the possibility of new mechanisms of disease centred around novel T-cell phenotypes. Identification of specific antigens and T-cell clones that drive the disease will be crucial steps in elucidating the pathogenesis of IgG4-related disease.

Contributors

All the authors contributed equally to the literature search, planning, writing, and editing of the Review and all have approved the submission of this version.

Declaration of interests

JHS is the principal investigator in a Genentech-funded trial of rituximab in IgG4-related disease and has consulted for Genentech on this disease. The other authors declare no competing interests.

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