IgG4-related disease: can non-classical histopathological features or the examination of clinically uninvolved tissues be helpful in the diagnosis?

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ABSTRACT
IgG4-related disease (IgG4-RD) is an increasingly recognised inflammatory and fibrosing condition that commonly shows multisystem involvement. The disease may mimic malignancy and other inflammatory or immune-mediated disorders, but usually has a good response to corticosteroid therapy, underlining the requirement for recognition of the condition. Accurate diagnosis requires careful interpretation of varying combinations of serum IgG4 levels, radiological features and characteristic histopathological appearances within an appropriate clinical setting. The presence of 'classical' histopathological features together with an elevated tissue IgG4+ plasma cell count and IgG4 to IgG ratio is often diagnostic and at the very least can strongly support a clinicopathological diagnosis of IgG4-RD. The authors describe the most recent diagnostic criteria for IgG4-RD, especially the histopathological features. The authors then discuss the merits of examining tissues that may be more easily obtainable than those that commonly show the 'classical' histopathological features, but within which not all of these 'diagnostic' features may be present. The authors conclude that while a combination of 'classical' histopathological features and an elevated tissue IgG4+ plasma cell count is the gold standard for diagnosis, examination of tissues that show some but not all of these features can, in the appropriate context, provide useful supporting evidence for a clinicopathological diagnosis of IgG4-RD.

INTRODUCTION
Immunoglobulin G subclass 4-related disease (IgG4-RD) is a recently described fibro-inflammatory condition characterised by tumefactive lesions with characteristic histopathological features. While originally described in the pancreas and termed 'autoimmune pancreatitis' (AIP), the systemic nature of the disease has since become apparent.[1] Most organ systems have been reported to be involved and these are listed in box 1. Biopsies from extra-pancreatic lesions reveal histopathological features with striking similarities to those of AIP, although subtle differences between organs exist.[3] A dense lymphoplasmacytic infiltrate with abundant IgG4+ plasma cell infiltration, storiform fibrosis, obliterative phlebitis and variable presence of eosinophils are the histological hallmarks of the disease.

The epidemiology of IgG4-RD remains poorly described. Certain demographic features have been reported: the majority of patients being older than 50 years and male subjects (62%—83%).[4][5] The true incidence and prevalence of IgG4-RD is unknown; despite increasing recognition across many specialties, most practitioners are still unaware of the disease. In one nationwide study in Japan, the estimated prevalence of AIP was 0.8 cases per 100 000 persons.[6] In the USA, 11% of patients undergoing pancreatic resections for benign indications had AIP.[7] As it has become recognised that the spectrum of IgG4-RD involves a variety of clinical entities once regarded as entirely separate diseases, the reported prevalence of disease will undoubtedly increase (table 1).

DIAGNOSIS
The nomenclature and diagnostic criteria used to define this disease continue to evolve. At a recent consensus meeting of specialists in Boston, the term 'IgG4-related disease' (IgG4-RD) was adopted to include type I AIP and other systemic manifestations.[8] In contrast, type II AIP was considered a separate histopathological entity and not included in this characterisation.[9] Diagnostic criteria for AIP and later IgG4-RD have been defined and redefined by many groups in an attempt to incorporate the key clinical, radiological, immunological and histopathological features of disease. The most widely recognised criteria are listed in tables 2—4. The main challenge has become differentiating IgG4-RD from other causes of tumefactive lesions, especially those that are malignant and other disease mimics that require alternative therapy. This requires careful consideration of the clinical context in addition to supportive histopathological correlation in most cases.

The clinical manifestations of IgG4-RD are variable and depend on the activity of disease and the pattern of organ involvement. Some patients are asymptomatic at presentation, with abnormalities detected incidentally on radiology, biochemistry and immunology or when examining histopathology specimens. Others may present with urgent disease requiring immediate treatment to prevent organ dysfunction and permanent damage. Single or multiple organ disease may be evident at diagnosis or there may be evolution of organ involvement over months to years. A history of allergy is increasingly recognised with features such as atopy, eczema, asthma, or chronic sinusitis reported in up to 40% of patients.[13]

Box 1 Organs that may be involved in immunoglobulin G subclass 4-related disease[2]

- ► Pancreas
- ► Bile duct
- ► Liver
- ► Gastrointestinal tract
- ► Salivary and lacrimal glands
- ► Orbit
- ► Retroperitoneum and mesentery
- ► Aorta
- ► Thyroid
- ► Lung
- ► Kidneys
- ► Breast
- ► Skin
- ► Pituitary gland
- ► Meninges
- ► Prostate
- ► Lymph nodes
- ► Pericardium

Imaging of organs involved in IgG4-RD cannot reliably differentiate between cancer and benign disease. There may be radiological clues in organs such as the pancreas and the aorta but manifestations in the lung and kidney can be hugely variable.[14 15]

An elevated serum IgG4 concentration is not diagnostic of IgG4-RD and is non-specific and so must be considered in the appropriate clinical context. A polyclonal elevation of serum IgG4 concentration is seen in 70%—80% of patients, although also in 5% of healthy individuals and 10% of patients with pancreatobiliary malignancy.[16] A normal level may be seen in 20%—30% of patients and does not exclude the diagnosis.[17] Reported sensitivities and specificities of serum IgG4 in diagnosis vary from 68% to 95% and 80% to 99%, respectively.[18 19] Interpretation of these levels depends on the defined upper limits of normal for serum IgG4 across institutions, variable prevalence

Table 1 Conditions once viewed as separate disease entities and now recognised as a manifestation of immunoglobulin G subclass 4-related disease (adapted from Khosroshahi and Stone[2])

Original terminology	Organ target
Autoimmune pancreatitis	Pancreas
Sclerosing cholangitis	Biliary tree
Mikulicz's syndrome	Salivary and lacrimal glands
Kuttner's tumour	Submandibular glands
Riedel's thyroiditis	Thyroid
Retroperitoneal fibrosis (Ormond's disease)	Retro peritoneum
Mediastinal fibrosis	Mediastinum
Chronic sclerosing aortitis	Aorta
Inflammatory abdominal aortitis	Abdominal aorta
Orbital pseudotumour	Orbital adnexa
Eosinophilic angiocentric fibrosis	Orbits, sinuses and nasal cavities
Multifocal fibrosclerosis	Orbits, thyroid gland, retroperitoneum, mediastinum and other tissues
Idiopathic hypocomplementaemic tubulointerstitial nephritis with extensive tubulointerstitial deposits	Kidney

Table 2 Diagnostic criteria for AIP and IgG4-RD: The Japan—Korea consensus criteria for the diagnosis of AIP[10]

I-1	Pancreatic parenchymal imaging reveals diffuse/segmental/focal gland enlargement, occasionally with a mass and/or a rim of hypo attenuation
I-2	Pancreaticobiliary duct imaging reveals diffuse/segmental/focal duct narrowing, often with stenosis of the bile duct
II	Elevated serum IgG or IgG4 concentration and detection of autoantibodies
III	Lymphoplasmacytic infiltration of pancreatic tissue with abundant IgG4-positive plasma cells

A diagnosis of AIP requires the presence of criteria I-1 and I-2 plus either criterion II or criterion III.
AIP, autoimmune pancreatitis; IgG4-RD, immunoglobulin G subclass 4-related disease.

of type II AIP in studies and the timing of measurements in relation to disease activity and treatment. Retrospective studies of AIP suggest a level of twice the upper limit of normal (>2.8 g/l) has a specificity of 99% in differentiating AIP from pancreatic cancer, but this needs to be confirmed prospectively.[16] Multiple organ involvement has been associated with higher serum IgG4 concentrations.[20]

Elevated serum IgE, peripheral eosinophilia and inflammatory markers such as erythrocyte sedimentation rate and C reactive protein have been reported in association with the disease but are non-specific.[13] Serum antinuclear antibody titres are positive in almost half of patients and several autoantibodies have been identified in AIP but none have been validated as diagnostic markers.

TREATMENT

The necessity and urgency of treatment for patients with IgG4-RD depend on the involvement of vital organs and risk of organ dysfunction or failure. In some cases, watchful waiting is prudent and will lead to spontaneous resolution of manifestations, although this has been associated with a higher risk of relapse.[21] Patients often have a rapid but commonly unsustained response to glucocorticoid treatment.[22] The response is most dramatic in those with early inflammatory disease compared with patients in whom fibrosis is predominant. The clinical response is usually paralleled by radiological, biochemical and serological improvement. The serum IgG4 level declines but often remains elevated rather than completely normalising.[17] This persistent elevation of serum IgG4 has been inconsistently associated with a higher risk of disease relapse.[22] Small studies

Table 3 Diagnostic criteria for AIP and IgG4-RD: The Mayo Clinic criteria for the diagnosis of AIP, the HISORt criteria[11]

1. Histopathology: *one or both* criteria required	Characteristic appearances within biopsy or resection material*
	At least 10 IgG4-positive plasma cells per high power field within areas of lymphoplasmacytic infiltrate
2. Imaging & serology: *all three* criteria required	Diffusely enlarged pancreas with delayed and 'rim' enhancement
	Irregular pancreatic duct
	Increased serum IgG4 concentration
3. Response to steroid therapy: *all three* criteria required	Unexplained pancreatic disease after a full clinical workup, including exclusion of cancer
	Raised serum IgG4 concentration and/or extrapancreatic organ involvement with increased numbers of tissue IgG4-positive plasma cells
	Resolution or marked improvement in disease with steroid therapy

A diagnosis of AIP requires the presence of criteria within at least one of these groups.
*This includes a lymphoplasmacytic infiltrate, 'storiform' fibrosis and obliterative phlebitis; the inflammatory cell infiltrate alone is *not* sufficient to meet this criterion.
AIP, autoimmune pancreatitis; IgG4-RD, immunoglobulin G subclass 4-related disease.

Table 4 Diagnostic criteria for autoimmune pancreatitis and IgG4-RD: The Comprehensive Clinical Diagnostic (CCD) criteria for IgG4-RD[12]

1. Clinical examination showing characteristic diffuse/localised swelling or masses in single or multiple organs
2. Haematological examination shows elevated serum IgG4 concentrations (>135 mg/dl)
3. Histopathological examination shows:
    (1) Marked lymphocyte and plasmacytic infiltration and fibrosis
    (2) Infiltration of IgG4+ plasma cells: ratio of IgG4+ to IgG+ cells >40% and >10 IgG4+ plasma cells/HPF

Definite: 1 + 2 + 3
Probable: 1 + 3
Possible: 1 + 2

However, it is important to differentiate IgG4-RD from malignant tumours of each organ (eg, cancer, lymphoma) and similar diseases (eg, Sjogren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, Churg—Strauss syndrome) by additional histopathological examination.
Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4-RD.

HPF, high power microscope field; IgG4-RD, immunoglobulin G subclass 4-related disease.

have reported lessening of the lymphoplasmacytic infiltrate and reductions in IgG4+ plasma cell count after steroid therapy.[23]

In those with recurrent or refractory disease, second line agents have included azathioprine, mycophenolate mofetil and methotrexate, although there are no randomised or controlled clinical trial data to support their utility. B cell depletion with rituximab therapy is an alternative approach and a similar rapid clinical response with reductions in serum IgG4 level and tissue IgG4+ plasma cell numbers can occur.[24 25] Bortezomib, a proteasome inhibitor with cytotoxicity against plasma cells, has also been effective in case reports of recurrent IgG4-related lung and orbital disease.[26] However, long-term follow-up data are not available for these therapies.

HISTOPATHOLOGY

The classical histopathological features of IgG4-RD are based primarily on morphology, with the IgG4+ plasma cell count as important supporting evidence. This emphasis on morphological features is the focus of the recent consensus document prepared following discussions at the international symposium on IgG4-RD held in Boston.[8] The key classical morphological features are: (1) lymphoplasmacytic inflammation, (2) fibrosis that is at least focally storiform and (3) obliterative phlebitis. Eosinophils may also be prominent although this is a variable feature. The diagnosis can then be supported by the finding, on immunohisto-chemistry, of prominent IgG4+ plasma cells within the inflammatory cell infiltrate.

The minimum number of IgG4+ plasma cells required to provide useful support to a diagnosis of IgG4-RD is a matter of some debate but depending on the anatomical site of the lesion, between >10 and >200 IgG4+ plasma cells per high power microscope field (HPF), taken as the mean of the three fields containing the greatest number of such cells, is the current recommendation. The size of the HPF clearly varies between microscopes and it seems a good practice for research papers on this topic to include the size of the HPF for the microscope used in the study. However, in terms of the use of IgG4+ plasma cell counts in a diagnostic setting in individual cases, there are likely to be other factors that more significantly affect the reproducibility of the IgG4+ plasma cell count and therefore correction of the cell count for HPF size is not currently considered critical.[8] Early studies commonly used a cut-off of 10 IgG4+ plasma cells per HPF for this purpose and the latest Japanese diagnostic criteria still recommend this minimum cell count in the appropriate clinical context.[12] The recent Boston consensus document advises that a cut-off of 10 IgG4+ plasma cells per HPF does not generally provide sufficiently high diagnostic specificity and instead suggests minimum cell counts that vary according to anatomical site.[8]

Recently, it has become apparent that the ratio of IgG4+ plasma cells to the total number of IgG+ plasma cells is also important; an IgG4+ to total IgG+ plasma cell ratio of at least 40% is commonly recommended when considering a diagnosis of IgG4-RD.[27] This ratio has been adopted by the latest Japanese

Table 5 Conditions that may be characterised by prominence of tissue IgG4+ plasma cells in the absence of IgG4-RD

Site	Condition	Mean IgG4+ plasma cell count	Mean IgG4+ to total IgG+ plasma cell ratio
Strehl et al[28]			
Oral cavity	Epulis plasmacellularis Radicular cyst	69	0.32
Colon	Diverticulitis	19	0.11
Synovium	Rheumatoid arthritis	55	0.4
Skin	Inflammatory skin conditions	26	0.21
Various	Carcinoma-associated inflammatory response (esp. squamous cell carcinoma)	34	0.23
Other studies			
Lymph nodes*[29]	Castleman's disease	5	0.05
	Follicular hyperplasia	8	0.04
	Interfollicular plasmacytosis	27	0.08
Colon	Inflammatory bowel disease[30]		
Lung[31]	Rosai—Dorfman disease		
Aorta[32]	Periaortitis		
Various	Carcinoma, for example, pancreatic†[33] Lymphoma especially low-grade marginal zone and follicular‡[27]	10	

*This study found that when using a minimum cut-off of 50 IgG4+ plasma cells per HPF and an IgG4+ to total IgG plasma cell ratio of 0.4, only one case (interfollicular plasmacytosis) remained positive for increased tissue IgG4+ plasma cell numbers and this patient had a history of Hashimoto's thyroiditis.
†This study found 10 IgG4+ plasma cells per HPF in one of 20 cases of pancreatic adenocarcinoma.
‡Low-grade lymphoma may develop on the background of IgG4-RD.
HPF, high power microscope field; IgG4-RD, immunoglobulin G subclass 4-related disease.

diagnostic criteria but there is less emphasis on a precise minimum ratio within the Boston consensus criteria.[12] The latter suggests that while a ratio of 40% is increasingly commonly used, the morphological appearances are of primary importance and a high IgG4+ to total IgG ratio only provides useful supporting evidence in this context when the absolute number of IgG4+ plasma cells is also raised.[8]

Based on the morphological features and in the presence of appropriately increased numbers of IgG4+ plasma cells, the Boston consensus document recommends using the phrase 'histologically highly suggestive of IgG4-related disease' usually when at least two of the three key morphological features are present and 'probable histological features of IgG4-related disease' when only one morphological feature is present or when the specimen is a needle biopsy.

It is important to recognise that increased numbers of IgG4+ plasma cells in tissue alone are non-specific for IgG4-RD and a variety of other conditions may also have increased numbers present (table 5). The number of IgG4+ plasma cells per HPF seen in individual cases of non-IgG4-related inflammatory conditions can be very high (eg, over 100), while the mean IgG4+ to total IgG+ plasma cell ratio is usually no more than 0.4 (40%), although in individual cases can be greater than 0.8 (80%).[28] The inflammatory reaction associated with various carcinomas (including pancreatic adenocarcinoma) and certain low-grade lymphomas may also be associated with prominence of IgG4+ plasma cells.[28] [33] This is one of the key reasons for restricting a (histopathological) diagnosis of IgG4-RD to cases with appropriate clinical features and in which increased numbers of IgG4+ plasma cells are present in the context of characteristic morphological features, that is, using the histopathological features correctly within one of the sets of diagnostic criteria discussed earlier in this review. An exception to this general rule is sites such as the orbit, meninges and lymph nodes, where a diagnosis of IgG4-RD can be achieved without the requirement for (storiform) fibrosis (table 6). While pseudotumour formation with classical (storiform) fibrosis is often a characteristic feature

Table 6 Sites where a diagnosis of IgG4-RD may be established without the requirement for all of the classical morphological features described elsewhere, especially storiform fibrosis

Lymph nodes	Lymph nodes draining sites where 'classical' IgG4-related disease is present*[34]
Orbit	Dacroadenitis[35]
Meninges	Chronic meningitis[36]
Duodenum/ampulla of Vater	AIP/IgG4-related sclerosing cholangitis†[37]

In these tissues, the histopathological diagnosis is most commonly based on a combination of dense lymphoplasmacytic inflammation and prominent IgG4+ plasma cells.
*A diagnosis of IgG4-RD in this setting would require additional criteria, for example, characteristic histopathological features within a tissue/organ associated with the lymph nodes.
†Biopsies from this area may provide useful supporting evidence for the presence of IgG4-RD but biopsies from the duodenum alone are unlikely to show all of the classical features: prominent IgG4+ plasma cells have been described in association with type 1 AIP.
AIP, autoimmune pancreatitis; IgG4-RD, immunoglobulin G subclass 4-related disease.

of IgG4-RD, the condition can also be manifest in sites where the tissue involvement is more diffuse in nature but in which histopathological examination still reveals fibrosis in addition to lymphoplasmacytic inflammation. Examples of this pattern of involvement include interstitial nephritis and interstitial pneumonitis.[38] [39]

There are situations in which a diagnosis of IgG4-RD is under consideration on clinical grounds and where histopathological examination of accessible tissue that may not be clinically or radiologically involved in the disease process may be requested in order to attempt to support the diagnosis. This is often the case in patients with suspected AIP where endoscopic ultrasound guided aspiration and/or biopsy of a pancreatic mass can be challenging and yields insufficient material for analysis. The extent to which histopathological features and IgG4+ plasma cell counts or IgG4+ to IgG ratios can be used in this context is currently uncertain. Examples of tissues that may undergo histopathological examination in this and related situations include the ampulla of Vater, duodenum, bile duct, gallbladder and the colon.

Figure 1 An example of the classical histopathological features of type 1 autoimmune pancreatitis. (A) Acinar atrophy (top left) with storiform fibrosis (bottom right) (magnification ×200). (B) Prominent lymphoplasmacytic inflammation with a lymphoid aggregate and germinal centre (magnification ×200). (C) Lymphocytic venulitis (magnification ×400). (D) Prominent immunoglobulin G subclass 4 (IgG4)+ plasma cells within the inflammatory cell infiltrate (IgG4 immunohistochemistry; magnification ×400).
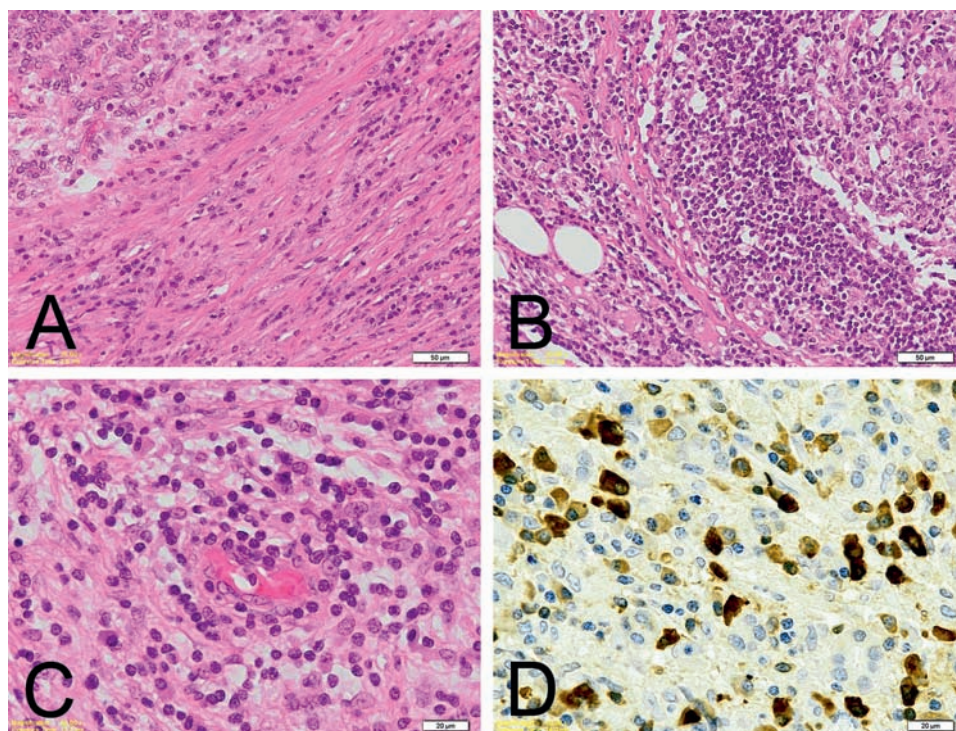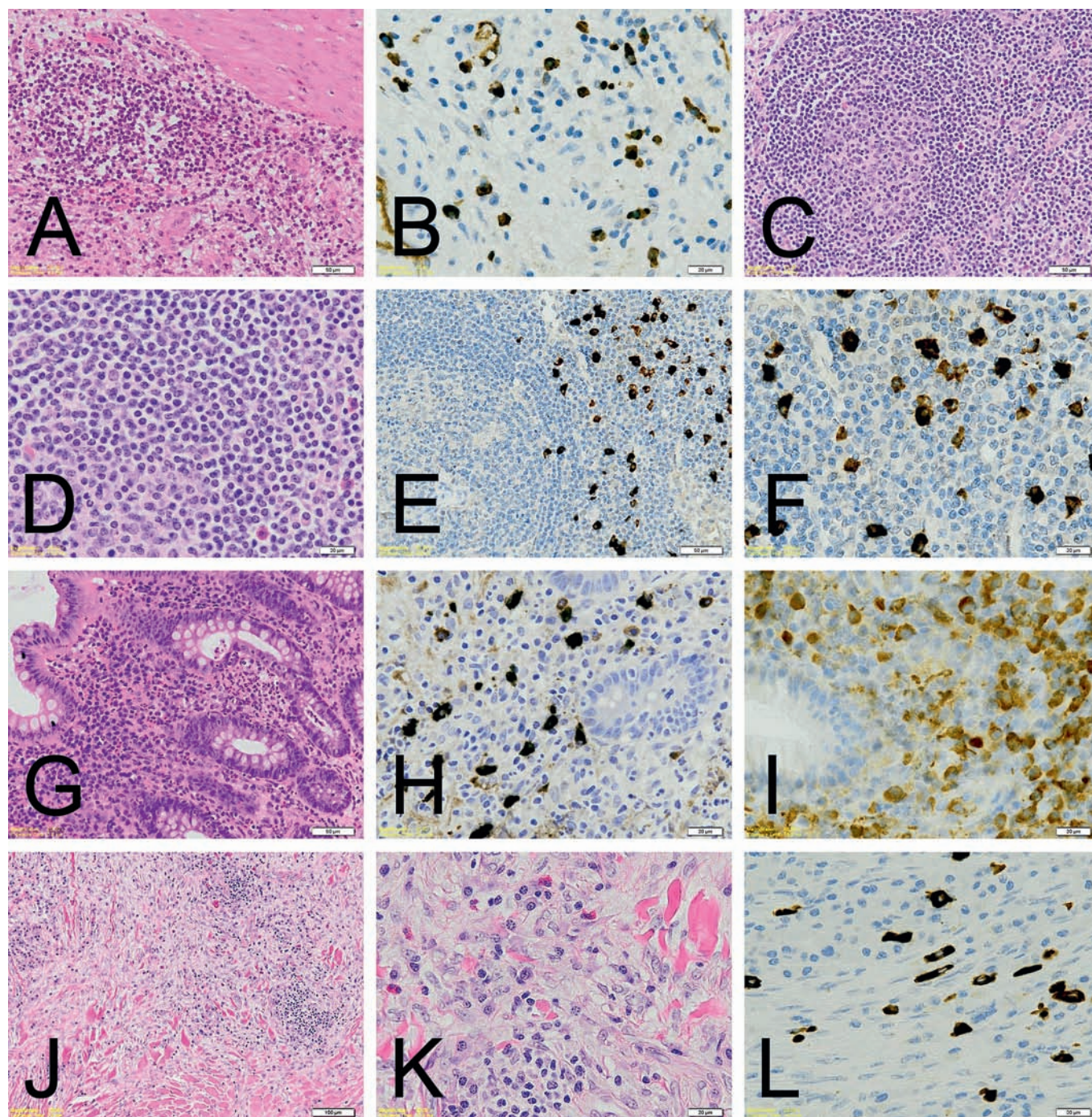
Figure 2 Examples of cases that include prominent immunoglobulin G subclass 4 (IgG4)+ plasma cells at extra-pancreatic sites. (A, B) Gallbladder wall from a patient with type 1 autoimmune pancreatitis (the same case as illustrated in figure 1) that may be useful even in the absence of pancreatic tissue when establishing the diagnosis of IgG4-related disease (IgG4-RD). (A) Prominent transmural lymphoplasmacytic inflammation and fibrosis was present, including this serosal lymphoid aggregate with associated fibrosis (magnification ×200). (B) Prominent IgG4+ plasma cells (IgG4 immunohistochemistry; magnification ×400). (C–F) Regional lymph node from a patient with IgG4-related chronic gastric ulceration (magnification ×200). (C) Reactive germinal centre. (D) Paracortex with occasional eosinophils (magnification ×400). (E) Prominent IgG4+ plasma cells within paracortex (IgG4 immunohistochemistry; magnification ×200). (F) Over 20 IgG4+ plasma cells/high power microscope field (IgG4 immunohistochemistry; magnification ×400). (G–I) Colonic biopsy from patient with chronic colitis and sclerosing cholangitis that was not believed to represent an example of IgG4-RD. (G) Colonic mucosa showing features consistent with active inflammatory bowel disease (magnification ×200). (H) Prominent IgG4+ plasma cells within lamina propria (IgG4 immunohistochemistry; magnification ×400). (I) Large numbers of IgG+ plasma cells in the lamina propria such that the IgG4+ to total IgG plasma cell ratio was 18%–20% (IgG immunohistochemistry; magnification ×400). (J–L) Extrahepatic bile duct in a case of IgG4-related sclerosing cholangitis. (J, K) Bile duct wall showing lymphoplasmacytic inflammation and prominent storiform fibrosis and the reason why a combination of duodenal and bile duct biopsies may be helpful in establishing a diagnosis of IgG4-RD (J: magnification ×100; K: magnification ×400). (L) Prominent IgG4+ plasma cells (IgG4 immunohistochemistry; magnification ×400).

Ampullary or distal duodenal biopsies may be taken when a diagnosis of AIP is being considered, even when the mucosa appears normal on endoscopic examination. Associations have been inconsistently described between the presence of increased numbers of IgG4+ plasma cells in the ampullary mucosa and the presence of AIP.[37 40] In one study of 19 patients with AIP, a minimum of 10 IgG4+ plasma cells within at least one HPF was required to consider a case as positive; this reportedly had 100% specificity and 53% sensitivity for diagnosing AIP.[37] However, as the histopathological features of the ampullary mucosa were otherwise normal, the appearances would not allow assessment even as 'probable histological features of IgG4-related disease' under the Boston criteria.[8] Another study of 29 patients with AIP or IgG4-related sclerosing cholangitis found that bile duct biopsies commonly contained prominent IgG4+ plasma cells (at least 10 IgG4+ plasma cells per biopsy specimen) as well as showing storiform fibrosis and therefore recommended both duodenal/ampullary and bile duct biopsies in patients where these conditions are suspected.[40] In contrast, a further study of 19 patients with AIP found no association between the presence of this condition and increased numbers of IgG4+ plasma cells within corresponding gastric or duodenal biopsies, although the total number of plasma cells in the gastric mucosa was increased in AIP patients compared with controls.[41] Overall, it seems reasonable to suggest that the finding of prominent IgG4+ plasma cell numbers in a duodenal or ampullary biopsy can be used as supporting evidence for the presence of IgG4-RD in the appropriate context, but also that absence of this feature does not exclude this diagnosis.

Cholecystectomy specimens are regularly received by histopathology laboratories and while they most commonly show a spectrum of acute and/or chronic cholecystitis related to gallstones, they may also show both morphological and immunohistochemical features that can, in the appropriate clinical context, support a diagnosis of IgG4-RD. In particular, a combination of variably dense lymphoplasmacytic inflammation and (storiform) fibrosis may be seen. On initial examination and without knowledge of the full clinical details, these appearances could easily be interpreted as florid non-specific chronic cholecystitis. Furthermore, eosinophils are not uncommonly prominent within the inflammatory cell infiltrate even when the process has occurred secondary to cholelithiasis. Such specimens are present within departmental archives and retrospective examination, especially when combined with IgG4+/total IgG+ plasma cell immunohistochemistry, while not entirely specific for the presence of IgG4-RD, can be very useful in terms of supporting a diagnosis of IgG4-RD.[42] Indeed, such retrospective examination can provide valuable histopathological evidence for IgG4-RD without the requirement for an additional invasive procedure to obtain further tissue.

The relationship between chronic colitis and IgG4-RD is complex. There appears to be a clinical association between inflammatory bowel disease (IBD) and chronic pancreatitis in that just over 1% of IBD patients also have chronic pancreatitis with or without symptoms.[43] Patients with proven AIP may also have a chronic colitis; a study of 71 patients with AIP revealed IBD (ulcerative colitis or Crohn's disease) in around 6% (vs around 0.5% in the general population) and demonstrated 10 IgG4+ plasma cells per HPF within the colonic mucosa of the single ulcerative colitis patient from which colonic biopsy material was available.[30]

Inflamed colorectal mucosa from patients with active IBD that is not believed to be IgG4-related may contain prominent IgG4+ plasma cells, with over 20 such cells per HPF possible in this setting.[28] However, this study documented that the mean IgG4+ plasma cell count was not usually above 10 per HPF and the IgG4+ to total IgG+ plasma cell ratio was low (eg, not above 0.1/10%). In contrast, patients with proven IgG4-RD (especially AIP) may have an (often clinically refractory) IBD-like colitis and in this situation the numbers of IgG4+ plasma cells within the colorectal mucosa may be greater than 10 per HPF.[44] Therefore, significant overlap exists between the colorectal mucosa IgG4+ plasma cell counts in colitis patients with and without an established diagnosis of IgG4-RD. It is probably best to restrict a diagnosis of IgG4-RD colitis to cases where the overall clinical features support this diagnosis and in which the IgG4+ to total IgG plasma cell ratio is at least 40%. As an isolated feature, the IgG4+ plasma cell count within colonic biopsies is not likely to provide clear supporting evidence for—or against—the presence of IgG4-RD in most situations.

IgG4-RD may also be manifest within the gastrointestinal tract via the development of inflammatory polyps that show the classical morphological and immunohistochemical (ie, IgG4+ plasma cells) features of IgG4-RD.[45] These lesions are easily accessible with an endoscope for biopsy or polypectomy and may support a diagnosis in the appropriate clinical context or prompt an active search for other systemic disease. Portal tract fibro-inflammatory nodules have similarly been described in one manifestation of IgG4-related sclerosing cholangitis.[23] These fibro-inflammatory nodules are not essential for the diagnosis; the portal tracts may contain a prominent IgG4+ plasma cell infiltrate but with only relatively mild fibrosis.[46] Identification of IgG4-related sclerosing cholangitis is important as the disease is often steroid-responsive in its inflammatory phase, but progresses more rapidly to liver failure if unrecognised and untreated.[47]

CONCLUSION

The concept of IgG4-RD is evolving rapidly and while diagnostic algorithms have been developed to aid identification of the condition when characteristic clinical, radiological and/or

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Take-home messages

► IgG4-related disease (IgG4-RD) is an evolving entity with the potential for multisystem involvement and therefore very varied patterns of clinical presentation. Recognition of the disease is essential in order to allow differentiation from malignancy and prompt treatment with immunosuppressant agents, which is often very successful.

► Accurate diagnosis of IgG4-RD relies on a combination of clinical, radiological and histopathological features. The emphasis for the last of these is now on the classic morphological criteria of dense lymphoplasmacytic inflammation, storiform fibrosis and obliterative venulitis, supported by the presence of prominent IgG4+ plasma cells.

► Examination of tissues from sites such as the duodenum/ampulla of Vater and the gallbladder can provide useful supporting evidence for a diagnosis of IgG4-RD in the appropriate clinical context. However, colonic biopsy specimens from patients with inflammatory bowel disease may also contain prominent IgG4+ plasma cells and therefore examination of these may be less useful when attempting to substantiate a diagnosis of IgG4-RD.

histopathological features are present, it is very unlikely that any single criterion will be diagnostic if used in isolation. Overlaps with similar diseases that do not appear to form part of the spectrum of IgG4-RD are becoming increasingly recognised and differentiation of these from 'true' IgG4-RD is both important and challenging. Within histopathology, this is particularly true when tissues show prominence of IgG4+ plasma cells in the absence of the classical morphological features. However, when interpreted in the context of the overall features of a case, it is possible that histopathology can still provide useful—if sometimes circumstantial—supporting evidence for the diagnosis in this setting.

We believe that the best way of refining the criteria for the diagnosis of IgG4-RD, as with any definition of a novel condition, must be in relation to clinical outcome, for example, response to treatment and long-term prognosis. This highlights the need for studies looking at the whole spectrum of patients in whom this diagnosis has been considered—those fulfilling current diagnostic criteria as well as those with some but not all of the criteria—and then relating all of the clinical and pathological findings to clinical follow-up.

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