

An overview of the diagnosis and management of immunoglobulin G4-related disease

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Patients with immunoglobulin G4-related disease (IgG4-related disease) can present to any clinical specialty. It is an uncommon, immune-mediated, fibroinflammatory process that can progress to organ failure and death if untreated.

Presentation is protean and can mimic other conditions, including systemic diseases (e.g., sarcoidosis), single-organ disorders (e.g., primary sclerosing cholangitis) and malignant disease (i.e., hematologic [lymphoma] and mass lesions [pancreatic cancer]). However, IgG4-related disease is eminently manageable; early treatment prevents organ damage and long-term morbidity. Nevertheless, recognition of IgG4-related disease is challenging and requires clinicians to have an awareness of the disease.

We provide an overview of current understanding of the cause, pathogenesis, diagnosis and management of IgG4-related disease, and we outline challenges to be addressed to improve care for patients (Box 1).

What is IgG4-related disease?

Immunoglobulin G4-related disease is a systemic immune-mediated fibroinflammatory disease that presents as organ dysfunction or mass lesions with lymphoplasmacytic infiltration in single or multiple organs. It can result in organ failure or death if untreated. This disease has been recognized as a distinct clinical entity since the beginning of the 21st century,¹ when investigators in Japan reported that extrapancreatic manifestations of autoimmune sclerosing

pancreatitis shared a distinct histopathologic signature with the parent disease.² Since then, the histologic features of infiltrative IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis have been reported in almost every organ (Table 1)^{3–14} and share similar features with apparently unrelated pathologic entities, such as dacryoadenitis (Mikulicz disease) to retroperitoneal fibrosis (Ormond disease).

What pathophysiologic mechanisms are involved in IgG4-related disease?

The pathophysiology of IgG4-related disease is uncertain. Both genetic predisposition and environmental triggers may prompt aberrant immune pathways to perpetuate the disease.¹⁵ An overview of current understanding of the disease is shown in Figure 1.^{15–23}

The pathology seems to be primarily affected by B cells. Patients with IgG4-related disease carry dominantly expanded clones of tissue B cells that produce immunoglobulins with greater antigen affinity and, preferentially, make more IgG4. However, the pathogenic role of IgG4 remains a contentious issue in view of its immune-modulating properties.^{15,24} Expansion of regulatory T cells is observed,²² which may contribute to fibrosis. Furthermore, a modified type 2 T-helper (Th2) cellular response²⁵ augments B-cell changes.^{26,27} Maturation of B cells may also be directly stimulated by microbial components.²⁸

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Box 1: Search strategy

We searched publications in MEDLINE and PubMed from 2001 onwards (when the multisystem nature of the disease was recognized) using the key phrases "IgG4," "IgG4-related," "IgG4-associated," "IgG4 pancreatitis" and "autoimmune pancreatitis." Recommendations are based on information from international consensus guidelines.

KEY POINTS

- IgG4-related disease is a multisystem fibroinflammatory disorder that can present to any clinical specialty and can lead to organ failure if left untreated.
- The pathophysiology is unclear but is likely to be affected by B-cell lineage with a modified type 2 T-helper cell response, supporting and contributing to fibrosis.
- The diagnosis requires prior awareness of the disease and a skillful correlation of clinical, biochemical, radiologic and histopathologic clues.
- IgG4-related disease is sensitive to glucocorticoid therapy, but the best way to maintain remission remains unclear.

Certain serotypes of human leukocyte antigens (HLA) and non-HLA polymorphisms of immune-related genes may confer genetic predisposition to type-1 autoimmune pancreatitis, the pancreatic manifestation of IgG4-related disease.^{29–32} However, the trigger mechanisms remain elusive. Molecular mimicry of *Helicobacter pylori* antigens with human counterparts¹⁹ may act as a trigger — most patients with autoimmune pancreatitis have antibodies against the plasminogen-binding protein of *H. pylori*²⁰ — although this theory still requires confirmation. Only half of patients with autoimmune pancreatitis express autoantibodies.^{16,33} (Figure 1).

How does IgG4-related disease present?

A detailed understanding of the geoepidemiology of IgG4-related disease will require the introduction and widespread use of easily accessible diagnostic tools or biomarkers. Studies of

autoimmune pancreatitis involving patients in Japan showed that it is an uncommon disease, with an incidence and prevalence of 0.14 and 0.46 per 1 000 000 population, respectively.^{15,34} Patients usually present between the ages of 50 and 70 years and are more likely to be men (3:1).³⁵ However, this can vary between disease sites: a sex ratio of 1:1 has been reported for disease occurring in the head and neck.^{36,37}

IgG4-related disease can present as a consequence of organ involvement anywhere in the body. Therefore, it is within the remit of all adult medical and surgical specialties, although the organs most frequently involved are the pancreas, salivary and lacrimal glands, biliary tree, kidneys, thyroid and lungs.³⁸

The rarity, diverse presentation and lack of a gold standard test often result in delayed diagnosis, usually after investigation for malignant growths has occurred.^{39,40} Thus, an understanding of the clinical, radiologic, laboratory tests (in particular serum concentrations of IgG4) and a focused histopathology examination are

Table 1: Manifestations of IgG4-related disease in different organ systems

Organ system	Common clinical presentation	Preferred name ³
Pancreas	Painless obstructive jaundice and endocrine failure (secondary diabetes mellitus); frequently associated with IgG4-related sclerosing cholangitis ⁴	Type 1 autoimmune pancreatitis*
Lacrimal and salivary glands	Mikulicz disease: ⁵ bilateral dacryoadenitis, and enlargement of the parotid and submandibular glands with associated xerophthalmia and xerostomia Küttner tumour/chronic sclerosing sialadenitis: ⁶ hard indurated masses of submandibular (or parotid) glands; associated xerostomia is common	IgG4-related dacryoadenitis and IgG4-related sialadenitis
Orbits	Proptosis due to dacryoadenitis, local myositis or orbital pseudotumours; scleritis, uveitis and locoregional neuronal damage can occur from mass effect ^{7,8}	IgG4-related ophthalmic disease
Lungs	Dyspnea, wheeze, cough Mild stridulous symptoms can be associated with upper respiratory tract (e.g., pharynx, trachea) inflammation; often diagnosed incidentally on imaging ⁹	IgG4-related lung disease
Thyroid gland	Riedel thyroiditis: ¹⁰ stony goiter — usually euthyroid or subclinical hypothyroid profile	IgG4-related thyroid disease
Lymph nodes	Nontender generalized lymphadenopathy or localized disease near other affected organs; often asymptomatic and diagnosed incidentally on imaging	IgG4-related lymphadenopathy
Arterial system	Aortitis of either the thoracic or abdominal aorta; aneurysmal disease can present with pain or vascular insufficiency but can also be acute and catastrophic. ¹¹ Coronary arteritis may be associated with ischemic heart disease ¹²	IgG4-related aortitis or periaortitis
Retroperitoneum	Ormond disease: poorly localized lower back pain and chronic renal failure Ureteric obstruction, hydronephrosis and renal failure	IgG4-related retroperitoneal fibrosis
Kidneys	Diffuse renal enlargement and chronic renal failure; ¹³ commonly, tubulointerstitial nephritis associated with a profound hypocomplementemia Proteinuria due to coexistent glomerulonephritis (membranous) is common	IgG4-related kidney disease
Biliary tree	Jaundice, weight loss and abdominal pain that closely mimicks PSC or cholangiocarcinoma; associated cholecystitis is usually asymptomatic	IgG4-related sclerosing cholangitis
Meninges	Headache, nerve palsies and radiculomyelopathy	IgG4-related pachymeningitis

Note: PSC = primary sclerosing cholangitis. Other involvement includes IgG4-related skin disease, prostatitis, mastitis, mesenteritis, mediastinitis and hypophysitis.
*Should not be confused with type 2 autoimmune pancreatitis. Type 2 autoimmune pancreatitis is also called idiopathic duct centric pancreatitis and is not related to IgG4-RD, affects younger patients with no sex preponderance,¹⁴ is less common than type 1 but is also treated with steroids.

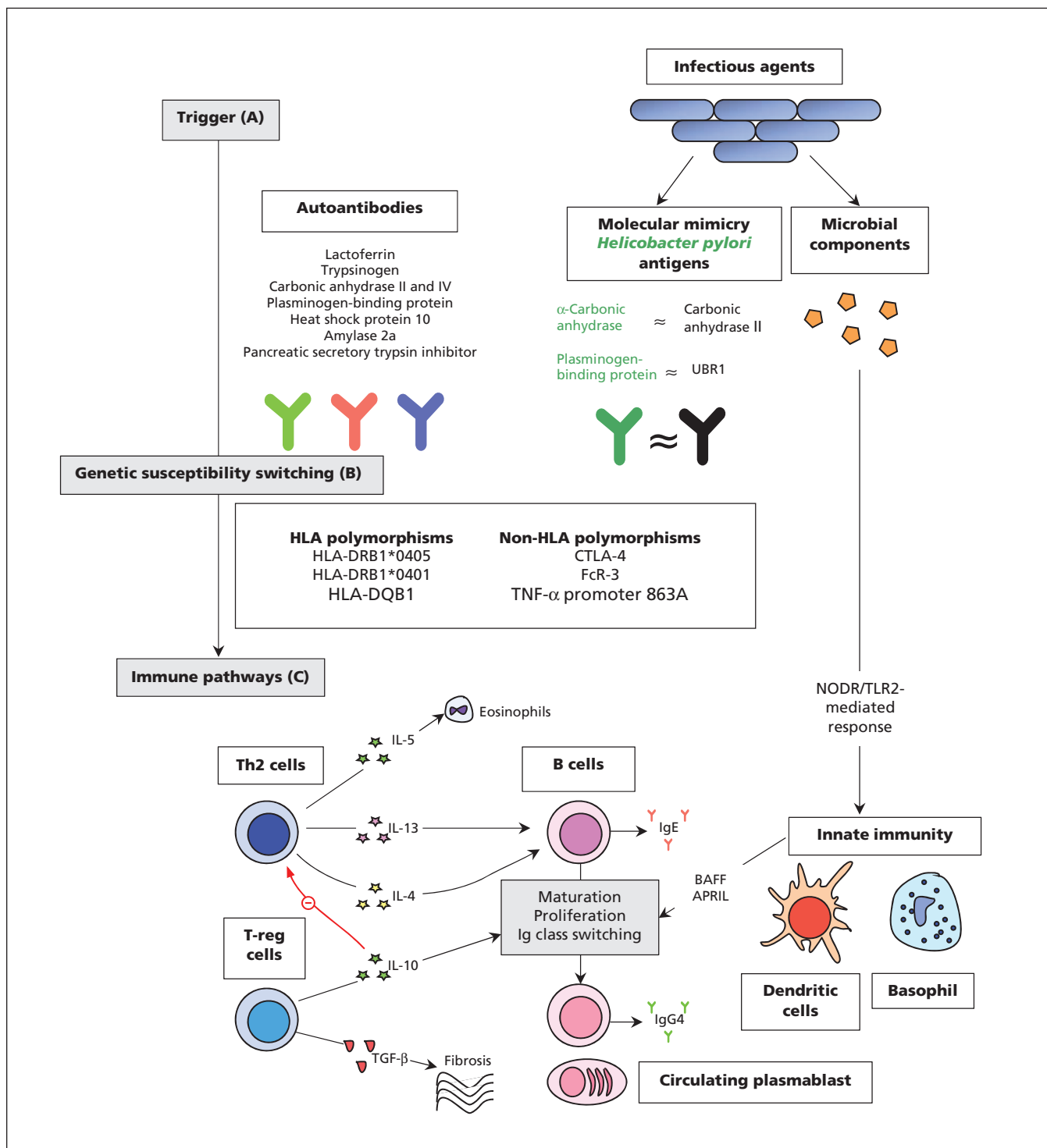


Figure 1: Mechanisms of pathogenesis for IgG4-related disease. (A) Antibodies versus antigens commonly found in exocrine organs may drive Th2-cell response. Most have only been investigated in type 1 AIP, are nonspecific, and none have been consistently found in active disease.¹⁶⁻¹⁸ Molecular mimicry of *Helicobacter pylori* antigens with human counterparts may be a trigger for type 1 AIP.^{19,20} Microbial components may stimulate innate immune mechanisms by activating NODR and TLR2 to produce BAFF and APRIL which lead to changes to B cells in a T cell-independent manner.²¹ (B) Polymorphisms of both HLA and non-HLA antigens have been implicated in the development of type 1 AIP.¹⁵ (C) A dominant Th2-cell (and associated cytokine) response occurs systemically and within affected organs. An expansion in T-reg cells may contribute to both B-cell Ig class switching and fibrosis.²² A treatment-sensitive expansion in circulating plasmablasts is present in active disease,²³ although their exact role in pathogenesis remains unclear. Elevated levels of IgG4 in serum is a hallmark of the disease and is a consequence of a modified Th2-cell response.¹⁵ Note: AIP = autoimmune pancreatitis, APRIL = a proliferation-inducing ligand, BAFF = B cell-activating factor belonging to the TNF family, B cell = beta cell, HLA = human leucocyte antigens, Ig = immunoglobulin, NODR = nucleotide-binding oligomerization domain receptor, T cell = T lymphocyte cell, TGF = transforming growth factor, Th2 = type 2 T helper, TLR2 = toll-like receptor 2, T-reg = regulatory T cell, TNF = tumour necrosis factor, UBR1 = ubiquitin-protein ligase E3 component n-recognin 1.

required to ensure that IgG4-related disease has been considered in the differential diagnosis.^{41,42} Organ-specific guidelines, such as the HISORt (histology, imaging, serology, other organ involvement, response to steroid therapy) criteria for IgG4-related sclerosing cholangitis, facilitate this multimodal diagnostic approach but may blind specialists to clinical manifestations outside their area of interest.⁴¹ In recognition of this, an international panel of experts described comprehensive consensus recommendations to aid clinicians in the management and treatment of IgG4-related disease (summarized in Figure 2).^{43,44} The evolving nature of this novel disease means the research to guide the consensus was limited, and recommendations to instruct a diagnostic approach were supported by expert opinion and limited data. Organ-specific diagnostic criteria, such as those for IgG4-related pancreatitis, cholangiopathy, kidney disease and dacryoadenitis, should be used concurrently (Table 1 and Figure 2).

Signs and symptoms

Systemic symptoms can develop insidiously over several months; asthenia (26%) and weight loss (21%) were common in the patient populations of studies conducted in France⁴⁵ and China.⁴⁶ Although most patients with IgG4-related disease have multiorgan involvement, 40% of patients have single-organ involvement at the time of diagnosis.³⁸

Abdominal symptoms are common: in a review of relevant articles published between Jan. 1, 2000, and Nov. 1, 2014, Stone and colleagues reported that pain, jaundice and diarrhea occurred in 40%, 23% and 6% of patients, respectively.⁴⁷ Sicca syndrome and respiratory symptoms were reported in 13%–15% of patients involved in the studies conducted in France and China.^{45,46} Stone and colleagues reported that patients with head and neck disease usually presented with organ swelling, and they noted that swelling of the salivary and lacrimal glands, and lymphadenopathy were common sentinel signs.⁴⁷

Investigations

Routine blood tests

Routine blood tests may direct attention to the organs involved (e.g., abnormal results for liver function tests would prompt focused investigation of the liver and pancreas). However, such testing gives little indication to suggest an underlying diagnosis of IgG4-related disease. A study in Massachusetts involving patients with IgG4-related disease reported elevated counts for peripheral eosinophilia in 27% of these patients (mean 1062 cells/ μ L; normal count < 500 cells/ μ L).⁴⁸ Elevated levels of inflammatory markers (i.e., C-reactive protein and erythrocyte sedimentation rate) were reported in one-fifth of cases in a case series study conducted in Japan.⁴⁹

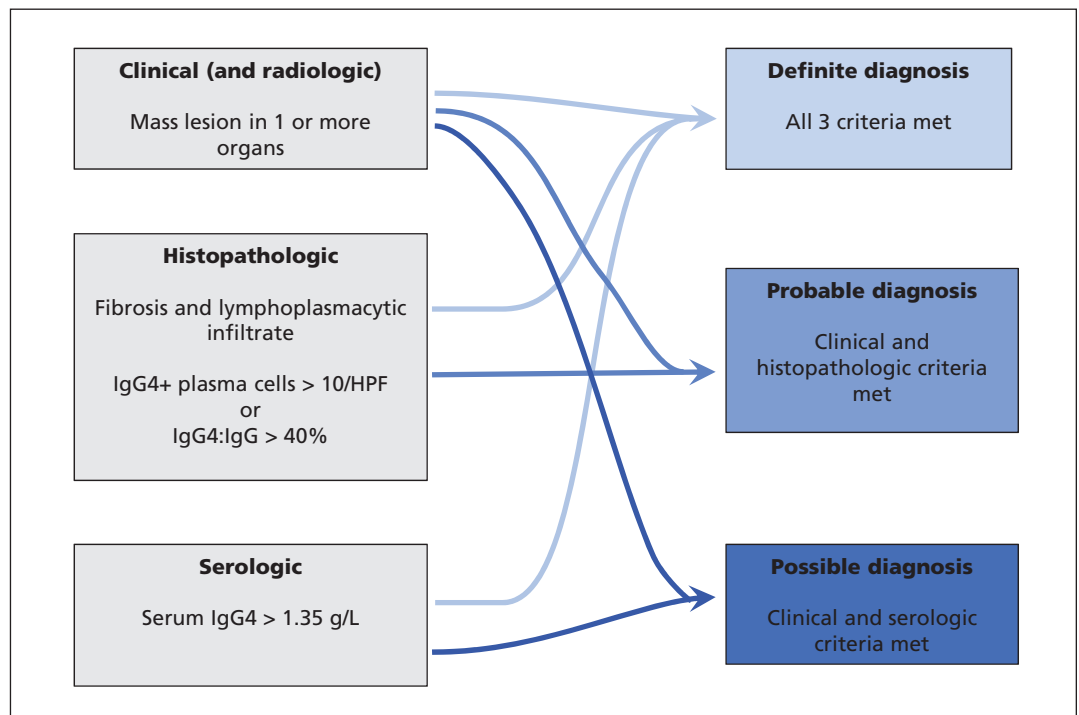


Figure 2: Diagnostic criteria for IgG4-related disease. HPF = high-powered field. (Adapted from Khosroshahi A, Wallace ZS, Crowe JL, et al. *Arthritis Rheumatol* 2015;67:1688-99).⁴³

Immunologic blood tests

Stone and colleagues reported that polyclonal hypergammaglobulinemia was detected in the sera of 80% of patients and an elevated level of IgE in 60% of patients.⁴⁷ One-third of patients have hypocomplementemia; this finding may be particularly associated with IgG4-related kidney disease,¹³ presumably as a consequence of proteinuria. A systematic review that examined the clinical features of patients with a diagnosis of IgG4-related disease showed that only 32% and 20% of patients had detectable antinuclear antibodies and rheumatoid factor, respectively.^{47,50} The presence of specific autoantibodies should prompt consideration of alternative diagnoses.⁴⁷

Serum IgG4 levels are elevated in as many as 84% of patients^{47,50} with IgG4-related disease, and this is an important diagnostic tool; however, clinicians should be aware of the limitations of the test.⁵¹ The reported sensitivity (80%–

90%) of an elevated level of IgG4 in serum is likely to be inflated by selection bias.^{51,52} In a study that required histologic proof of IgG4-related disease as an inclusion criterion, only 50% of the patients had elevated levels of serum IgG4 before treatment.⁵³ Elevated levels of IgG4 in serum can occur in many other conditions, including some pancreatobiliary diseases (e.g., primary sclerosing cholangitis, cholangiocarcinoma), hematologic malignant disease and infectious diseases (e.g., chronic sinusitis, recurrent pneumonia, aspergillosis).⁵¹

An elevated IgG4 level in serum (upper limit of normal = 1.35 g/L) has low specificity and a positive predictive value under 40%.⁵² Nevertheless, higher serum concentrations may suggest a positive diagnosis (mean = 6.70 g/L) over alternatives;⁵¹ a threshold of four times the upper limit of normal provides a positive predictive value of 100% for the investigation of IgG4-

Table 2: Radiographic findings in IgG4-related disease

Organ system	Typical findings
Pancreas ⁵⁸	CT: focal (more common) or diffuse pancreatic enlargement with delayed enhancement and a low-density "halo"; pancreatic atrophy is uncommon Cholangiography: diffuse irregular narrowing of the pancreatic duct
Salivary gland	CT: swelling is often bilateral and preferentially involves the submandibular glands US: ⁵⁹ multiple hypoechoic lesions in affected glands MRI: ⁶⁰ homogenous enhancement in hypointense or isointense T_2 -weighted imaging
Orbits ⁶¹	CT: involvement of any surrounding structures including lacrimal glands, nerves, extraocular muscles and maxillary and frontal bony structures
Lungs ⁹	CT: four major categories of findings (solid nodular masses, localized ground glass opacities, diffuse ground glass opacities associated with honeycomb lung and bronchovascular thickening); mediastinal lymphadenopathy is common Diffuse tracheal inflammation and subglottic stenoses may also be seen
Arterial system ⁶²	CT: adventitial sclerosing inflammation characterized by diffuse wall thickening and late-phase enhancement
Retroperitoneum ⁶³	CT: perivascular fibrosis concentrates around the aorta, iliac vessels and vena cava. Occasionally, fibrotic disease will dominate perirectal and retrovesicular spaces. Associated lymphadenopathy and aortitis is common.
Kidneys ⁶⁴	CT: abnormalities noted in 70% of patients with renal disease include bilateral diffuse enlargement, solitary nodules and atrophy MRI: low-density lesions with T_2 -weighting hypointensity, with progressive enhancement pattern
Biliary tree	Cholangiography: stricturing disease is difficult to differentiate from other causes of sclerosing cholangitis. Common bile duct thickness of > 2.5 mm and continuous strictures can be suggestive of IgG4-RD rather than PSC; ⁶⁵ 4 patterns of stricturing disease have been described, but the clinical relevance of the different types is not obvious ⁶⁶ Cholangioscopy: direct mucosal visualization may give diagnostic clues, although this requires thorough validation ⁶⁷
Meninges and brain ⁸	CT: diffuse dural thickening or perineural masses as large as 3 cm in diameter; pituitary lesions require MRI

Note: CT = computed tomography, IgG4-RD = immunoglobulin G4-related disease, MRI = magnetic resonance imaging, PSC = primary sclerosing cholangitis, US = ultrasonography.

related sclerosing cholangitis.⁵² For moderately elevated serum IgG4 concentrations (up to 2 times the upper limit of normal; positive predictive value = 28%), the IgG1:IgG4 ratio in serum (> 0.24) may improve diagnostic yield for IgG4-related sclerosing cholangitis (positive predictive value = 55%; negative predictive value = 90%), although the use of IgG1:IgG4 ratios in serum has not been validated outside this setting.⁵²

Higher concentrations of IgG4 in serum are associated with multiorgan involvement (mean concentration: 6.99 g/L in multiorgan v. 2.33 g/L in single-organ disease) or a greater burden of localized disease that is prone to relapse after initial treatment.^{51,54,55}

Imaging studies

Computed tomography (CT) may delineate a mass and identify the extent of multiorgan involvement; however, the assessment of multiorgan involvement may be better served by ¹⁸F-fluorodeoxyglucose positron emission tomography/CT.⁵⁶ Magnetic resonance imaging of affected areas generates a low signal on *T*₂-weighted imaging.⁵⁷ An overview of the typical radiographic findings in different organs is described in Table 2.^{8,9,58–67} Of these, only the classical CT findings of autoimmune pancreatitis

(i.e., a diffusely enlarged, sausage-shaped pancreas with an enhancing rim; Figure 3)⁶⁸ are pathognomonic, and may forego the need for histologic assessment⁴⁴ (Figure 3 and Table 2).

Histologic assessment

The purpose of histologic assessment of affected organs is to exclude other differential diagnoses (notably malignant disease) and to provide evidence of a diagnosis of IgG4-related disease before treatment starts.⁴³ Tissue procurement can be difficult with deep-seated disease, although modern techniques, such as endoscopic ultrasonography with fine-needle aspiration for pancreatic and biliary disease, have overcome some of these challenges. Nevertheless, needle biopsy and fine-needle aspiration often deliver insufficient tissue for assessment and can miss patchy disease.⁶⁹

Gross morphologic changes are often organ specific: a tumefactive mass is common in pancreatic involvement, with diffuse enlargement of the entire organ;⁵⁸ in organs such as salivary glands, discrete areas of disease are seen on a background of unaffected tissue even though no discernible difference in tissue constituency can be observed.⁷⁰

Lymphoplasmacytic infiltrate laden with IgG4-positive plasma cells on a background of storiform fibrosis and obliterative phlebitis describes the distinctive histopathology that unifies the diagnosis of IgG4-related disease.⁷¹ Thus, a comprehensive and meaningful assessment of tissue in this setting will require IgG4 immunostaining. In glandular organs, the infiltrate will typically concentrate around major ductal (biliary and bronchiolar) structures and can manifest as long regions of wall thickening.^{71,72} Lymphocytes are prominent, with T cells distributed throughout and B cells organized in germinal centres. Although diffusely infiltrating IgG4-positive plasma cells are not specific to IgG4-related disease, they are a prerequisite for histopathologic diagnosis.^{43,71} High relative density of IgG4-positive plasma cells has high diagnostic utility; some researchers have adopted an IgG4:IgG plasma cell ratio of greater than 40% (50% for aortic disease⁷³) as highly discriminatory when supported by clinical and pathologic features — an approach supported in the consensus statement on the pathology of IgG4-related disease.⁷¹

Fibrosis is an early feature of IgG4-related disease and is arranged in radial fibres that interlace in a storiform pattern throughout the tissue. This storiform pattern may be absent in IgG4-related dacryoadenitis (although fibrosis is often dense) and lymphadenopathy, making the diagnosis in isolated lymph node disease challenging.^{71,74}

Obliterative phlebitis describes a partial or complete obliteration of medium-sized veins, which may look like an inflammatory nodule, in

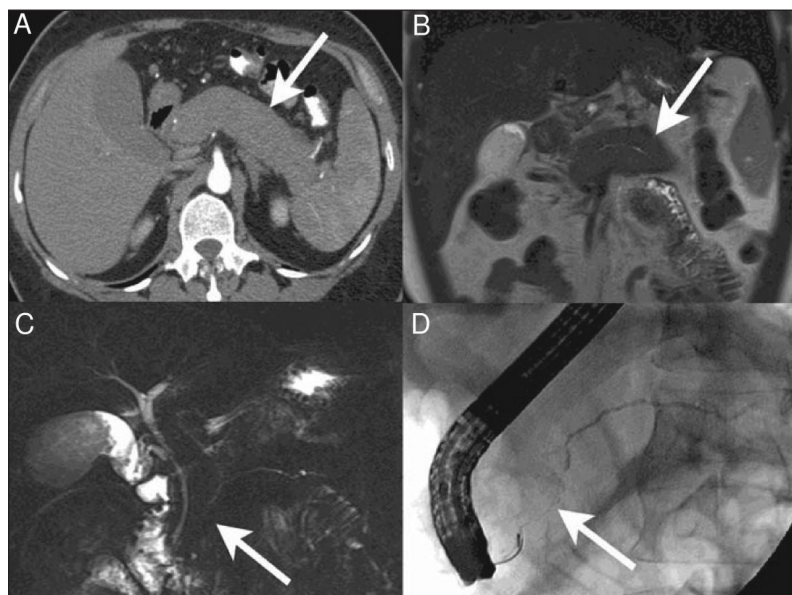


Figure 3: Diffuse autoimmune pancreatitis.⁶⁸ (A) Axial computed tomography (CT) image in the pancreatic parenchymal phase of the typical enlarged and poorly enhanced pancreas in a patient with diffuse autoimmune pancreatitis⁶⁸ (arrow). Note the lack of inflammatory change around the organ, which differentiates the disease from acute pancreatitis and necrosis. (B) View of the pancreas using coronal *T*₂-weighted magnetic resonance imaging (MRI) that shows low signal intensity in the pancreas (arrow) because of the diffuse fibrosis in the gland. (C) Coronal magnetic resonance cholangiopancreatography image showing a diffusely irregular pancreatic duct with stenosis distally in the pancreatic head (arrow). (D) Endoscopic retrograde cholangiopancreatography image that confirms the MRI findings, including ductal stenosis (arrow). Images reproduced from reference 68 under Creative Commons licence 2.0 (<http://creativecommons.org/licenses/by/2.0/legalcode>).

proximity to an unaffected artery. This is invariably present in pancreatic or submandibular disease but scarce in lacrimal gland disease.⁷¹

In addition to the classical triad, an eosinophilic infiltration is common and can be dense.^{72,75,76} Neutrophilic infiltration and granulomata are rare.⁷⁴

The phase of the disease may determine the predominant pathologic findings and predict response to treatment. Retroperitoneal disease is often diagnosed late, and histology shows a relatively paucicellular and dense fibrosis that does not respond well to glucocorticoid therapy.⁷⁷ End-stage or “burnt-out” disease of this type may manifest in different organ systems (e.g., cryptogenic cirrhosis, honeycomb lung, chronic pancreatitis).³⁴

How is IgG4-related disease treated?

Currently, there are no robust data available to inform treatment guidelines, and recommendations are made based on expert opinion and limited data. A suggested treatment schematic based on the international consensus guidance

statement on the management and treatment of IgG4-related disease is shown in Figure 4.⁴³

The treatment model is to induce suppression of the inflammation and maintain the disease in a quiescent state. It should be started early in patients with clinical, biochemical or radiologic evidence of major organ involvement and/or symptomatic disease.⁴³ However, asymptomatic indolent disease in noncritical systems, such as IgG4-related lymphadenopathy, may only need monitoring.¹⁵ At the other end of the spectrum, burnt-out fibrotic disease, as in some cases of retroperitoneal fibrosis, may be resistant to available treatments.¹⁵ Occasionally, mechanical biliary drainage may be needed for urgent cases of autoimmune pancreatitis or cholangiopathy.⁴³

Induction

IgG4-related disease is usually sensitive to glucocorticoid therapy, which is the recommended first-line treatment; a weight-based dosing regimen for prednisolone of 0.6 mg/kg body weight has been suggested in the treatment of autoimmune pancreatitis.⁷⁸ A typical starting dose for prednisolone taken orally is 40 mg;⁴³ however, a nationwide

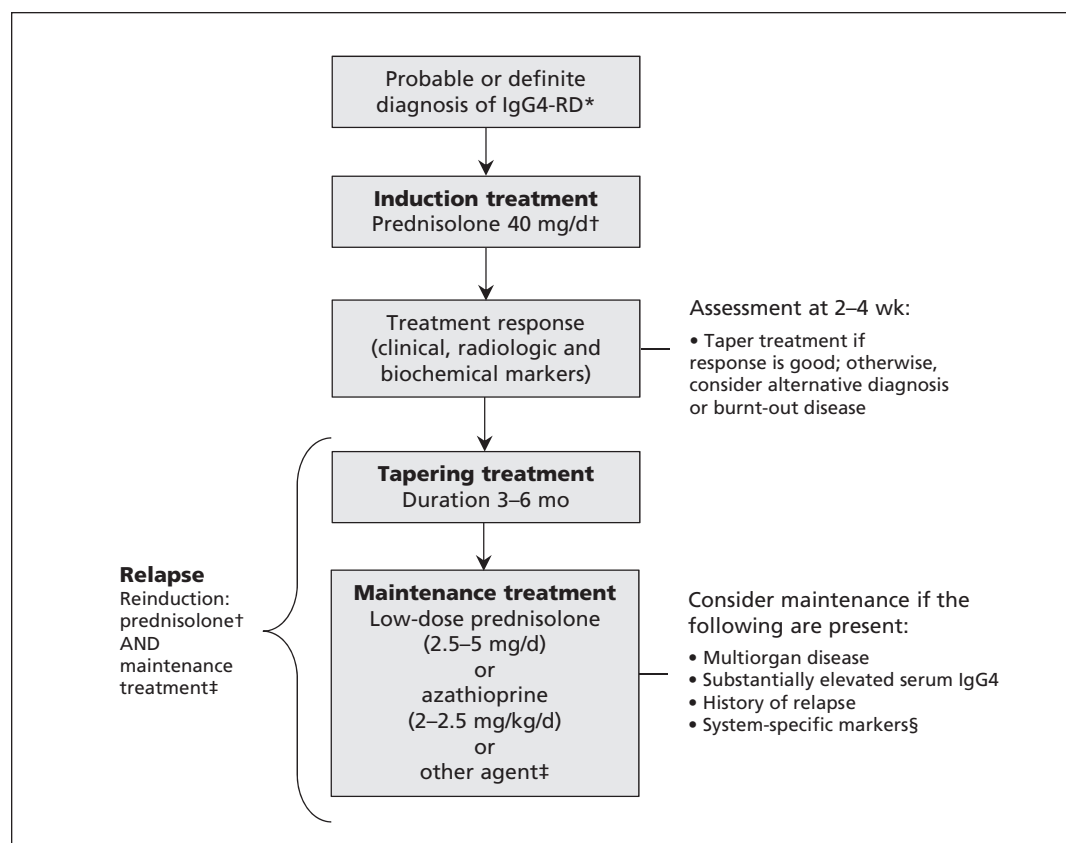


Figure 4: Treatment schematic for IgG4-related disease. *As diagnosed by international consensus guidance.⁴³ †Consider B-cell depletion if the patient is resistant to or intolerant of glucocorticoids and therapies available to the clinician. ‡Other agents include calcineurin inhibitors, cyclophosphamide, mycophenolate mofetil and methotrexate. B-cell depletion could be considered. §Predictors of relapse in IgG4-related sclerosing cholangitis or autoimmune pancreatitis include coexisting diabetes, or a high burden of biliary involvement. Note: IgG4-RD = IgG4-related disease.

survey in Japan reported no significant differences in outcomes among patients treated with 30 or 40 mg of prednisolone.⁷⁹ Glucocorticoid tapering and discontinuation can be associated with disease relapse; however, there is little consistent guidance on how to taper glucocorticoids. Centres in North America aim to stop treatment with glucocorticoids within 11 weeks,¹⁴ whereas some centres in Japan continue low-dose (5 mg) prednisolone for as much as three years.⁷⁸ International consensus is to take a pragmatic approach: start to taper the drug after two to four weeks of induction dosing and aim to stop treatment within three to six months, dependent on patient response.⁷⁸

Depletion of B cells by rituximab has been shown to be highly effective at inducing and maintaining remission in early phase two trials, and it may serve as an alternative for those with steroid-refractory disease.^{43,80} However, B-cell depletion treatment is not readily available everywhere, and some specialists have little or no experience with its use. Thus, the consensus guidance statement suggested its use should be at the discretion and comfort of the prescribing physician.⁴³ The short- and medium-term safety of rituximab is well established for other autoimmune and hematologic malignant diseases.^{81–83} However, long-term safety data are lacking, and concerns remain about long-term immunosuppression in certain populations, particularly among children.⁸⁴

There is little evidence to support the use of other induction agents.²¹

Following treatment, relapsing disease occurs in about 30%–54% of patients and requires reinduction therapy.^{35,78,79} The practice of adding a second agent (e.g., azathioprine, 6-mercaptopurine or mycophenolate mofetil) is still common, but there is yet little evidence to suggest a relapse-free survival advantage.⁸⁵

Treatment response

At present, there are no standardized outcomes by which to measure response to treatment. Serum

IgG4 levels do not reliably reflect disease activity,⁸⁶ and the utility of serum IgG4-positive plasmablast concentrations²³ and the IgG4-responder index⁸⁷ require validation studies. Clinicians must use clinical, laboratory and radiologic markers on a case-by-case basis to gauge response to treatment.

Response is usually seen within two to four weeks.^{88,89} A lack of improvement within this time frame should prompt a review of the diagnostic evidence and consideration of burnt-out disease⁷⁷ or other diagnoses, especially cancer.

Maintenance

The aim of maintenance treatment is to prevent recurrence of disease following remission. The risk factors for relapse are not well described, although anecdotal evidence suggests multiorgan disease, substantially elevated serum IgG4 concentrations and history of disease relapse are associated with recurrence after remission.⁴³ A higher burden of biliary involvement or coexisting diabetes in patients with autoimmune pancreatitis or IgG4-related sclerosing cholangitis predicts a higher relapse rate.⁷⁸

Studies investigating the efficacy of low-dose prednisolone (2.5–5 mg/d) treatment showed a reduction in relapse rate from 34% to 23% compared with patients who were not receiving maintenance immunosuppression.⁹⁰ It is unclear how long to continue maintenance treatment with low-dose steroids, and risks related to long-term glucocorticoid treatment in older patients are not insignificant.⁹¹ These issues will need further evaluation before any firm recommendations can be made.

Several agents have been used as steroid-sparing maintenance treatment^{85,92,93} after remission has been achieved. The use of azathioprine (2–2.5 mg/kg body weight) is suggested,⁹⁴ although data to support the use of one agent over another are limited.⁸⁵ The use of rituximab as maintenance treatment for patients who are at high risk of relapse has been acknowledged in the international consensus guidance statement; however, the optimal frequency and duration of treatment with the drug are subject to further evaluation,^{23,36,80,85,95,96} and its practical use is under the aforementioned caveats of physician preference and sparse long-term safety data (Figure 4).

Conclusion

In just over a decade since its recognition as a clinical entity, the diverse clinical presentation of IgG4-related disease has been mapped, and recent efforts have been geared to optimize its diagnosis and management. However, shortcomings in our understanding and approach persist (Box 2)^{23,80,87,91} and need to be addressed. Awareness of the poten-

Box 2: Future perspectives and unanswered questions

- Promising noninvasive diagnostic markers (e.g., flow cytometry for circulating plasmablasts) may circumvent the need for tissue diagnosis and skilled histopathologic assessment.^{23,80,97}
- There is an urgent clinical imperative for validated specific outcome measures that will allow prognosis and treatment response to be monitored. Circulating plasmablast levels may fulfil this role, and an IgG4-responder index is currently under validation.⁸⁷ This will need to be linked to long-term studies to ascertain the optimal maintenance strategy for those patients who achieve remission.
- The pathophysiology of IgG4-related disease is elusive, and the links between the serologic and histologic findings are unclear. Treatment response (especially with B-cell depletion) and laboratory modelling of the disease may provide invaluable insights into the disease and interplay between immune pathways in other immune-mediated diseases.

tial for IgG4-related disease to mimic a range of disorders and an understanding of how to investigate and manage treatment in patients by the current criteria will lead to earlier treatment and better outcomes (Box 2).

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