IgG4-related disease

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Abstract

Immunoglobulin (Ig) G4-related disease is an immune-mediated fibro-inflammatory condition that can involve virtually every organ system. Our knowledge and understanding of this condition has expanded rapidly over the last decade, with insights into adaptive and innate immunological mechanisms, identification of novel risk factors, definition of disease subsets based on organ distribution, discovery of circulating biomarkers that correlate with disease activity and relapse, and novel treatment approaches. However, many challenges remain. The diagnostic work-up remains complex, requiring a combination of clinical examination, serology, imaging and histological evaluation with cross-speciality input. This requires the exclusion of a broad variety of differential diagnoses. Treatment often dampens inflammation, although relapse remains common on tapering or discontinuation of best available immunosuppression. Progressive fibrosclerotic disease and an increased risk of malignancy are recognized outcomes.

Keywords Fibrosis; IgG4; IgG4-related disease; immune; inflammation; MRCP

Key points

- IgG4-related disease (IgG4-RD) is a multiorgan condition presenting with 'inflammatory' mass lesions, strictures and/or 'fibrotic' encasement of body regions
- All organs affected by IgG4-RD share similar histopathological features, specifically a lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells and a storiform pattern of fibrosis
- Four broad disease subsets have been described, defined by the predominant pattern of organ involvement, with differences in age, gender, ethnicity, serum IgG4 concentrations and time to presentation
- The new American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for IgG4-RD (2019) focus on important exclusion criteria to help minimize misdiagnosis
- IgG4-RD is typically corticosteroid-responsive. B cell depletion with rituximab is safe and efficacious in reducing disease relapse and corticosteroid-related adverse events
- Disease progression with organ dysfunction, organ failure and an increased risk of malignancy can occur, warranting careful follow-up

IgG4-related disease

Definition: immunoglobulin (Ig) G4-related disease (IgG4-RD) is a multisystem immune-mediated fibro-inflammatory condition characterized by histopathological evidence of a lymphoplasmacytic infiltrate predominated by IgG4-positive plasma cells and a storiform pattern of fibrosis.

History: IgG4-RD was recognized as a unified disorder in 2003. However, clinical presentations of Mikulicz disease, Kuttner's tumour and Reidel's thyroiditis, now recognized to be part of the IgG4-RD spectrum, appeared in the literature as early as the 1800s. Elevated serum IgG4 concentrations were first reported in 2001.

Epidemiology: the epidemiology of this condition is poorly defined. It is often underdiagnosed as it presents to many different generalists and specialists. It is misdiagnosed as other malignant, inflammatory and infective aetiologies.[1] A nationwide survey in Japan in 2009 defined an incidence of 1.4 per 100,000 and a prevalence of 4.6 per 100,000 cases of autoimmune pancreatitis, with an estimated 8000 patients in Japan with systemic IgG4-RD (62 per million inhabitants). There are no similar studies in Europe or the USA.

Clinical presentation: there is a male preponderance, in the sixth decade of life. Clinical symptoms are usually determined by the organ(s) affected, but many individuals are asymptomatic for long periods, with a mean time to diagnosis of 3.2 years (see Wallace et al., 2019 in Further reading). Irreversible organ injury may therefore occur before a diagnosis has been secured and treatment initiated. The condition presents as a mass-like lesion in the 'inflammatory' subtype (e.g. glandular and epithelial tissues such as the pancreas and salivary glands) or by causing strictures or encasement of a body region in the 'fibrotic' subtype (e.g. sclerosing cholangitis, retroperitoneal fibrosis, sclerosing mesenteritis).

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Disease subsets: four broad disease subsets have recently been described, defined by the predominant pattern of organ involvement, which may offer insights into therapy and prognosis. These groups incorporate the hepato-pancreato-biliary, retroperitoneum and aorta, limited head and neck, and systemic disease, although there are many overlapping features. These phenotypes differ in terms of age, gender, ethnicity, serum IgG4 concentrations and time to presentation (see Wallace et al., 2019 in Further reading).

Autoimmune pancreatitis type 1 and IgG4-related sclerosing cholangitis (IgG4-SC) are the pancreatic and biliary manifestations of IgG4-RD. Pancreatic involvement often presents with obstructive jaundice (70–80%), weight loss and abdominal pain. There may be symptomatic pancreatic exocrine and endocrine insufficiency. Serum IgG4 concentrations are raised in most (65–80%) patients at diagnosis, but are non-specific and can be elevated in other malignant, inflammatory and autoimmune pathologies, and in 5% of healthy individuals. Raised serum IgE concentrations and/or peripheral eosinophilia are well documented. Although the classical imaging description of autoimmune pancreatitis is with a diffuse sausage-shaped pancreas, over half of patients have a discrete pancreatic head mass with distal common bile duct involvement because of a mass effect, which mimics pancreatic cancer. Localized lymphadenopathy is common and does not distinguish it from malignancy. Evidence of extrapancreatic organ involvement supports the diagnosis.

Risk factors: a number of disease associations have been reported, including occupational exposures to chemicals and dusts ('blue collar workers') in patients with sclerosing cholangitis, smoking and asbestos exposure in those with retroperitoneal fibrosis, and atopy and an allergic history predominantly in those with glandular disease.[2]

Diagnostic criteria: a number of organ-specific and general diagnostic criteria can be applied to support a diagnosis of IgG4-RD. The Mayo HISORt (histology, imaging, serology, other organ involvement and response to therapy) criteria and Japanese International Consensus Diagnostic Criteria are most frequently used for pancreatic and biliary disease. The Boston Consensus Histopathological Criteria are valuable where there are histological biopsy or resection specimens.[3] The new American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for IgG4-RD (2019) have defined exclusion criteria to help minimize misdiagnosis, and now require validation in real-life clinical practice. There is a broad differential diagnosis and we advocate discussion of these complex patients in a specialist multidisciplinary team.

Pathology: all organs affected by IgG4-RD share similar histopathological features. Histological hallmarks include a dense lymphoplasmacytic infiltrate with predominant IgG4-positive plasma cells, an irregular whorled 'storiform' pattern of fibrosis and variable presence of obliterative phlebitis and eosinophilic infiltration (Figure 1).[3] Granulomas, necrosis, multinucleated giant cells and neutrophil infiltrates suggest an alternative pathology.

Radiology: cross-sectional imaging can raise clinical suspicion of IgG4-RD, with a classical sausage-shaped pancreas and irregular pancreatic duct seen in autoimmune pancreatitis (Figure 2). Other organ manifestations often have a wide differential diagnosis. Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) has demonstrated clinically silent organ involvement at diagnosis and after disease relapse (Figure 3), although the relevance of this remains unknown.

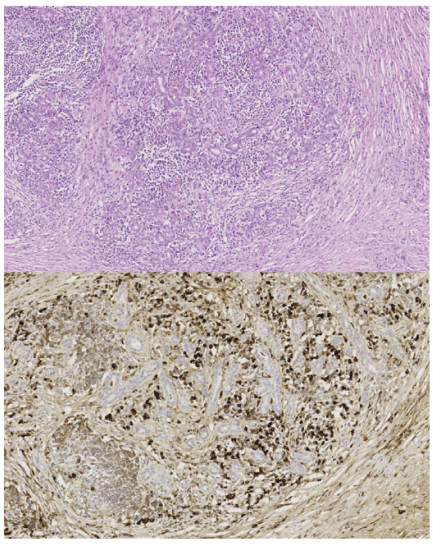

Figure 1 A dense lymphoplasmacytic infiltrate in the lobule of a submandibular gland (H&E stain; ×100 magnification). IgG4 immunostaining ×150 magnification demonstrated >50 IgG4-positive plasma cells per high-power field.

Pathophysiology: the past decade has witnessed an extraordinary expansion in our understanding of the pathophysiology of this condition. Both the adaptive and innate immune systems have been implicated, with an emphasis on the role of memory B cells, T follicular helper (Tfh) cells, CD4 + cytotoxic lymphocytes (CTLs) and alternative macrophages. The expansion of clonally restricted CD4 + CTLs (SLAMF7+) in the circulation and infiltrating tissue in patients with IgG4-RD is believed to be central to its pathogenesis, producing a number of pro-fibrotic cytokines and interacting with B cells (antigen-driven). B cell depletion leads to profound clinical responses as well as a decline in plasmablasts and CD4 + CTLs.

Auto-antibodies against different antigens such as galectin 3, prohibin, anexin 11 and laminin 511-E8 have been reported; all are ubiquitous proteins expressed with variable frequencies (20–75%) in different organs. Genetic studies have reported a human leukocyte antigen type II association, and a number of single-nucleotide polymorphisms have been defined.

Biomarkers of disease: elevated serum IgG4 concentrations are seen in most patients. Elevated IgG4 at diagnosis can be tracked to suggest a response to treatment and disease flares, and can also reflect the extent of disease.[1] Elevated serum IgE concentrations are often seen and can correlate with disease activity. Hypocomplementaemia (C3, C4) is most frequently seen in individuals with IgG4-related tubulo-interstitial nephritis, and declines as disease activity worsens. Other potential biomarkers

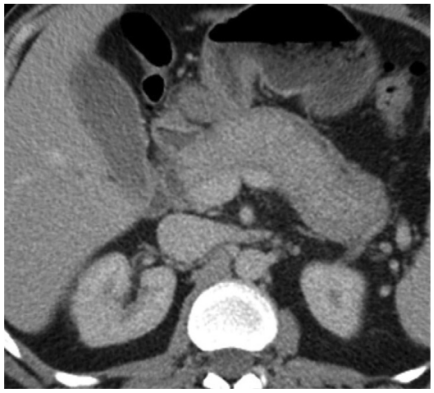

Figure 2 Portal-phase axial computed tomography of the pancreas showing a classical sausage-shaped pancreas with a pseudocapsule in autoimmune pancreatitis.

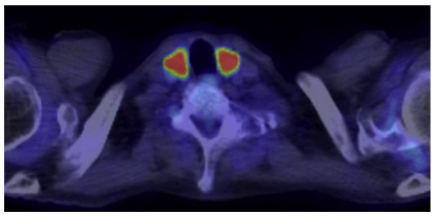

Figure 3 Clinically silent disease in the thyroid on FDG CT-PET, in the patient with autoimmune pancreatitis in Figure 2.

include circulating plasmablasts, Tfh-2 cells, CD4 + CTLs and chemokine CCL18, which have all been associated with disease activity and show declining concentrations with treatment. The IgG4-RD responder index is a research tool used to longitudinally track disease activity, organ progression and damage in individual patients.[4]

Management: the main goals are to reduce inflammation, maintain disease remission, preserve organ function and prevent complications, while minimizing adverse effects of treatment. All patients with active and symptomatic disease require treatment, some more urgently than others, and those who are asymptomatic can have vital organ involvement (e.g. peri-aortitis). Even in individuals who experience spontaneous improvement of single-organ disease, recurrence in the same or other organs is frequent, and close follow-up is warranted. Watchful waiting is appropriate in only a minority of patients.

Glucocorticoids are the mainstay first-line treatment for patients with IgG4-RD, and those with 'inflammatory' subset disease typically respond well, within days to weeks. The induction dose is typically 30–40 mg/day for 2–4 weeks, with higher doses considered if vital organs are involved, and lower doses in elderly individuals and those with co-morbidities. Tapering by 5 mg every 1–2 weeks is guided by clinical improvement, biochemistry and follow-up imaging. Remission is defined by substantial improvement and/or correction of biochemical and radiological abnormalities. An absence of response prompts a thorough search for an alternative diagnosis.

In certain situations, medical interventions such as temporary stent placement (biliary, ureteral) are complementary to medical therapies to prevent obstructive complications such as infection. Maintenance treatment is often individualized based on the perceived risk of relapse. Risk factors for relapse include male gender, IgG4-SC, the number of organs involved at baseline, serum IgG4 and IgE concentrations at diagnosis, and speed of tapering treatment.

Second-line immunosuppressive therapies such as azathioprine and methotrexate (see comment regarding mycophenolate below) are often used alongside glucocorticoids, although there are minimal data that these obtain deeper remission or prevent relapse yet can reduce corticosteroid-related adverse events. Cyclophosphamide has been shown to reduce the rate of disease recurrence in a prospective study, but suffers from considerable adverse effects in middle-aged/elderly populations. Mycophenolate plus corticosteroids has been shown to reduce the risk of relapse compared to corticosteroids alone in a randomised controlled trial. B cell depletion with rituximab in a prospective open-label trial showed an excellent response, with complete remission in 40% of patients at 12 months from the induction dose alone. A subsequent multicentre study assessing long-term efficacy and safety supported the use of maintenance rituximab doses to reduce relapse, and reported a high rate of infections in one-third of patients. Other therapies such as abatacept (fusion protein of CTLA4 and FcIgG1), B cell inhibition with Xmab5871 (CD19 and FcγIIRB) and elotuzumab (anti-SLAM F7) are currently in clinical trials.

Progression and follow-up: delays in diagnosis and institution of treatment can lead to major organ dysfunction and failure.[5] An increased risk of any malignancy has been reported, most often within the first year of diagnosis. Long-term follow-up is currently advocated to identify individuals with disease relapse or progression, and to guide the need for immunosuppression.

What are the main challenges in IgG4-RD?

Major challenges are:

- determining an accurate diagnosis: a multidisciplinary approach
- accurately defining individuals at risk of disease relapse and in which organ system
- identifying those who will develop progressive and fibrotic disease
- choosing the best treatment strategy, including when and in whom to use biological agents, and the optimal duration of treatment
- assessing the true risk of malignancy and how to screen for it given overlapping features.

Cross-disciplinary expertise in an IgG4 multidisciplinary team, establishment of national IgG4-RD registries and prospective cohorts with bio-banking of clinical samples are vital to tackling these challenges. ◆

KEY REFERENCES

1 Culver EL, Sadler R, Simpson D, et al. Elevated serum IgG4 levels in diagnosis, treatment response, organ involvement, and relapse

in a prospective IgG4-related disease UK cohort. *Am J Gastroenterol* 2016; **111:** 733–43.
2 Culver EL, Sadler R, Bateman AC, et al. Increases in IgE, eosinophils, and mast cells can be used in diagnosis and to predict relapse of IgG4-related disease. *Clin Gastroenterol Hepatol* 2017; **15:** 1444–52.
3 Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012; **25:** 1181–92.
4 Wallace ZS, Khosroshahi A, Carruthers MD, et al. An international, multispecialty validation study of the IgG4-Related Disease Responder Index. *Arthritis Care Res* 2018; **70:** 1671–8.
5 Huggett M*, Culver EL*, Kumar M, et al. Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. * represents joint first authorship. *Am J Gastroenterol* 2014; **109:** 1675–83.

FURTHER READING

Wallace Z, Zhang Y, Perugino C, Naden R, Choi HK, Stone JH. ACR/EULAR IgG4-RD Classification Criteria Committee. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. *Ann Rheum Dis* 2019; **78:** 406–12.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 52-year-old man presented with a 4-week history of jaundice, pruritus and weight loss. He had a history of atopy, with eczema and allergic rhinitis. On clinical examination, he was jaundiced.

Investigations

- Haemoglobin 145 g/litre (130–180)
- White cell count 6.7 x 10^9/litre (4.0–11.0)
- C-reactive protein 6 mg/litre (<10)
- Bilirubin 140 micromol/litre (1–22)
- Alkaline phosphatase 630 U/litre (45–105)
- Alanine aminotransferase 75 U/litre (5–35)

CT scan of the abdomen revealed a bulky head of pancreas, an irregular main pancreatic duct, distal common bile duct obstruction, localized lymphadenopathy and bilateral enlarged kidneys.
Endoscopic ultrasound-guided pancreatic core biopsy showed a lymphoplasmacytic infiltrate, obliterative phlebitis and eosinophils with an IgG4-positive plasma cell count of 20 per high-power field.

Which of the following is the best treatment option?

A. Supportive management
B. Prednisolone
C. Surgical resection
D. Rituximab
E. Biliary stent

Question 2

A 45-year-old man presented with bilateral swellings in the face, weight loss and loose stools. On clinical examination he had bilateral submandibular gland enlargement.

Investigations

- Stool elastase 130 μg/g (>200).

CT scan pancreas showed a sausage-shaped pancreas with a pseudocapsule and irregular pancreatic duct.

Which of the following are believed to be important in driving the pathophysiology of IgG4-related disease?

A. Reduction of T regulatory cells in blood and tissue
B. Expansion of CD4 + cytotoxic T cells in blood and tissue
C. Exhaustion of T follicular helper cells in blood and tissue
D. Expansion of T helper type 1 cells in blood and tissue
E. Deficient B cells and plasmablasts in blood and tissue

