

CME Review

IgG4-related disease: a primer on diagnosis and management



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At the conclusion of this activity, participants should be able to:

- Describe the various clinical manifestations and identify the histopathological hallmarks characteristic of IgG4-related disease.
- Discuss the management options for patients diagnosed with IgG4-related disease.

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Introduction

The disorder referred to as IgG4-related disease (or IgG4-RD) is characterized by diffuse organ infiltration by plasma cells expressing IgG4 and is often associated with a fibroinflammatory histopathologic change, allowing it to fall into the spectrum of multisystem inflammatory disorders such as vasculitis or sarcoidosis.^{1–3} The disorder has been referred to variably as IgG4-associated disease, IgG4-related sclerosing disease, and IgG4-related autoimmune disease. Clinically, as reviewed below, a spectrum of disorders might fall under the umbrella of IgG4-RD, such as Mikulicz syndrome, Riedel thyroiditis, and forms of retroperitoneal fibrosis (Table 1). For the allergist immunologist, nasal sinus disease, dermatitis, headaches, and respiratory symptoms associated with elevated IgE and/or eosinophilia might result in referral for evaluation of atopic or immunologic disease.^{1,3}

Epidemiologic Features

Although the disease has been described worldwide, the true epidemiology of IgG4-RD remains unknown because few studies have been performed. One cross-sectional study conducted in Japan in 2009 estimated an incidence of 60 individuals per million inhabitants and a prevalence of 8,000.⁴ The disease usually presents in the sixth or seventh decade of life, with a median age of diagnosis of 59 to 68 years, leading to some confusion with a possible diagnosis of malignancy. Unlike most autoimmune disorders, IgG4-RD appears to have a male predominance, estimated at 2.8 to 1 by 1 Japanese study.¹ The retroperitoneal manifestations of the disease (autoimmune pancreatitis [AIP], retroperitoneal fibrosis, or tubulointerstitial nephritis) more predominantly affect men, whereas head and neck manifestations tend to affect men and women.⁴

Clinical Features

Historically, many manifestations of IgG4-RD were identified in specific organs, with a unique nomenclature for each organ-system manifestation. The following sections describe organ- and system-specific manifestations of the disease.

Allergy

Many patients with IgG4-RD have features of atopic disease, as mentioned earlier. Patients can present with pulmonary symptoms compatible with asthma, including coughing, wheezing, and dyspnea.^{5,6} Dermatologic and ocular manifestations also can lead to diagnostic confusion with atopic disorders.^{7–9} Eczema-like skin disease and urticaria or urticarial vasculitis can occur.^{10,11} Rhinosinusitis, otitis, and eosinophilia can complicate the disease, hence mimicking type 1 hypersensitivity.^{10,11} Stone et al¹ estimated that up to 40% of these patients might have evidence of atopic disease, such as bronchial asthma and allergic rhinitis. Atypical manifestations of asthma or sinusitis requiring steroids for amelioration, weight loss, hepatomegaly, renal dysfunction, or enlargement of lachrymal or salivary glands should alert the allergist immunologist to the possibility of this disease.

Pancreas

It has been known for some time that AIP presents in 2 distinct subtypes (types 1 and 2) that differ in clinical manifestation and histopathologic features.^{1,12–16} Clinically, patients with type 1 AIP present in the elderly (usually of Asian descent) with mild abdominal symptoms of a more slowly progressive nature usually without acute attacks of pancreatitis. Type 2 AIP occurs in younger whites and is typified by acute pancreatitis and near normal IgG4 levels. The pain is of the same quality as typical acute pancreatitis but usually of weaker intensity, is exacerbated by food, and is accompanied by epigastric tenderness. Occasionally, obstructive

Table 1

Adapted from Beyer et al¹⁴

Terminologies used	Organ involved
Mikulicz syndrome	Salivary glands of head and neck (1892)
Riedel thyroiditis	“Eisenharte struma” (1896); thyroid inflammation and fibrosis
Küttner tumor	Submandibular gland tumor (1896)
Chronic sclerosing aortitis	Aortic inflammation
Autoimmune pancreatitis/sclerosing pancreatitis	Pancreatic inflammation
Sclerosing cholangitis	Biliary ductal inflammation and fibrosis
Orbital pseudotumor	Periorbital tissue
Autoimmune hepatitis	Liver parenchymal inflammation and fibrosis
Multifocal fibrosclerosis	Multisystem disease
Retroperitoneal fibrosis	Scarring disease of retroperitoneum; multiple etiologies including metastatic malignancy

jaundice will occur simultaneously. Laboratory studies will show elevated amylase and lipase and possibly elevated IgG4 levels or levels of total IgG (more in type 1). Computed tomography or magnetic resonance imaging will usually demonstrate diffuse pancreatic enlargement (Fig 1A), a peripancreatic capsule-like rim, and late-phase contrast enhancement. Strictures of the pancreatic duct or common bile duct can be visualized at endoscopic retrograde or magnetic resonance cholangiopancreatography (Fig 1B, C).

Bile Duct

Another common manifestation of IgG4-RD is sclerosing cholangitis, which typically presents as localized or diffuse thickening of the bile duct^{1,17,18} (Fig 1C). This eventually leads to stenosis of the duct and leads to abdominal discomfort, obstructive jaundice, and weight loss. There is a strong association between bile duct involvement and AIP in IgG4-RD because most patients with AIP are shown to have wall thickening and sclerosing changes in bile ducts outside the pancreas at endoscopic ultrasonography.

Pulmonary

A plethora of pleuropulmonary and airway disease can complicate IgG4-RD, leading to confusion with allergic airway disorders and systemic conditions such as vasculitis or sarcoidosis. Mediastinal adenopathy, pleuropulmonary masses, lung nodules, interstitial lung disease, serositis, pleural effusions, and lesions resembling mesothelioma can occur^{19–22} (Fig 1D). Suzuki et al²³ reported on the occurrence of organizing pneumonia, air space consolidation, and interstitial inflammation that later proved to be IgG4-RD histopathologically. IgG4-RD can account for a large fraction of patients with retroperitoneal fibrosis.²⁴ Other manifestations are possible, including suppurative lung disease. Pifferi et al²⁵ described a 15-year-old boy with bronchiectasis and lung tissue infiltration by IgG4-bearing plasma cells. Although the incidence of malignancy in IgG4-RD seems unclear and appears not to be heightened, Inoue et al²⁶ described a case of lung and gastric cancer complicated by infiltration of lung tissue by IgG4⁺ plasma cells, the significance of which is unclear at best. Systemic or localized lymphadenopathy is common in IgG4-RD. Although fever, night sweats, and weight loss are uncommon in IgG4-RD, the differential diagnosis of lymphadenopathy includes lymphomas, metastatic disease, sarcoidosis, and Castleman disease. The presence of enlarged mediastinal lymph nodes in patients with interstitial pneumonitis and lung consolidation of the lower lobes should raise the specter of IgG4-RD.²⁷ Matsui et al²⁸ showed that patients with lung involvement tended to be middle-age or elderly men with mediastinal adenopathy and subpleural or peribronchial consolidation. Most pulmonary and airway disease manifestations tend to

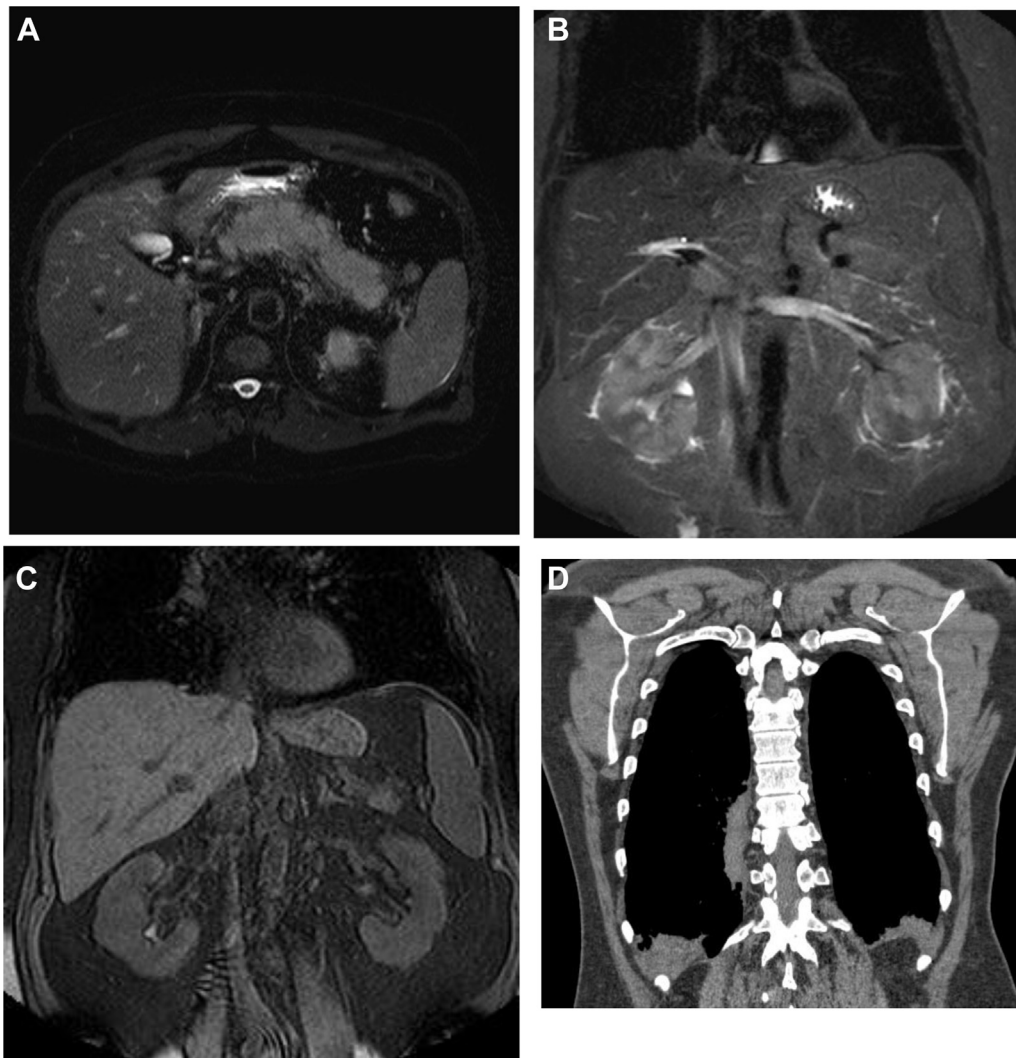


Figure 1. (A) Magnetic resonance image showing diffuse pancreatic body and tail enlargement with homogeneously increased T2 signal, consistent with autoimmune pancreatitis. (B) Magnetic resonance image demonstrating globular renal masses. (C) Localized left hepatic lobe biliary ductal dilation, with abnormal plaque-like wall thickening and enhancement of the adjacent downstream left hepatic duct. This could be one manifestation of a more diffuse sclerotic or inflammatory process. (D) Computed tomogram of the chest demonstrating parenchymal nodules and paraspinal and subpleural inflammatory masses.

respond to glucocorticoids and/or immunosuppressive or biological agents.²⁴

Cardiac

Many complications of IgG4-RD have been reported arising from the involvement of the cardiovascular system.^{24,29–32} These include valvular disease, aortitis, constrictive pericarditis, aortic aneurysms, ischemic stroke, pulmonary hypertension, coronary periarthritis, sudden cardiac death, and inflammatory pseudotumors.

Kidney

The kidney can be affected in different ways in IgG4-RD.^{2,33–35} The classic manifestation is tubulointerstitial nephritis presenting as acute or chronic renal failure or renal mass lesions.^{36,37} Hypocomplementemia and elevated IgE, IgG and IgG4 levels are seen.³⁵ Imaging typically shows multiple renal parenchymal lesions affecting the renal cortex bilaterally, which could appear as small nodules, round lesions, wedge-shaped lesions, or diffuse patchy infiltration. Collecting duct infiltration by plasma cells and fibroinflammatory strictures can lead to cyst formation and tumor-like appearance at imaging.³⁶ There also might be evidence of

irregular nodules in the renal sinuses, diffuse wall thickening of the renal pelvis, or a rim of soft tissue surrounding the kidney, masquerading as masses.³⁷ Inflammatory “pseudotumors” (Fig 1B) can greatly distort renal parenchyma and raise the possibility of renal malignancies.³⁸ Retroperitoneal fibrosis occurring in IgG4-RD can cause ureteral obstruction and renal failure.³⁹ The presence of crescents and necrotizing vasculitis might be the only distinguishing features of renal small vessel vasculitis that differentiates it from IgG4-RD, because IgG4-expressing plasma cells can be seen in these 2 conditions.⁴⁰ Reports of testicular inflammation occurring in IgG4-RD have appeared in the literature.⁴¹

Retroperitoneum and Aorta

Retroperitoneal fibrosis (RPF) is a rare condition often considered secondary to infection, radiation, medication, malignancy, or trauma.^{42,43} Some patients with RPF have shown pathologic features similar to IgG4-RD at biopsy examinations and some reports have observed patients with IgG4-RD developing RPF. In RPF, there is progressive fibrosis of retroperitoneal tissue. This eventually can involve the abdominal or thoracic aorta, leading to aneurysm and possible rupture.

Salivary and Lacrimal Glands

Salivary glands are among the most commonly affected organs in IgG4-RD.^{1,24} Historically, the term *Küttner tumor* had been used to describe a unilateral sclerosing sialadenitis.^{33,44,45} There is glandular swelling (most commonly affecting the submandibular glands) and sicca symptoms. Compared with patients with Sjögren syndrome, those with IgG4-RD tend to experience less xerophthalmia and xerostomia because the lymphocytic infiltration and follicle formation do not injure the structure of the salivary ducts. Patients with IgG4-RD do not usually test positive for anti-Sjögren syndrome-related antigens A and B, rheumatoid factor, or antinuclear antibody but instead tend to have the elevated IgG4 levels and IgE levels typical of this disease.^{44,45}

Ophthalmic

Tumors of ocular adnexa are typically caused by lymphoproliferative disorders. Although many of these are secondary to malignant lymphomas and other forms of orbital inflammations, they can be present in IgG4-RD.⁴⁶ These tumors can affect adjacent structures such as nerves, extraocular muscles (restricting eye movement), periorbital membrane, lacrimal sac, and might rarely bone destruction. Visual disturbances might be present if the optic nerve is involved. Lid swelling and proptosis are common but pain is rare. The lacrimal glands also are commonly affected, causing IgG4-RD dacryoadenitis.⁴⁷ Other orbital complications, including thickening of the optic nerve,⁴⁸ masses around optic nerves,⁴⁹ scleritis,⁵⁰ oculomotor palsies, cavernous sinus thrombosis,⁵¹ and retinopathy due to hyperviscosity⁵² also have been described.

Thyroid

Thyroid involvement in IgG4-RD has been described as far back as the late 19th century, when Riedel first documented a fibrotic form of thyroiditis that bears his name. Oriot et al⁵³ recently reported on a biopsy-confirmed fibrotic form of thyroiditis associated with retroperitoneal fibrosis in a 48-year-old woman who also had documented elevations in IgG4 levels and showed improvement with glucocorticoid administration. The diagnosis of IgG4-RD of the thyroid might be a difficult one to make, owing to the anatomic location and the rare requirement for biopsy examination. It is likely that some patients reported as having classic Hashimoto thyroiditis might have IgG4-mediated disease. This was reported recently in a 55-year-old man with longstanding hypothyroidism who presented with an enlarging goiter, resulting in surgical exploration and excision of the enlarged lobe. Further histopathologic study confirmed the diagnosis of IgG4-mediated (Riedel) thyroiditis.⁵⁴

Central Nervous System

Rare cases of IgG4-RD affecting the central nervous system have been reported.⁵⁵ Parenchymal and structural brain lesions have been described, confirmed by biopsy examination, which showed improvement with glucocorticoids and rituximab.⁵⁶ Aside from the impingement of cranial nerves by expanding orbital tumors, the disease can cause hypertrophic pachymeningitis.⁵⁷ Chronic inflammation causes diffuse or localized thickening of the cranial or spinal cord dura mater. This can present with headache, cranial nerve palsies, vision disturbance, motor weakness, limb numbness, sensorineural hearing loss, and seizures. Imaging might depict linear dural thickening or a bulging mass. Involvement of the pituitary gland can cause hypopituitarism or diabetes insipidus.^{58,59}

Other Manifestations

Sclerosing mesenteritis, a rare condition characterized by inflammation of the root of the small bowel mesentery, has been observed in IgG4-RD. This usually appears as a mass-like soft tissue

thickening encasing the mesenteric vessels at imaging. Few cases of IgG4-RD involvement of the prostate have been reported, usually presenting with enlarged prostate or prostate mass and lower urinary tract symptoms. IgG4-positive cells were eventually discovered at biopsy examination. In the testicles, IgG4-RD has been reported to cause paratesticular pseudotumor or epididymo-orchitis. IgG4 is known to cause erythematous plaques, subcutaneous nodules, angiolymphoid hyperplasia, psoriasiform eruptions, nonspecific maculopapular eruptions, Raynaud phenomena, and purpura.¹¹ Also, inflammatory pseudotumors have been reported in multiple other organs, including breasts, liver, stomach, duodenum, ileum, colon, and nares.

Mechanisms and Pathology

The exact pathogenic mechanisms behind IgG4 RD remain unclear and several theories have been proposed. A genetic predisposition has been associated with the development of AIP. These include certain HLA alleles (DRB1*0405 and DQB1*0401)⁶⁰ and single-nucleotide polymorphisms in immune-related genes (such as cytotoxic T-lymphocyte–associated antigen-4 and tumor necrosis factor- α).² One theory proposes that development of the disease could be related to a form of molecular mimicry, an example being infection with *Helicobacter pylori*, which leads to the formation of antibodies targeted against certain molecular components on the bacteria that share homology to antigens on certain human cells. Others postulate an important role for aberrant immune responses.

Roles of Cytokines and T Cells

Several researchers have attempted to study the role of T-cell–derived cytokines in IgG4-RD. Some researchers have suggested that these antibodies could act as autoantibodies and induce disease.⁶¹ Others have proposed a biphasic pathogenic mechanism in which T-helper type 1 (T_H1) cells produce cytokines that induce the disease and T-helper type 2 (T_H2) cells contribute to the progression of the disease. During the initial “induction” phase, the decreased levels of naive regulatory T cells (T-reg) observed in patients with IgG4-RD cause T_H1-type immune response and release of proinflammatory cytokines.¹⁴ This eventually upregulates T_H2 cells and memory T-reg cells, which results in B-cell maturation and proliferation. During this “progression” phase, interleukin (IL)-10 produced by T_H2 or T-reg cells leads to expansion of IgG4-producing plasma cells and increased transforming growth factor- β can lead to fibrosis.^{14,16}

The hallmarks of IgG4-RD include the rich lymphoplasmacytic infiltration in association with fibrosis and an obliterative phlebitis. These changes are accompanied by an elevated level of IgG4 and increased numbers of IgG4-expressing plasma cells. The production of IgG4 is controlled primarily by T_H2-derived IL-4 and IL-13 enhancing the production of IgG4 and IgE and of T-reg–derived IL-10 and IL-12 and IL-21, thus favoring IgG4 over IgE.⁶² Some of these immunologic findings might mimic Mikulicz syndrome or primary Sjögren syndrome, with the latter demonstrating more of a T_H1 than a T_H2 response compared with patients with IgG4-RD.⁶² It needs to be emphasized that the pathogenesis of the condition is poorly understood, but summarizing current knowledge, T_H2 cells (IL-4 and IL-13) activate B cells to class switch to IgE and IgG4, with factors such as transforming growth factor- β , vitamin D, and IL-10 inducing an IgG4 response. The presence of IL-10, IL-12, and IL-21 seem to push the response more toward IgG4 than toward IgE, suggesting much of the observed pathology represents the type of cytokine cocktail elaborated during the aberrant immune response in these individuals with IgG4-RD.⁶² Recent studies by Furukawa et al⁶³ also have demonstrated a role for macrophage-derived IL-10 and chemokine ligand-18 in tissue fibrosis in IgG4-related dacryoadenitis and sialadenitis. Other organ-specific factors can

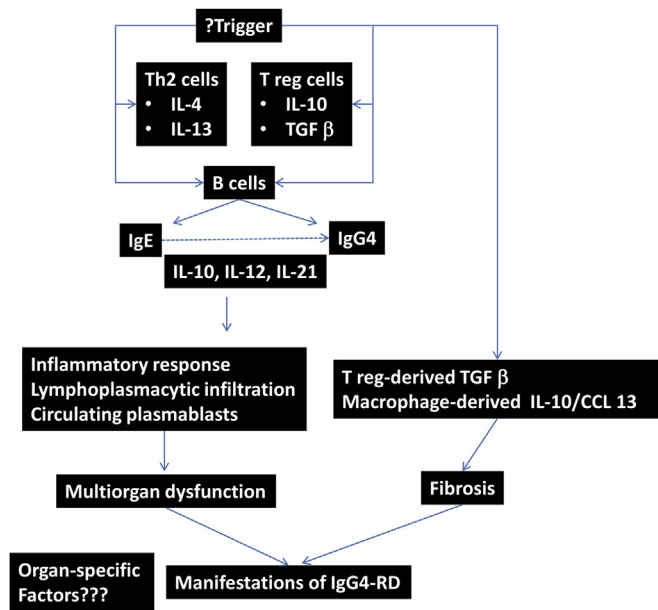


Figure 2. Cartoon depicting components of the immune response that could lead to altered eosinophil, IgE, total IgG, IgG4, and immunoregulatory cytokine levels culminating in the observed pathologic effects of fibrosis (fibrosclerotic disease) and multiorgan dysfunction. T_H2 cells (IL-4 and IL-13) activate B cells to class switch to IgE and IgG4, with factors such as TGF- β , vitamin D, and IL-10 inducing an IgG4 response. The presence of IL-10, IL-12, and IL-21 seem to push the response more toward IgG4 than toward IgE, suggesting much of the observed pathology represents the type of cytokine cocktail elaborated during the aberrant immune response in these individuals with IgG4-related disease. Recent studies by Furukawa et al.⁶³ also have demonstrated a role for macrophage-derived IL-10 and CCL 18 in tissue fibrosis in IgG4-related dacryoadenitis and sialadenitis. Other organ-specific factors also can influence the evolution of unique or specific pathologic features. CCL 18, chemokine ligand-18; IL, interleukin; TGF β , transforming growth factor- β ; T_H2 , T-helper cell type 2; T-reg, T-regulatory cell.

influence the evolution of unique or specific pathologic features. Some of these interactions are depicted in cartoon format (albeit incompletely) in Figure 2.

Role of IgG4

Most patients with IgG4-RD have elevated serum levels of IgG4. In some studies, up to 30% to 40% of patients have normal levels of IgG4. To complicate things further, the recent description of 2 patients with clinical, radiologic, and histopathologic findings of IgG4-RD with normal serum levels of IgG4 and absent tissue infiltration by IgG4-expressing cells has raised questions regarding the actual role of the IgG4 antibody in disease pathogenesis.⁶⁴ IgG4 is typically the least abundant of the subclasses, making up only 5% of total IgG in serum of healthy adults except in patients with chronic exposure to a specific antigen (through occupation or immunotherapy) in whom it makes up 80% of total IgG and is thought to be involved in antigen desensitization.⁶⁵ IgG4 is a unique molecule in several respects. IgG4 interacts poorly with complement and with Fc γ RII and Fc γ RIII receptors, rendering the antibody relatively noninflammatory.⁶⁶ IgG4 can undergo heavy-chain exchange (or Fab-arm exchange), which involves exchanging the Fab-arm with other IgG4 molecules, leading to the formation of monovalent but bispecific antibodies.^{66,67} This prevents IgG4 from forming large immune complexes. Another unique feature is the ability of IgG4 to interact with the Fc fragment of another IgG molecule, mimicking the formation of IgG rheumatoid factors.⁶⁸ Moreover, being regulated predominantly by T_H2 cytokines, IgG4 responses are more likely directed toward non-microbial antigens and likely could explain the association between IgE-mediated allergic

Table 2

Clinical manifestations of IgG4-related disease

Organ system	Clinical manifestations
Pancreas	Type 1 autoimmune pancreatitis ²⁴
Bile duct	Multifocal biliary strictures that respond to glucocorticoids ¹
Liver	Portal inflammation, large bile-duct obstructions, portal sclerosis, lobular hepatitis, canalicular cholestasis ¹
Gastrointestinal tract	Gastritis, possible link with inflammatory bowel disease ¹¹
Salivary and lacrimal glands	Sclerosing sialadenitis (Küttner tumor), painless lacrimal and salivary gland swelling (Mikulicz disease) ^{32,44,45}
Orbit	Chronic sclerosing dacryoadenitis and inflammatory orbital pseudotumors ⁴⁶
Retroperitoneum	Marked fibrosis within retroperitoneal tissue can entrap abdominal organs ⁴²
Mesentery	Sclerosing mesenteritis, multifocal fibrosclerosis, and sclerosing mediastinitis ¹¹
Aorta	Abdominal or thoracic aortitis, can lead to abdominal aortic aneurysm or periaortitis ²
Thyroid	Riedel thyroiditis, fibrosing variant of Hashimoto thyroiditis ⁴²
Breast	Inflammatory pseudotumors within breast tissue, sclerosing mastitis ²⁹
Lung	Lung nodules, inflammatory pseudotumors, interstitial pneumonias ^{19–23}
Kidney	Inflammatory pseudotumors, tubulointerstitial nephritis and fibrosis ^{36,37}
Pituitary gland	Hypophysitis that resolves with glucocorticoids ⁵⁹
Meninges	Idiopathic hypertrophic pachymeningitis, hypertrophic pachymeningitis not confirmed, associated with multifocal fibrosclerosis ⁵⁷
Prostate	Prostatitis, glandular atrophy with fibrosis ¹¹
Skin	Erythematous or flesh-colored with histopathologic features papules, cutaneous pseudolymphoma ¹¹
Lymph nodes	Generalized lymphadenopathy without constitutional symptoms, lymphadenopathy adjacent to affected organ ²
Pericardium	Constrictive pericarditis ³⁰

processes and some autoimmune-appearing manifestations of IgG4-RD.⁶⁸ In atopic disease, IgG4 is associated with a “blocking effect” and results in decreased mediator release from mast cells and in decreased antigen-presenting cell-mediated T-cell activation.⁶⁸ These facts lead to some confusion regarding the actual role of the molecule in disease pathogenesis.

Diagnosis

The IgG4-RD can affect many different organs (Table 2) and present in many different ways.^{28,34} This heterogeneous clinical picture and the rarity of the disease often complicate the process of attaining the proper diagnosis. Appropriate clinical presentation in conjunction with serologic markers and pathologic examination of tissue should assist in the diagnosis (Table 3).

Serum IgG4 Levels and Other Inflammatory Biomarkers

As the name of the disease implies, many patients demonstrate elevated serum IgG4 levels out of proportion to other IgG subclasses. However, a significant portion of patients will have normal

Table 3

Comprehensive diagnostic criteria for IgG4-related disease^a

Diagnostic criteria
1. Characteristic clinical manifestations including diffuse or localized swelling or masses in single or multiple organs
2. Elevated serum IgG4 concentrations (>135 mg/dL)
3. Histopathologic examination showing
Marked infiltration of lymphocytes and plasmacytes with fibrosis (most commonly in storiform pattern)
Infiltration of IgG4 ⁺ plasma cells or ratio of IgG4 ⁺ to IgG ⁺ cells >40%

^aDiagnosis is definitive if all criteria are present, probable if only criteria 1 and 3 are present, and possible if only criteria 1 and 2 are present.

IgG4 levels. Moreover, there is no apparent correlation between serum IgG4 level and the progress of the disease, severity of the disease, or recurrences of the disease. The term *prozone phenomenon* refers to the possibility that in immunoassays, excess of antigen can cause a false low result and dilution of the sample is required to obtain an accurate quantitation. It is not current practice to perform manual dilutions of samples when testing for IgG4 levels by nephelometry, and therefore it is helpful to the clinical laboratory if the clinician specifies the diagnostic indication for assessing IgG4 and notifies the laboratory of the possibility of a prozone phenomenon. This would, on occasion, enable the testing laboratory to consider a prozone effect and automatically perform manual dilutions when such a sample is received (if such dilutions are allowed or possible for the specific laboratory in question). Thus, this would ensure that there is no “hook effect” leading to a spuriously low or normal IgG4 level.

Inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein might be elevated but could be normal. Similarly, complement levels could be low during acute disease process but not universally. There is typically polyclonal hypergammaglobulinemia and increased serum IgE levels. Imaging can be used to assess disease involvement in different organs that might yet be subclinical to determine appropriate tissue to biopsy. This should be guided by the patient's history, physical examination, and results of routine laboratory examinations.^{1,33}

Tissue Examination

Although IgG4-RD can present in a wide array of organ systems, all manifestations exhibit certain characteristic histopathologic features and elevated IgG4⁺ plasma cells at tissue biopsy examination.^{1,2,28,34} Therefore, tissue sample demonstrating these 2 attributes is required for a definitive diagnosis. There are 3 major histopathologic features associated with IgG4-RD: dense lymphoplasmacytic infiltrate, fibrosis arranged in storiform pattern, and obliterative phlebitis. If 2 of these are evident on the sample, then a pathologist can confidently diagnose IgG4-RD. There are some exceptions in specific organ systems and some features might not be observed owing to an advanced stage of disease. Other characteristics, such as phlebitis without obliteration of the lumen and increased number of eosinophils, are commonly observed but these are neither sensitive nor specific for IgG4-RD.^{1–3,14,17} There also could be evidence of arteritis (especially in the pancreas and lung) but this is typically non-necrotizing in IgG4-RD.^{1–3,17} Some histopathologic features are inconsistent with a diagnosis of IgG4-RD. These include the presence of epithelioid cell granulomas, giant cells, neutrophilic infiltrate, and evidence of necrosis.

Immunostaining of IgG4 to demonstrate an elevation in IgG4⁺ plasma cells is an essential test for the pathologic diagnosis of IgG4-RD, particularly in the 30% to 40% of patients who might not have an elevated serum IgG4 level. There are typically diffuse dense infiltrates of IgG4⁺ plasma cells on examination (Fig 3). However, the exact number of cells per high-power field varies with the site of biopsy and with the degree of fibrosis that has already taken place. Therefore, different cutoff values have been proposed for different organs. Another issue is that inflammatory diseases other than IgG4-RD can cause an increase in the number of IgG4⁺ plasma cells. Therefore some researchers have suggested that a ratio of IgG4⁺ to IgG⁺ plasma cells greater than 40% be used as a comprehensive cutoff for all organs. Although evidence shows this could be a better approach, it is not ideal because there are a few conditions other than IgG4-RD that can produce a similar ratio.¹⁷

Circulating Plasmablasts

Mattoo et al⁶⁹ demonstrated oligoclonal expansions of circulating plasmablasts in IgG4-RD using flow cytometry. These

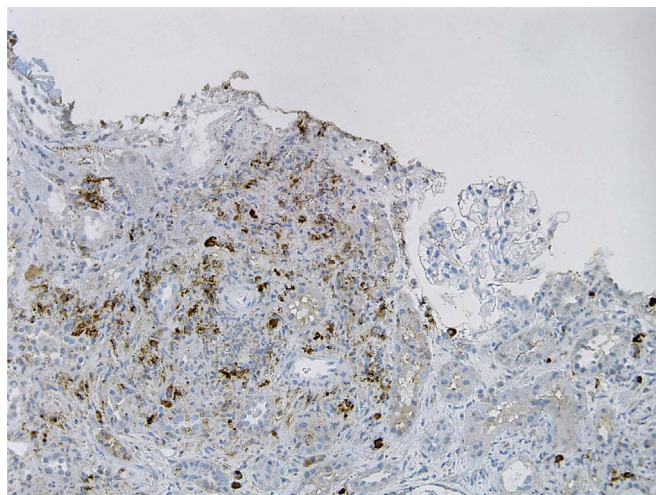


Figure 3. Immunopathology. An IgG4 immunohistochemical stain (200 $\times$) documents that many plasma cells in the infiltrate (approximately 40%) express IgG4 in 1 patient with IgG4-related disease. This represents immunopathologic findings from a kidney biopsy examination.

investigators found elevated numbers of CD19⁺, CD27⁺, CD20⁺, and CD38 (hi) IgG4⁺ plasmablasts in patients with IgG4-RD. Sequencing of flow-sorted B-cell populations was carried out in a small subset of these patients, which demonstrated oligo-clonality and extensive hypermutation. These oligoclonal populations decreased with rituximab therapy.⁶⁹ In patients with relapsing disease, a new or resurgent population of plasmablasts can reappear. Other investigators have reported similar findings.^{70,71} Based on these findings, it is likely that flow cytometry and analysis of populations of plasmablasts might provide an additional diagnostic tool, where multicolor flow cytometry is available.

Role of Food Allergen-Specific IgG4 Responses

Of interest to allergists, Culver et al⁷² demonstrated elevated IgG4 responses to multiple food allergens in IgG4-RD. In this study, investigators analyzed the IgG4 responses to a panel of food allergens, including egg yolk, milk, banana, peanut, rice, and wheat. Elevated polyclonal IgG4 responses were observed to multiple food allergens in IgG4-RD and primary sclerosing cholangitis associated with a high IgG4 level. Although this study suggests that the immune dysregulation seen in IgG4-RD results in aberrant responses to multiple food allergens, the diagnostic or etiologic value of this finding is unclear.

Treatment

Disease related to IgG4 can vary greatly in different patients with a wide spectrum of clinical manifestations and natural history. In some patients, the disease might be only minimally symptomatic or present with isolated lymphadenopathy. In these patients with a more indolent form of the disease, treatment might not be indicated and these patients could be monitored for disease progression. If a vital organ is affected by IgG4-RD, untreated disease can progress from lymphoplasmacytic inflammation to extensive fibrosis. Therefore, treatment is indicated in symptomatic patients to prevent serious organ dysfunction and failure. Treatment options are summarized below and in Table 4.

Glucocorticoids

The mainstay of treatment involves use of systemic corticosteroids; however, no randomized trials have been performed to guide treatment and treatment is typically guided by observational

Table 4
Selected treatment options²⁴

Drug	Dosing	Side effects	Monitoring
Prednisone	0.6 mg/kg/d × 2–4 wk	Diabetes, hypertension, osteoporosis, increased risk of infection, sleep disruption, changes in mood, easy bruising, poor wound healing, muscle weakness	Electrolytes, blood glucose level, blood pressure
Azathioprine	2–2.5 mg/kg/d	Increased risk of infection, GI discomfort, bone marrow suppression, hepatitis, pancreatitis, drug interaction with allopurinol	Screen for TPMT deficiency before starting, complete blood cell count, liver function tests
Mycophenolate	750 mg 2×/d	Increased risk of infection, GI discomfort, bone marrow suppression, teratogenesis, colonic bleeding	Pregnancy test, complete blood cell count
Rituximab	1,000 mg IV × 2 treatments 2 wk apart	Increased risk of infection, infusion reaction, delayed and transient neutropenia, contraindicated in pregnancy	Pregnancy test, complete blood cell count

Abbreviations: GI, gastrointestinal; IV, intravenously; TPMT, thiopurine methyltransferase.

studies. One consensus statement published in Japan recommended treating patients with initial dose of prednisolone at dose of 0.6 mg per kilogram of body weight daily for 2 to 4 weeks followed by taper to a dose of 2.5 to 5 mg/day for up to 3 years or taper off steroids completely within 3 months. The impressive response to steroids is a hallmark of the disease. If a patient shows no improvement on systemic steroids, then alternative diagnoses should be entertained.^{1,14,24} Glucocorticoids appear to be efficacious in most patients. Some patients started on steroid therapy demonstrate full resolution and remission, but it is not uncommon for patients to experience disease flares as steroids are tapered or discontinued or progression of the disease while on steroid therapy. For this reason, and owing to the well-known adverse effects of long-term systemic glucocorticoid therapy, alternative agents have been used to treat this disease.

Steroid-Sparing Agents

Steroid-sparing medications (such as azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, fludarabine, and bortezomib) have been used anecdotally with variable efficacy.³ Table 4 presents some useful information regarding azathioprine, mycophenolate mofetil, and rituximab.

Rituximab is a monoclonal antibody directed against the CD20 antigen on B lymphocytes that is known to deplete plasma cells and decrease serum IgG4 levels while maintaining stable levels of other IgG subclasses. Case reports have shown this to be effective as a steroid-sparing agent in refractory cases of IgG4-RD. In 1 case series, all 10 patients treated with rituximab could discontinue prednisone, 9 of whom demonstrated substantial clinical improvement within 1 month of first infusion.⁷³ Although some patients showed remarkable improvement with 1 dose of rituximab, some required serial rituximab infusions to achieve disease remission. Some did develop disease recurrences, but the flares responded quickly to repeat courses of rituximab. It also has been shown to be effective in patients whose serum IgG4 concentration was never elevated. Although most patients respond well to treatment, preventing further progression of inflammation and fibrosis, in patients with extensive fibrosis, no therapy has been shown to reverse the fibrosis that has already occurred.⁷³ A more recent study by Carruthers et al⁷⁴ demonstrated disease responses in 97% of patients treated with rituximab; 77% of patients demonstrated a significant decrease in IgG4 levels, and 47% remained in complete remission at 6 months and 40% at 1 year.⁷⁴ Interestingly, of 30 patients studied, only 19 had elevated baseline IgG4 levels, and of these patients, only 8 achieved normal IgG4 levels. Therefore, rituximab remains an effective option for the disease and continues to be used for disease relapses or when steroid adverse effects are intolerable.

A very recent consensus statement (March 2015) summarizes the need for therapy, use of glucocorticoids for induction, use of

selected steroid-sparing agents, management of relapses with glucocorticoids or with steroid-sparing medication, and the need for low-dose immunosuppression in some patients for maintenance of remission.⁷⁵ This review provides an excellent point-by-point discussion of various facets in the management of this multisystem disease.

Conclusion

IgG4 is a syndrome in rapid evolution. Much is known about the disease, and much remains to be known. Although elevated serum IgG4 levels are suggestive of the disease, the absence of this finding should not be considered an exclusion of the diagnosis. In all cases, the diagnosis is confirmed by histopathologic examination of the involved tissue. Treatment is usually effective but marred by adverse effects of medication and/or relapse of the primary disease.

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