



Immunoglobulin G4-Related Disease: An Update

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ABSTRACT

Immunoglobulin G4-related disease (IgG4-RD) is an increasingly recognized immune-mediated condition comprised of a collection of disorders that share specific pathological, serological, and clinical features. IgG4-RD is a fibroinflammatory condition with a tendency to form tumors with inflammatory infiltrate with IgG4 rich plasma cells and elevation of serum IgG4, which may affect virtually every organ and tissue. IgG4-related ophthalmic disease may present as dacryoadenitis, myositis, or involvement of other orbital tissue. Hypophysitis or pachymeningitis may manifest as cranial neuropathies. The diagnosis of IgG4-RD is based on a typical clinical scenario, supportive laboratory test, expected radiological characteristics, and distinct histopathological and immunohistochemical features. Corticosteroids and immunosuppressives form the mainline treatment.

Immunoglobulin G4-related disease (IgG4-RD) is a group of immune-mediated diseases with common clinical, serological, and pathological features.¹ This group is gaining increasing recognition in the field of medicine. Common features of IgG-RD include multiple organ involvements (which have swellings resembling tumors), fibrosis, tissue infiltrates (which are positive for IgG4 positive plasma cells), and a classical pathological form of storiform lesions. Previously these features, singularly or collectively, were believed to be distinct entities not related to IgG4-RDs.²⁻⁴

IgG4-RD often has multiple organ involvements. Classical manifestations include:

- Autoimmune pancreatitis (AIP) type 1.
- Involvement of the major salivary glands. The common lesions being enlargement or inflammation (sclerosing sialadenitis-formerly termed Mikulicz disease and Küttner's tumor).
- Proptosis, which occurs mainly due to the involvement of the orbital or lacrimal gland. Orbital pseudotumor is an important differentiating pathology.
- Retroperitoneal fibrosis, frequently occurring as chronic periaortitis.

Three classical features of IgG4-RD include swellings or masses that resemble or have a predilection

to form tumors, an IgG4 rich collection of plasma cells in the inflammatory infiltrate and elevated serum IgG4 levels. Such swellings or masses can press on nerves or blood vessels producing focal vascular and or neurological deficits. Common clinical conditions associated with IgG4-RD include dacryoadenitis, myositis, inflammatory orbital disorders, orbital pseudotumor, hypophysitis, meningitis, and the involvement of one or more cranial nerves.¹

Other systemic and ocular disorders that resemble IgG4-RD include inflammatory diseases and vasculitis such as sarcoidosis, granulomatosis with polyangiitis, giant cell arteritis, Behcet's disease, thyroid eye disease, inflammatory histiocytosis, or rheumatoid arthritis; neoplastic diseases such as lymphoma, inflammatory myofibroblastic tumor, neoplastic histiocytosis, meningioma, or metastasis; and infectious diseases such as tuberculosis. Also included are conditions in the inflammatory pseudotumor category, which are currently considered idiopathic.

The exact incidence of IgG4-RD is unknown. Wallace et al,² retrospectively examined 14 cases of pachymeningitis at their institution over 25 years and found that IgG4-RD accounted for four of those cases or 66% of previously labeled idiopathic cases. Therefore, cases previously labeled as idiopathic

inflammatory pseudotumor, should be re-examined for IgG4-RD (if the pathological sample is still available) or a repeat biopsy conducted.

Pathophysiology

The exact pathophysiology of IgG4-RD is not yet clear. Many patients suffer from allergic or atopic conditions thereby suggesting a modified T-helper cell type 2 response. An underlying autoimmune mechanism most likely drives IgG4-RD, but no precipitating factors have yet been identified. There is a higher risk for IgG4-RD in certain genotypes and there is immune complex deposition and increase in regulatory CD25 T-cells. However, molecular mimicry by causing an autoimmune reaction to a foreign antigen may be important. *Escherichia coli* and *Helicobacter pylori* have been implicated as possible candidates for such mechanism in AIP. Production of inflammatory tissue T-cell cytokines by mast cells suggest their role in pathogenesis.⁴ IgG is a large structure consisting of four subgroups. IgG4 comprises only 6% or less of that. Both IgG3 and IgG4 can cause bacterial opsonization, but IgG4 differs from IgG3 in that it cannot activate the complement.

Epidemiology

Middle-aged males have more predilections for overall IgG4-RD. However, the gender ratio has been found to be almost equal to IgG4-related inflammatory disorders of the salivary glands (sialadenitis) and ophthalmic diseases.^{3,5}

Organ manifestations

With the recognition of IgG4-RD as an important and separate entity, the nomenclature for many mainly inflammatory systemic and ocular diseases has changed [Table 1].

Single or multiple organs can be involved in IgG4-RD. The presentation is usually subacute with the development of a localized mass or nodule as in the orbit, kidney, and lungs or diffuse enlargement of an organ such as the pancreas.^{1,6-8} Takeuchi et al,⁴ and Sah et al,⁹ reported multiple organ involvements in 60–90% of patients with IgG4-related disorders. For a clinician, the clinical, histopathological, and laboratory (serum-related) similarities between IgG4-RD and sarcoidosis may be challenging. Sato et al,⁷ reported that 40% of patients with IgG4-RD have lymphadenopathy and asthma or allergy-

Table 1: IgG4-RD newly laid nomenclature.

Old	New
Mikulicz's disease	IgG4-related dacryoadenitis and sialadenitis
Sclerosing sialadenitis	Küttner's tumor, IgG4-related submandibular gland disease
Inflammatory orbital pseudotumor	IgG4-related orbital inflammation or orbital inflammatory pseudotumor
Chronic sclerosing dacryoadenitis	Lacrimal gland enlargement, IgG4-related dacryoadenitis
'Idiopathic' retroperitoneal fibrosis (Ormond's disease) and related disorders	IgG4-related retroperitoneal fibrosis, IgG4-related mesenteritis
Chronic sclerosing aortitis and periaortitis	IgG4-related aortitis or periaortitis
Riedel's thyroiditis	IgG4-related thyroid disease
IgG4-related interstitial pneumonitis and pulmonary inflammatory pseudotumors	IgG4-related lung disease

IgG4-RD: immunoglobulin G4-related disease.

related symptoms, however, early in the course, they may be asymptomatic. Those with multiorgan disease often lose weight over months before they are correctly diagnosed. IgG4-RD is often recognized incidentally after an abnormal finding on imaging or histopathology examination of a tissue specimen. Hamano et al,¹⁰ observed that in patients with AIP, extrapancreatic involvement might be common and varied; these include hilar lymphadenopathy (80%), extrapancreatic bile duct lesions (74%), lacrimal and salivary gland lesions (39%), hypothyroidism (22%), and retroperitoneal fibrosis (13%).

Orbital IgG4-related disorders are common in adults and have three classical features:

- The ocular adnexal tissues show typical lymphoplasmacytic infiltrations, which are IgG4-positive.
- Elevated serum IgG4 and IgE levels.
- Hypergammaglobulinemia.

Two entities that need to be differentiated from orbital IgG4-RD include idiopathic orbital inflammation and marginal zone B-cell lymphoma of orbital adnexal tissues because the treatment profiles of the diseases are different. Usually patients with orbital IgG4-RD present with chronic symptoms like lid swelling, proptosis usually mild or no signs of inflammation or periocular pain. Ocular motility is

restricted mildly if at all despite the presence of one or more enlargements of the large extraocular muscles.¹¹ There are generally no visual disturbances although they may occur due to apical orbital lesions. Imaging studies show infiltrative lesions in ocular adnexal tissues such as the lacrimal glands,¹²⁻¹⁴ extraocular muscles,^{11,12} infraorbital nerves,¹² optic nerve sheath,¹² lacrimal sac,¹² and even cavernous sinus or the intracranial extension.¹² Plaza et al,¹² studied a series of patients with orbital IgG4 disorders and found bilateral orbital lesions in 62% of cases, and bilateral lacrimal gland involvement in 48% of cases. It is important to differentiate idiopathic orbital inflammations and idiopathic orbital myositis from orbital IgG4-RD. The former two have unknown etiology and are associated with acute onset of signs and symptoms of orbital inflammation like periocular pain, swelling and redness of the eyelids, proptosis, ptosis, and ocular motility restrictions.¹⁵ These differ from the signs and symptoms of orbital IgG4-RD, which has a chronic course. However, some cases of idiopathic orbital inflammation may have an atypical presentation without acute onset and minimal signs of inflammation.

The histological features of ocular adnexal marginal zone B-cell lymphomas resemble those of orbital IgG4-RD. Nine percent of patients with ocular adnexal marginal zone B-cell lymphomas have infiltration of IgG4-positive plasma cells and elevated IgG4 serum levels.^{16,17} However, the two entities can be differentiated by southern blot analysis, which shows light-chain restrictions by hybridization and immunoglobulin heavy chain gene rearrangements. Bijlsma et al,¹⁸ indicated a possible link between ocular adnexal lymphomas and IgG4-related sclerosing dacryoadenitis. However, the causal relationship between lymphomas and IgG4-RD remains unclear.

Antineutrophil cytoplasmic antibody (ANCA)-related vasculitis often infiltrates in ocular adnexal lesions. ANCA-related vasculitis includes nonspecific inflammatory lesions, and may also have abundant IgG4-positive plasma cells.¹⁹ Orbital IgG4-RD differs from other IgG4-RD in the body in that it arises from non-glandular lesions and is not associated histologically with obliterative phlebitis.

Salivary and lacrimal gland involvement

The common presentation is swelling due to enlargement of lacrimal and salivary glands,

most frequent being parotid and submandibular glands. The most common clinical diagnosis is chronic sclerosing sialadenitis.^{20,21} These clinical conditions were previously wrongly labeled as subcategories of sclerosing sialadenitis.²² Plaza et al,¹² reported that nearly 40% of patients with IgG4-related pancreatitis also have concomitant salivary or lacrimal gland involvement. They also reported a 17% incidence of AIP in patients with sialadenitis.¹² It has been observed sialadenitis often precedes AIP. The histopathological features in IgG4-related sialadenitis and dacryoadenitis include lymphoplasmacytic infiltrate, IgG4-positive cells, obliterative phlebitis, and fibrosis.²³ Raised serum IgE levels are also found along with elevated IgG4. Such histopathologic and laboratory findings help to distinguish between IgG4-related sialadenitis and sclerosing sialadenitis.

Masaki et al,²¹ laid down four-point characteristic clinical features of IgG4-related sialadenitis, which help in differentiating this disease from sclerosing sialadenitis. These include:

- Mild dryness of mouth and eyes despite the marked involvement of salivary and lacrimal glands.
- Allergic rhinitis and bronchial asthma.
- IgG4-related autoimmune pancreatitis and interstitial nephritis (which occur in high frequency).
- Presence of autoantibodies like rheumatoid factor, antinuclear antibodies, anti-Sjögren's syndrome A and anti-Sjögren's syndrome B (which occur in low frequency).

Orbital pseudotumors may account for 25–50% of IgG4-RD group.²⁴ Lately, idiopathic orbital myositis has also been recognized as an IgG4-related entity.²⁵

IgG4-related disorders affecting other body organs

Multiple organ involvements in IgG4-RD is so varied, it resembles mimickers like sarcoidosis. There is a long list of tissues and organs involved in IgG4-RD and laying clinical and laboratory details of each one of them is beyond the parameters of this review. However, supporting references would help the reader in getting full details, bearing in mind that many such reports in the literature are based on single case reports or small case series. Some of the common and listed tissues and organs that can be afflicted with IgG4-RD are:

- Lymph nodes (IgG4-related lymphadenopathy), which is very common in AIP (80%).¹²
- Retroperitoneum (retroperitoneal fibrosis).²⁶
- Mesenteries (sclerosing mesenteritis).²⁷
- Mediastinum (sclerosing mediastinitis).²⁷
- Aorta and periaortic tissue (aortitis – periaortitis).²⁸
- Thyroid gland (IgG4-related thyroid disease, formerly called Reidel's thyroiditis) and variant of fibrous Hashimoto's thyroiditis.²⁹
- Lungs and pleura (IgG4-related pulmonary disease).^{30,31}
- Kidneys: Most common diagnosis is IgG4-related tubulointerstitial fibrosis.^{32,33}
- Skin: Lesions are common in head and neck area. Common diagnosis is cutaneous pseudolymphoma.^{34,35}
- Liver (IgG4-related hepatopathy). It resembles autoimmune hepatitis and inflammatory hepatic pseudotumor.^{36,37}
- Stomach and pancreas (IgG4-related lymphoplasmacytic gastritis and IgG4-related autoimmune pancreatitis, respectively).³⁸
- Breast (sclerosing mastitis and inflammatory pseudotumors of the breast).^{39,40}
- Pituitary gland (IgG4-related hypophysitis).^{41,42}
- Meninges (IgG4-related pachymeningitis).^{43,44}
- Prostate (IgG4-related prostatitis).⁴⁵
- Pericardium (IgG4-related constrictive pericarditis).^{46,47}
- Nasopharynx.^{48,49}
- Thoracic midline-destructive lesion.⁵⁰

Diagnosis

The clinical diagnosis of IgG4-RD is supported by laboratory investigations, imaging, histopathology, and immunohistochemistry. Elevated total IgG and IgG4 serum levels are the hallmarks of IgG4-RD. However, serum concentrations of IgG4 alone are not the diagnostic marker. Frulloni et al,⁵¹ reported that 20–40% of patients with biopsy-proven IgG4-RD have normal IgG4 concentrations at the time of diagnosis even before the start of therapy. Carruthers et al,⁵² estimated that elevation of serum IgG4 concentration had a sensitivity of 90% and specificity of 60% with a high negative predictive value of 96% but low positive predictive value of 34% in the diagnosis of IgG4-RD. Cerebrospinal fluid (CSF) analysis in patients with IgG4-RD of the central nervous system may reveal mild to moderate lymphocytic pleocytosis, a nonspecific

finding. Therefore, the main value of CSF testing in those cases is the exclusion of infection and cancer. Further, it is unclear how sensitive or specific IgG4 measurement in CSF really is.

Katsura et al,⁵³ reviewed the radiological features of the head, neck, and brain of 17 histopathologically confirmed cases of IgG4-RD, which included computed tomography (CT) and magnetic resonance imaging (MRI). The general radiological features found included well-defined soft tissue masses showing homogeneous attenuation/signal intensity which enhanced homogeneously. Erosive and sclerotic changes without destruction were seen in bones adjacent to the lesions. Diffuse thickening of the dura mater was also seen. Lacrimal, salivary, and pituitary glands were preferentially affected. Cranial nerves, mainly the trigeminal nerve, show perineural spread. Hardy et al,⁵⁴ found enlargement of the infraorbital nerve and canal in patients with both IgG4-RD and benign reactive lymphoid hyperplasia with orbital involvement.

Diagnostic criteria

A consensus statement from a multinational expert group on IgG4-RD laid guidelines for the diagnosis of the disease. The classical histopathological features consist of a triad of lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. Tissue eosinophilia and raised IgG4-positive plasma cells add to the accuracy of diagnosis. Tissue certain parameters (like IgG4 cell counts and IgG to IgG4-positive cell ratio) form second-line in confirmation of the histopathological diagnosis.^{21,55} Tissue diagnosis requires a minimum of 30–50 IgG4-positive cells per high power field (HPF). This is not mandatory, for example, for kidney tissue even 10 IgG4-positive cells per HPF may be sufficient to aid diagnosis.⁵⁵

Establishing the diagnosis after the initial assessment

The following recommendations have been laid to confirm the diagnosis of IgG4-RD after the preliminary evaluation:

- Imaging: This may require CT scans, positron emission tomography and MRI of the affected tissues and organs.
- Urinalysis in IgG4-related tubulointerstitial nephritis (TIN).
- Serology mainly for complement levels (C3, C4).

Example: Low complement levels may strongly suggest IgG4-related TIN.

- Allergic markers in IgE-related allergic diseases.

Management

Since there are no clear guidelines for the treatment of IgG4-RD, the current approach to treat this entity is based on the experience of individual or group observation, case reports, and case series. The commonest subgroup that has been treated is AIP.⁵ The highest success rate has been achieved with rituximab, which causes B-cell depletion.^{56,57} Unfortunately, no randomized clinical trial has been conducted so far to evaluate the treatment modality for IgG4-RD as a whole or any of its subsets. The commonest and the safest drugs currently used are corticosteroids. The response to steroids is apparent within a few weeks in terms of symptomatic improvement, a reversal in the size of the masses, reduction in organ enlargement, improvement in organ function, and decrease in IgG4 serum levels. Such a response is not universal. Patients may take months to respond or not respond at all (e.g., those with severe fibrotic disease). An IgG4-RD responder index has been developed to elucidate the drug response clinically and find improvement in laboratory parameters.⁵⁸

Patients with mild disease with mild 'symptoms and signs' like small lung nodules or mild lymphadenopathy may be observed only. However, patients with major organ disease with moderate to severe symptoms need to be treated. These include IgG4-related lacrimal gland disease, orbital masses with proptosis, submandibular and parotid gland involvement, IgG4-related tubulointerstitial nephritis, AIP, retroperitoneal fibrosis, and hydronephrosis. Treatment with prednisone, usually at a dose of approximately 40 mg/day is recommended. A response is frequently seen within two to four weeks and often sooner. Once a significant response is clinically evident in the affected organ system, the dose of glucocorticoids is gradually tapered, with a planned reduction over a two-month period, as tolerated, and the goal of discontinuing the medication entirely.

Rituximab is a safe, first-line treatment and effective alternative in patients who either have unacceptable side effects with the conventional dose of steroids or are resistant.^{5,49} The main advantage of rituximab is it causes a reduction in serum IgG4 due

to B-cells without affecting other immunoglobulins. Rituximab also reduces the concentration of blood plasmablasts.

The second-line drugs also indicated as steroid-sparing agents include azathioprine (2 mg/kg/day) and mycophenolate mofetil (up to 2.5 g/day).

Prognosis

The prognosis of IgG4-RD is not yet fully established. This is probably due to it being a new entity in the world of medicine. Some patients may show an improvement in signs and symptoms without specific treatment, but the majority of patients with chronic disease may relapse or not respond effectively. Stone et al,⁵⁹ reported an unfavorable prognosis with significant mortality and morbidity in IgG4-related diabetes mellitus, biliary obstruction, aortic aneurysms, cirrhosis, portal hypertension, and retroperitoneal fibrosis.²⁸

CONCLUSION

IgG4-RD is an amalgamation of inflammation against an autoimmune background. It is recognized as a common cause of inflammatory pseudotumor disorders affecting almost every organ or tissue in the body. It is likely of autoimmune mechanism and has a variable but usually progressive clinical course. The main characteristic features being the formation of tumor-like masses with IgG4-rich plasma cell lymphocytic tissue infiltrate and raised serum IgG4 levels. The common complication and sequel being fibrosis. The diagnosis is based on clinical presentation with a characteristic appearance on MRI and distinctive features on histopathological and immunohistochemical studies. Most appropriate treatment currently consists of steroids and immunosuppressants. IgG4-RD should always be considered by any clinician suspecting an inflammatory condition because, although it may be an uncommon disease, it is likely underdiagnosed.

Disclosure

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