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The spectrum of IgG4-related diseases

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Abstract

IgG4-related disease (IgG4-RD) is now recognized as a worldwide disease. It is a rare systemic fibro-inflammatory disorder. The evaluation for IgG4-RD should include a comprehensive clinical history, physical examination, and selected laboratory investigation, along with appropriate radiologic studies.

A wide variety of organs can be involved in IgG4-RD. Confirmation of the diagnosis by biopsy is important for the exclusion of malignancy and other disorders that may mimic IgG4-RD.

Consequently, diagnostic criteria for IgG4-RD have been proposed recently. The hallmarks of IgG4-RD are lymphoplasmacytic tissue infiltration of mainly IgG4-positive plasma cells and small lymphocytes, which may be accompanied by fibrosis, obliterative phlebitis, and, in the majority of patients, elevated serum levels of IgG4.

The serum IgG4 level is elevated above the upper limit of normal (>135 mg/dL). The serum IgG4 concentration tends to increase with the number of organs involved and usually decreases after treatment with glucocorticoids.

Among several autoantibodies identified so far, autoantibodies against lactoferrin and carbonic anhydrase II are most frequently detected in serum of IgG4-disease patients.

Glucocorticoids, azathioprine, micophenolate mofetil, methotrexate and rituximab are therapeutical options.

Keywords: IgG4, IgG4-related diseases, (IgG4-RD), diagnosis

INTRODUCTION

IgG4

In sera of normal individuals there are four IgG isotypes (subclasses): IgG1, IgG2, IgG3 and IgG4. IgG4 levels in the serum of normal individuals are quite low (60 mg/dl). IgG4 is a subclass of IgG, which is the most common form of immunoglobulin. IgG accounts for 75% of antibodies circulating in the blood. There are 4 subclasses of IgG. Subclass IgG4 is the least common of these, accounting for less than 5% of total IgG in serum in healthy persons. IgG4 has unique structure. Its specific biological role is uncertain (1,2). The production of IgG4 antibodies appears to be driven in part by T helper 2 (Th2) cytokines that mediate allergic responses and IgE production (3).

IgG4 does not bind complement and therefore does not generate a significant inflammation. IgG4 can bind to Fcy receptor I (CD64), which presents on monocytes, macrophages and neutrophils, but not to the other Fcy receptors. IgG4 production is controlled by T helper 2 cells (interleukins 4 and 13) (4).

IgG4 is an immunoglobulin subtype that has many physiologic and morphologic peculiarities. Similar to other IgG subclasses, IgG4 can cross the placenta into the fetal circulation, which has pathologic implications. IgG4 is able to act as a blocking antibody, it is practically unable to form large immune complexes. Such re-

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duction in the capacity to form immune complexes significantly decreases the risk of auto-damage. IgG4 does not activate the complement via the classical pathway (although it may do, via the alternative pathway and to its low affinity for C1q and Fc receptors, results in IgG4 having a low theoretical potential for immune activation. IgG4 autoantibodies are able to activate leukocytes, induce leukocyte-dependent tissue damage. Basophils as well as mastocytes have membrane receptors that are able to bind IgG4 (5).

DISCUSSIONS

IgG4-related diseases

The nomenclature for IgG4-related disease continues to evolve (1). IgG4-related disease (IgG4-RD) is a newly-described rare syndrome consisting of many disease entities that were previously thought to be unrelated. These conditions have the common pathological features of: inflammatory pseudotumours, i.e., swelling of organs (organomegaly) or nodules within an organ; lymphoplasmacytic infiltration of tissues with many IgG4-positive plasma cells; storiform fibrosis (scarring involving cells arranged like a cartwheel on histology). The preferred name for the overall condition is IgG4-RD (6,7).

IgG4-related disease generally occurs most commonly in middle-aged and older men. The mean age at diagnosis is approximately 60 years and there is a decided male predominance for many clinical features, with an overall male:female ratio of 8:3. The epidemiology of this disease has not been explored in detail.

IgG4-related disease is a protean condition that mimics many malignant, infectious, and inflammatory disorders. It was recognised as a unified entity only 10 years ago.

In addition, elevated serum concentrations of IgG4 are found in 60 to 70 percent of patients with IgG4-RD.

Glucocorticoids are typically the first line of therapy. The majority of patients respond to glucocorticoids, particularly in early stages of disease (1).

Major presentations of this protean condition, which often affects more than one organ, include: type 1 (IgG4-related) autoimmune pancreatitis (AIP), salivary gland disease, which can present as major salivary gland enlargement or as sclerosing sialadenitis. The constellation of lacrimal, parotid, and submandibular gland enlargement was formerly termed “Mikulicz disease.” Isolated submandibular gland swelling was termed “Küttner’s tumor”, orbital disease, often complicated by proptosis because of lacrimal gland enlargement, involvement of the extraocular muscles, or other orbital pseudotumor, retroperitoneal fibrosis, which frequently occurs in the larger context of chronic periaortitis and can often affect the ureters, leading to hydronephrosis and renal injury.

Nomenclature for individual organ involvement is shown in Table 1 (9)

Yet there remain many unknowns with regard to IgG4-RD cause, pathogenesis, various clinical presentations, approach to treatment, disease monitoring, and long-term outcomes. Increased awareness may avoid delay in diagnosis. As IgG4-RD may affect virtually every organ, this disease is of interest not only for internal medicine physicians but also for other specialties such as ear, nose and throat, dermatology, ophthalmology, and neurology. Prognosis of IgG4-RD is variable. It may spontaneously resolve or persist, with remitting and relapsing symptoms (10,11).

In the recent years, new systemic IgG4-RD has been described, and new concepts regarding the implication of IgG4 in many diseases (inflammatory and tumoral) have appeared (5).

Etiology and pathogenesis

At present, the pathogenetic mechanism and underlying immunological abnormalities in IgG4-RD remain unclear. Little is known about the initiation process of IgG4-RD or how and why these specific organ infiltrations occur. Genetic studies have suggested that several human leukocyte antigen (HLA) and non-HLA haplotypes/genotypes are associated with susceptibility to IgG4-RD or to disease relapse after steroid therapy. Despite the effectiveness of steroid therapy, for IgG4-RD, the condition has often been misdiagnosed as a malignant tumor, lymphoma, Sjögren’s syndrome, or other diseases. The cause of IgG4-RD is unknown. Some studies have suggested a possible role for molecular mimicry involving *Helicobacter pylori.* The pathogenesis of IgG4-RD is poorly understood; findings consistent with both an autoimmune disorder and an allergic disorder are present. Immune complex deposition in the pancreas, kidneys, and certain other affected tissues has been reported. Although autoreactive IgG4 antibodies are observed in IgG4-RD, there is no evidence that they are directly path-

TABLE 1. *Nomeclature for individual organ involvement (9)*

Organ or site	Preferred names	Previously used names
Head and neck		
Salivary gland	IgG4-related sialadenitis	Chronic sclerosing sialadenitis, Küttner's tumor (submandibular glands), Mikulicz's disease (salivary and lacrimal glands)
Lacrimal gland	IgG4-related dacryoadenitis	Mikulicz's disease (salivary and lacrimal glands)
Orbit	IgG4-related ophthalmic disease (IgG4-ROD)	Idiopathic orbital inflammatory disease, orbital pseudotumor
Paranasal gland		Chronic sinusitis, eosinophilic angiocentric fibrosis (orbits and upper respiratory tract
Pharynx	IgG4-related pharyngitis	
Thyroid gland	IgG4-related thyroid disease	Riedel's thyroiditis or Riedel's struma
Soft tissues of the head and neck		Idiopathic cervical fibrosis, sclerosing cervicitis, cervical fibrosclerosis
Central Nervous System		
Pituitary gland	IgG4-related hypophysitis: – IgG4-related panhypophysitis (all of pituitary gland), – IgG4-related adenohypophysitis (anterior pituitary), – IgG4-related infundibuloneurohypophysitis (posterior pituitary and pituitary stalk)	Autoimmune hypophysitis
Meninges	IgG4-related pachymeningitis (dura mater), IgG4-related leptomeningitis (arachnoid and pia mater)	Idiopathyc hypertrophic pachymeningitis
Chest and abdomen		
Pancreas	IgG4-related pancreatitis	Type 1 autoimmune pancreatitis, lymphoplasmacytis sclerosing pancreatitis, chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct
Lung	IgG4-related lung disease	Pulmonary inflammatory pseudotumor
Pleura	IgG4-related pleutritis	
Liver	IgG4-related hepatopathy	
Bile duct	IgG4-related sclerosing cholangitis	
Gallbladder	IgG4-related cholecystitis	
Aorta	IgG4-related aortitis, IgG4-related periaortitis	Inflammatory aortic aneurysm, chronic periaortitis
Branches of the aorta (including coronary, renal or iliac arteries)	IgG4-related periarteritis	
Pericardum	IgG4-related pericardis	
Mediastinum	IgG4-related mediastinitis	Fibrosing mediastinitis
Retroperitoneum	IgG4-related retroperitoneal fibrosis	Retroperitoneal fibrosis, Albarran-Ormond syndrome, Ormond's disease, perirenal fasciitis, Gerota's fasciitis/ syndrome, periureteritis fibrosa, sclerosing lipogranuloma, sclerosing retroperitoneal granuloma, non-specific retroperitoneal inflammation, sclerosing retroperitonitis, retroperitoneal vasculitis with perivascular fibrosis
Mesentery	IgG4-related mesenteritis (subtypes are: mesenteric panniculitis, mesenteric lipodystrophy and retractile mesenteritis)	Sclerosing mesenteritis, systemic nodular panniculitis, liposclerosis mesenteritis, mesenteric Weber-Christian disease, mesenteric lipogranuloma, xanthogranulomatous mesenteritis
Breast	IgG4-related mastitis	Sclerosing mastitis
Genitourinary		
Kidney	IgG4-related kidney disease (IgG4-RKD): – IgG4-related tubulointerstitial – nephritis (IgG4-TIN), – IgG4-related membranous – glomerulonephritis	Idiopathic tubulointersitial nephritis
Prostate	IgG4-related prostatitis	
Vas deferents	IgG4-related perivasal fibrosis	Chronic orchalgia
Scrotum	IgG4-related paratesticular pseudotumor IgG4-related epididymo-orchitis	Paratesticular fibrous pseudotumor, inflammatory pseudotumor of the spermatic cord, pseudosarcomatous myofibroblastic proliferations of the spermatic cord, proliferative funiculitis, chronic proliferative periorchitis, fibromatous periorchitis, nodular periorchitis, reactive periorchitis, fibrous mesothelioma
Other		
Lymph nodes	IgG4-related lymphadenopathy	
Skin	IgG4-related skin disease	Angiolymphoid hyperplasia with eosinophilia, cutaneous pseudolymphoma
Nerve	IgG4-related perineural disease	

ogenic. A "modified" Th2 response is critical to this condition. IgG4-RD lesions are infiltrated by Th cells, which likely cause progressive fibrosis and organ damage. IgG4 antibodies are generally regarded as noninflammatory. Although autoreactive IgG4 antibodies are observed in IgG4-RD, there is no evidence that they are directly pathogenic. The contribution of autoantibodies to IgG4-RD remains unclear (11).

The hypocomplementemia is observed in some patients with IgG4-RD. The precise mechanisms of hypocomplementemia require elucidation but may relate to immune complexes in the blood and those detected in some organs, particularly the kidney and pancreas. Native IgG4 is a non–complement-fixing isotype, at least for the classical complement pathway. IgG4 antibodies are generally regarded as noninflammatory. Although IgG autoantibodies against various exocrine gland antigens have been described in IgG4-RD, whether they are members of the IgG4 subclass is unknown. Recently, Th2 immune reaction has been suggested to be predominant in IgG4-RD. Regulatory immune reactions are activated in IgG4-RD. It has features of an allergic disorder: abnormal high Th2 cytokines (cell messenger proteins) in tissues, raised IgE and increased T-reg lymphocytes in blood and raised eosinophil count in 40% of patients. Cytokines IL-10 (interleukin 10) and TGF-β (transforming growth factor beta) are known to support IgG4 production and are at elevated levels in IgG4-related disease. Autoimmunity has been considered the most probable pathogenesis of IgG4-RD, but has not been completely proved so far. Involvement of major organs is common and IgG4-RD may lead to organ failure, particularly in the pancreas, liver and biliary tree, kidneys, thyroid gland, lungs, and aorta (12).

In contrast to many autoimmune disorders, IgG4-RD seems to have a skewed T- cell response towards a Th2 phenotype. Increased tissue levels of Th2-cytokines such as Interleukin-4 (IL-4), −5 (IL-5) and −13 (IL-13) were found in IgG4-RD. Well-fitting to a Th2 immune response, IgG4-RD is characterized by both systemic and localized IgG4 production. It is currently unclear, whether these antibodies are acting as pathogenic antibodies or are just a bystander phenomenon (11,12).

Laboratory features

Laboratory findings in IgG4-RD are often inconspicuous. Inflammatory markers such as ESR and CRP may be highly elevated, but can be normal despite active disease in a substantial proportion of patients. The majority of patients with IgG4-RD have elevated serum IgG4 concentrations, but the range varies widely. Approximately 30% of patients have normal serum IgG4 concentrations, despite classic histopathological and immunohistochemical findings (1).

Anti-nuclear antibodies, anti-SS-A as well as anti-SS-B antibodies are negative in the majority of patients, while low complement levels (C3 and C4) are not uncommon. Elevated serum IgG4 is the most remarkable feature of IgG4-RD, and a large number of lymphocytes and IgG4 positive plasma cells can be seen in the involved tissue (13).

Polyclonal hypergammaglobulinemia is often found in IgG4-RD. Increased serum IgE levels and allergic diseases are present in about one third of patients. IgG subclass analyses reveal highly elevated serum IgG4 levels in many but not all patients. It should be underlined that IgG4 levels can be substantially misleading when they are used as a sole criterion for diagnosis (or exclusion) of IgG4-RD. On the one hand, a number of other diseases, such as cancer, infections and autoimmune diseases, including vasculitis, are associated with increased IgG4 levels. A number of IgG4-RD patients may have normal IgG4 levels. Thus, the sensitivity of IgG4 in IgG4-RD was found to be 90% and the specificity 60% in one study (14).

In another study the positive predictive value of an elevated serum IgG4 for IgG4-RD was found to be as poor as 10%. Thus, elevated IgG4 levels have become a surrogate marker for IgG4-RD in clinical practice (15,16).

It is suspected but unclear, whether IgG4-RD truly belongs to the group of autoimmune disorders. There is evidence of autoantibodies such as antinuclear, rheumatoid factor, and others in some patients. However, these autoantibodies are far beyond from being specific for IgG4-RD (17).

Further, 40% of IgG4-RD patients have increased serum IgE levels and allergic diseases are common. Moreover, tissue eosinophilia is typical for IgG4-RD. Some studies also suggested an increased activation of regulatory T cells (Treg), which might be due to the over-expression of transforming growth factor β (TGF-β), an important regulator of Treg development. Interestingly, low C3 and C4 complement levels can be observed in one third of IgG4-RD patients with renal involvement indicating immune com-

plex formation. Investigation in suspected IgG4-RD requires a combination of clinical, endoscopic, radiological and serological tests looking for organ involvement and end organ damage (e.g., hormonal abnormalities). Patients with lymphadenopathy may exhibit elevated serum IgG4, serum IgG and IgE, polyclonal hypergammaglobulinemia, and elevations in the erythrocyte sedimentation rate (ESR). The negative predictive value of a serum IgG4 assay in these groups was 96 percent, but the positive predictive value was only 34 percent. Detection of serum IgG4 is measured by latex-enhanced nephelometric immunoassay (18).

Analysis of the serum IgG4/total IgG ratio did not improve these test characteristics.

Blood plasmablast concentrations may be a better biomarker than the serum IgG4 concentration. Plasmablasts were identified through flow cytometry of peripheral blood. These studies of circulating plasmablasts confirm that these cells are elevated to high levels in patients with active IgG4-RD, even in patients with normal serum IgG4 concentrations. Plasmablast counts therefore are a potentially useful biomarker for diagnosis, assessing response to treatment, and determining the appropriate time for retreatment. The number of IgG4-positive plasma cells per high-power field (HPF) that is regarded as consistent with or suggestive of IgG4-RD varies somewhat from tissue to tissue (19).

Elevations in serum and tissue IgG4 concentrations are not specific to IgG4-RD. Anti-nuclear antibodies are sometimes present, and autoantibodies have been described against lactoferrin and carbonic anhydrase II. It has not been well clarified whether or not those autoantibodies belong to an IgG4 subclass. Urinalysis – asymptomatic proteinuria may be an indication of subclinical IgG4-related tubulointerstitial nephritis (TIN). Serum complement levels – Serum C3 and C4 concentrations are typically low, often profoundly so, in the setting of TIN. Following serum complement concentrations in such patients can be a useful means of gauging response to therapy. Markers of allergic disease – such as serum IgE concentrations and the peripheral eosinophil count, should be tested at baseline and, if abnormal, at follow-up (20-22).

Eosinophilia and elevated serum IgE levels, both observed in approximately 40% of patients with IgG4-RD (1)

Aberrant immunological findings have been observed inpatients with IgG4-RD. For example, the Th2-dominant immune response and the production of Th2-type cytokines, such as IL-4, IL-5, IL-10, and IL-13, are increased. Over-expression of the regulatory cytokines IL-10 and transforming growth factor β (TGF-β) has also been reported in patients with IgG4-RD. IL-10 and TGF-β have potent activities in directing B cells to produce IgG4 and induce fibroplasias, respectively. IL-4, IL-5, and IL-13 are important for class switching to IgE production and eosinophil migration. Therefore, abnormalities in the production of these cytokines may be involved in the pathogenesis of IgG4-RD (23).

Correlation with specific histopathological findings is essential, regardless of the serum IgG4 concentration , the number of IgG4-positive plasma cells in tissue, or the ratio of IgG4 to IgG in tisue. The key morphologic features of IgG4-RD are a dense lymphoplasmacytic infiltrate that is organized in a storiform pattern, obliterative phlebitis, and a mild-to-moderate eosinophil infiltrate. The inflammatory infiltrate is composed of an admixture of T and B lymphocytes (1)

Clinical manifestations

IgG4-related disease is a fascinating condition recognised as a systemic disease in 2003. The clinical features of several IgG4-RD can mimic those of autoimmune disorders. IgG4-related disease can involve one or multiple organs. The clinical symptoms are different for different organs involved (1,23,24).

Multiple organs are affected in 60 to 90 percent of patients with IgG4-RD. Practically any organ can be affected, having in common a key pathological feature consisting in dense lymphocyte and plasma cell infiltrate rich in IgG4-positive plasma cells, storiform fibrosis and often an elevated serum IgG4 concentration. Lymphadenopathy is common, and symptoms of asthma or allergy are present in approximately 40 percent of patients. IgG4-related disease can mimic autoimmune rheumatic diseases such as systemic lupus erythematosus, Sjögren's syndrome, or granulomatosis with polyangiitis. In addition, patients with IgG4-RD have an increased prevalence of allergic rhinitis and bronchial asthma (25).

DIAGNOSIS

IgG4-RD is attracting strong attention as a new clinical entity. Diagnosis of IgG4-RD can be difficult, as multiple organs may be involved si-

multaneously. Diagnostic criteria have not been fully developed (23,24).

IgG4-RD can occur in various organs, including the central nervous system, salivary glands, thyroid gland, lungs, pancreas, biliary duct, liver, gastrointestinal tract, kidneys, prostate gland, retroperitoneum, and lymph nodes, but that vlinical symptoms depend on the location of the lesion (23).

IgG4-related disease should be suspected in patients presenting with unexplained enlargement or swelling of one or more organs.

The diagnosis of IgG4-RD relies on the coexistence of various clinical, laboratory and histopathological findings, although none is pathognomonic by itself.

The diagnosis of IgG4-RD is based upon biopsy findings demonstrating the characteristic histopathology.

Serum IgG4 levels should be measured, and isolated elevated levels are a significant aid in diagnosis, although they are not diagnostic.

The diagnosis of IgG4-RD is based upon biopsy findings demonstrating the characteristic histopathologic findings and immunohistochemical staining. These findings include lymphoplasmacytic tissue infiltration of mainly IgG4-positive plasma cells and lymphocytes, accompanied by fibrosis that has storiform features and often by obliterative phlebitis. A modest tissue eosinophilia is often present.

Serum IgG4 levels should be measured, and isolated elevated levels are a significant aid in diagnosis, although they are not diagnostic.

Patients at high risk for having IgG4-RD are those with any of the following: pancreatitis of unknown origin, sclerosing cholangitis, bilateral salivary and/or lacrimal gland enlargement, retroperitoneal fibrosis, orbital pseudotumor or proptosis.

The likelihood of IgG4-RD for patients presenting with at least one of these conditions is significantly increased if high serum levels of IgG4, allergic symptoms, and/or other fibrotic processes are also present (26,27).

Histopathology [a dense lymphoplasmacytic (lymphocytes and plasma cells) infiltrate rich in IgG4-positive plasma cells**]** is the key to diagnosis. The three central pathology features of IgG4-RD are lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis (the venous channels are obliterated by a dense lymphoplasmacytic infiltrate, within both the venous walls and the lumen). IgG4 immunostaining needs to be specifically requested and performed in order to detect IgG4-positive plasma cells. The histopathological and immunohistochemical staining features of IgG4-RD are strikingly similar in different tissues, regardless of the organ or tissue involved. It is important to distinguish the IgG4-RD from traditional organ-specific autoimmune disease to guide therapy (2,24)**.**

Misdiagnoses of IgG4-RD are increasingly common because of excessive emphasis on moderate elevations of serum IgG4 concentration and overreliance on the finding of IgG4-positive plasma cells in tissue (1).

IgG4-RD is characterized by one or several fibroinflammatory organ involvements with typical pathological findings. A serum IgG4 elevation above 1.35 g/L is currently retained as an important biomarker of the disease, included in the diagnosis criteria (27).

Diagnosis criteria of IgG4-RD are shown in Table 2 (23).

CONCLUSIONS

IgG4-related disease is often recognized incidentally based upon a radiologic finding or histopathologic examination of a tissue specimen. The list of organs associated with this condition is growing steadily. Polyclonal elevations of serum IgG4 are found in most but not all patients.

The diagnosis of IgG4-RD cannot be based upon serum concentrations of IgG4 alone, because serum IgG4 concentrations are neither sufficiently sensitive nor specific for this disease. Thus, we strongly prefer confirmation of the diagnosis by biopsy of an involved organ whenever this is possible.

IgG4-related systemic disease is an increasingly recognized syndrome of unknown etiology, most often occurring in middle-aged and older men, which is comprised of a collection of disorders that share specific pathologic, serologic, and clinical features.

Many questions and problems still remain to be elucidated, including its pathogenesis, the establishment of diagnostic criteria, and the role of IgG4.

TABLE 2. *Diagnostic criteria for IgG4-RD (23)*

1	2	3	Diagnosis of IgG4-RD
Organ involvement: dysfunction, localized or diffuse swelling	Serum IgG4 >135 mg/dl	Histopathology: IgG4/IgG ratio >0.4 and >10 IgG4+cells per HPF	Definite
Organ specific criteria for IgG4-RD (e.g. AIP, Mikulicz'disease)			Definite
Organ involvement: dysfunction, localized or diffuse swelling	Serum IgG4 <135 mg/dl	Histopathology: IgG4/IgG ratio >0.4 and >10 IgG4+ cells per HPF	Probable
Organ involvement: dysfunction, localized or diffuse swelling	Serum IgG4 >135 mg/dl	Histopathology: Not available or not diagnostic	Possible
Organ involvement: dysfunction, localized or diffuse swelling	Serum IgG4 <135 mg/dl	Histopathology: Not available or not diagnostic	No

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