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IgG4-Related Disease: Recommendations for the Nomenclature of this Condition and its Individual Organ System Manifestations

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Introduction

During the first decade of this century, recognition of a multi-organ system disease known as IgG4-related disease (IgG4-RD) has grown. Serum IgG4 elevation (in some patients) and tissue infiltration with IgG4-positive plasma cells (in essentially all patients)(1–3) are common threads that connect a variety of seemingly disparate conditions observed previously in multiple organs (4). A highly characteristic histopathology and immunohistochemical staining pattern are found in the involved organs (5–7). Japanese investigators recently agreed on the name “IgG4-related disease” for this multifocal disorder (7).

An International Symposium on IgG4-related disease (IgG4-RD) was held in Boston, Massachusetts from October 4–7, 2011 [http://www2.massgeneral.org/pathology/symposium/IgG4_related_systemic_dis.asp]. The Organizing Committee, comprised of 35 IgG4-RD experts from Japan, Korea, Hong Kong, the United Kingdom, Germany, Italy, Holland, Canada, and the United States, included clinicians, pathologists, radiologists, and basic scientists. This group represents broad subspecialty expertise in pathology, rheumatology, gastroenterology, allergy, immunology, nephrology, pulmonary medicine, oncology, ophthalmology, and surgery. Nomenclature was a specific focus for part of the International Symposium. In this manuscript, we report on the recommendations of the Organizing Committee related to terminology for the overall disease, with an emphasis on the individual organ system manifestations.

Description of IgG4-RD and its Unifying Pathological Features

Certain clinical and pathologic features help define IgG4-RD and distinguish it from its potential mimics. IgG4-RD is a fibro-inflammatory condition characterized by a tendency to form tumefactive lesions; a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma

cells; storiform fibrosis; frequent but not invariable elevations of serum IgG4; and a swift initial response to glucocorticoids, provided that tissue fibrosis has not supervened.

IgG4-RD is analogous in many ways to sarcoidosis, another systemic disease that affects virtually all organ systems, unified by a distinctive histologic appearance regardless of the organ involved. The pancreas was the first organ in which IgG4-RD was identified, but the disease has now been described in virtually every organ system: the biliary tree, salivary glands, orbital tissues (e.g., lacrimal gland, extra-ocular muscles, and retrobulbar space), kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid gland, pericardium, retroperitoneum and skin (5, 6, 8, 9). The histopathologic features vary slightly across some organs but with the exception of IgG4-related lymphadenopathy and the membranous glomerulonephritis that is occasionally associated with this condition, the organ findings generally bear striking similarities. Increased numbers of infiltrating IgG4-bearing plasma cells are found within involved organs and are the *sine qua non* of this diagnosis. However, the diagnosis of IgG4-RD cannot be made purely on the basis of staining for IgG4 (10). Rather, certain light microscopic features are also critical to the diagnosis (see below).

Existing Terminology for Multi-focal Disease and Proposed Terminology

We are aware of no fewer than ten alternative names for IgG4-RD (Table 1). The multi-system nature of this condition and the fact that many organ manifestations can have multiple potential names compound the confusion in the literature (Table 2). Japanese investigators have reached a consensus to refer to this newly-emerged disease as IgG4-RD (7), specifically selecting this term over alternatives such as “IgG4-related systemic disease”, “IgG4-related sclerosing disease”, and “IgG4-positive multi-organ lymphoproliferative syndrome”.

The issue of naming the disease after IgG4 was debated at the Symposium. Because of many unresolved issues regarding the role of IgG4 in pathogenesis and the use of serum concentrations as a biomarker for this disease (see below), reservations were expressed by some experts about naming the disease after IgG4 without qualifications. However, recognizing that efforts to “speak the same language” are important in facilitating collaboration and disseminating information more widely about this newly-recognized condition, the Organizing Committee for the 2011 International IgG4-RD Symposium in Boston endorsed the consensus name chosen by the Japanese group. The Organizing Committee acknowledged that much remains unknown about the behavior of the IgG4 molecule *in vivo*, the pathways through which this immunoglobulin participates in the disease, and whether or not the role of IgG4 is primary or secondary. In time, discoveries pertaining to the etiology and pathophysiology of this condition may suggest a name that is more appropriate. For the present, the term “IgG4-RD” recognizes aptly the ubiquity of IgG4 within involved organs. This fact, not the frequency with which patients have increased serum IgG4 concentrations, is the fundamental basis for using this term in the name of the disease.

Individual Organ System Manifestations: Existing Terms and Suggested Nomenclature

Several eponymic conditions known for decades or even more than a century are now identified as part of the IgG4-RD spectrum (Table 2). Some of these eponyms have been applied loosely and imprecisely, leading to confusion and uncertainty about the precise clinical syndromes to which they refer. Now that evidence exists for a larger, systemic disease context for these disorders, it is appropriate that these eponyms be replaced in favor of terms that offer more information about particular pathophysiological mechanisms and patterns of disease pathology.

Agreement upon the consensus term “IgG4-RD” facilitates a consistent nomenclature whereby individual organ involvement can be referred to in a style that employs “*IgG4-related-*” as a prefix, regardless of the organ system affected. As examples, type I autoimmune pancreatitis (AIP), now firmly entrenched in the gastroenterology literature, might be termed “type I AIP (IgG4-related pancreatitis)”. Similarly, chronic sclerosing sialadenitis (sometimes termed a Küttner’s tumor when it involves the submandibular gland) might be called “IgG4-related sialadenitis” or “IgG4-related submandibular gland disease”. Such nomenclature underscores the belief that the same fundamental pathophysiologic processes are operative across organ systems in this disease, regardless of whether the role of IgG4 is viewed as primary or secondary.

Specific Recommendations for IgG4-RD Organ System Nomenclature

The recommendations of the Organizing Committee are shown in Table 3. We discuss some potentially problematic areas below:

“Related” versus “Associated”

The terms “related” and “associated”, both used in the medical literature in the context of this disease, are intended to convey the fact that IgG4-RD is linked in some fashion to IgG4-bearing plasma cells in tissue. We prefer the term “related” because it echoes the consensus name for the overall condition – IgG4-*related* disease – and has been used more consistently in the medical literature.

Pancreas

The pancreatic manifestation of IgG4-RD was termed “autoimmune pancreatitis” in the mid-1990s, before the entity of IgG4-RD had been conceptualized (11). The basis for considering this pancreatic condition to be “autoimmune” has not been established firmly, and no autoantibody has been identified consistently. AIP has since been divided into two types – type 1 and 2 – which share certain clinical similarities but are vastly different in terms of pathology and extra-pancreatic features (12–14). Type 1 AIP is regarded as a prototypical organ manifestation of IgG4-RD, which can occur alone or either simultaneously or metachronously with other organ complications. In contrast, type 2 AIP is not part of the IgG4-RD spectrum and appears to be a disease of its own (15).

Over time, we anticipate that the term “type 1 AIP” might be replaced entirely with “IgG4-related pancreatitis”. Because type 1 AIP is widely accepted among gastroenterologists and pancreatic surgeons now, however, we propose adding “IgG4-related pancreatitis” in parentheses: type 1 AIP (IgG4-related pancreatitis). This serves at least two purposes: 1) education of the broader medical community about the relationship between IgG4-RD and this subset of pancreatic disease; and, 2) avoidance of the issue of what to call type 2 AIP if type 1 AIP were removed entirely from the nomenclature.

Bile ducts

IgG4-RD accounts for a subset of patients previously considered to have primary sclerosing cholangitis (16). The distinction between the primary and IgG4-related forms of sclerosing cholangitis is essential (but not always possible) because of the significant differences in treatment responses observed in these two conditions (17). At this time, it is unclear if patients with isolated biliary disease and elevated serum concentrations of IgG4 who meet imaging and clinical criteria for primary sclerosing cholangitis actually have IgG4-RD.

Gastroenterologists and gastrointestinal pathologists on the Organizing Committee emphasized the importance of including “sclerosing” in the name of IgG4-related biliary tract disease as a means of linking this condition with, but still distinguishing it from, primary sclerosing cholangitis. Thus, we proposed that IgG4-related disease of the biliary tree be termed “IgG4-related sclerosing cholangitis”, even though residual “sclerosis” of the bile ducts is not always observed after glucocorticoid therapy in IgG4-RD.

Mikulicz’s disease/syndrome

The term Mikulicz’s disease has been used to denote idiopathic bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands, often in the context of IgG4-RD (18). However, “Mikulicz’s syndrome” can be caused by many different conditions and, indeed, the true diagnosis of the index patient described by Mikulicz is not clear (19). Some evidence suggests that the patient had an extra-nodal marginal zone lymphoma of the mucosa-associated lymphoid tissue type (i.e., a MALT lymphoma) rather than IgG4-RD (20). Moreover, the term “Mikulicz’s disease” has been applied inconsistently and even incorrectly for decades, sometimes being regarded as part of the spectrum of Sjögren’s syndrome (21).

Thus, it seems appropriate to discard “Mikulicz’s disease” when referring to patients with involvement of the lacrimal, parotid, and submandibular glands and to employ instead terms that refer to specific individual organ system; i.e., IgG4-related dacryoadenitis for those with lacrimal gland disease; IgG4-related parotitis for those with parotid disease; and IgG4-related sialadenitis or IgG4-related submandibular gland disease for those with submandibular gland involvement.

Küttner’s tumor

A Küttner’s tumor refers to enlargement of the submandibular gland, sometimes as the result of stones in Wharton’s duct (22). The use of the term by pathologists has been overly broad, often without full consideration of the underlying cause (or in the absence of knowledge of

IgG4-RD). A significant proportion of cases of “Küttner’s tumor” represent manifestations of IgG4-RD. Important pathologic differences can be demonstrated between Küttner’s tumors associated with sialodocholithiasis and submandibular gland enlargement caused by IgG4-RD (23). For example, the fibrotic lesions that occur within the lesions of IgG4-related sialadenitis are characterized by intense inflammation within the areas of fibrosis, in contrast to the bland fibrotic lesions observed in Küttner’s tumors caused by salivary duct stones. Another important clinical difference is that IgG4-related sialadenitis is more likely to affect both submandibular glands.

Many patients with IgG4-related submandibular gland disease have been diagnosed in the past as having primary Sjögren’s syndrome (SjS). In this regard, it is worth noting that patients with primary SjS rarely (if ever) have isolated submandibular gland enlargement to the degree observed in IgG4-RD. Primary SjS is far more likely to involve the parotid glands out of proportion to the submandibular glands or to involve both of these glands together (24). IgG4-RD, in contrast to primary SjS, is not associated with antibodies to either the Ro/SS-A or the La/SS-B antigen (18).

Ophthalmic disease

IgG4-RD is now recognized to be an important cause of “idiopathic” orbital inflammation and a major component of the differential diagnosis that includes lymphoma, granulomatosis with polyangiitis (formerly Wegener’s), Graves’ orbitopathy, and other conditions (25). IgG4-RD must be excluded before the label of “idiopathic” is applied. (As discussed below, serum IgG4 measurement is not sufficient to exclude IgG4-RD if the concentration is normal, nor does an elevated concentration confirm the diagnosis). We recognize that in some patients with IgG4-related ophthalmic disease, the process extends beyond the orbit to include, for example, part of the course of the trigeminal nerve (26,27). Hence, when referring to eye involvement in general, the broader term “IgG4-related ophthalmic disease” is proposed instead of “IgG4-related orbital disease”.

Although IgG4-related ophthalmic disease is the recommended general term for disease involving the lacrimal glands, extra-ocular muscles, and other portions of the orbit (and beyond), it is preferable when possible to refer to IgG4-RD involvement of the ophthalmic region by specific terms. Thus, lacrimal gland involvement should be termed IgG4-related dacryoadenitis, and IgG4-RD affecting the extraocular muscles should be called IgG4-related orbital myositis. The proposed term for orbital pseudotumor occurring in the context of IgG4-RD is IgG4-related orbital inflammation. Generalized IgG4-related orbital disease that affects multiple anatomic structures of the orbit simultaneously should be termed “IgG4-related pan-orbital inflammation”.

Thyroid

Riedel’s thyroiditis has long been known to be associated with multifocal fibrosclerosis (28). Most cases of multifocal fibrosclerosis, in turn, are now recognized to be multi-organ system manifestations of IgG4-RD. Riedel’s thyroiditis has been proven with immunohistochemical staining to be part of the IgG4-RD spectrum (29). We propose that the term “IgG4-related thyroid disease” be used now in lieu of Riedel’s thyroiditis. Whether the “fibrosing variant”

of Hashimoto's thyroiditis is part of the IgG4-RD spectrum remains to be clarified by studies of additional cases.

Kidney

Tubulointerstitial nephritis [TIN] is the most common renal feature of IgG4-RD, but glomerular disease (e.g., membranous nephritis) has also been described (30). The TIN associated with IgG4-RD can be differentiated histopathologically and immunohistochemically from other causes of TIN (31, 32). Further studies of the relationships between the membranous glomerulonephritis that sometimes occurs in IgG4-RD and the "idiopathic" form of this disease are needed, because this issue is still controversial. However, we propose referring to both TIN and membranous glomerulopathy that occur in the setting of IgG4-RD as "IgG4-related kidney disease". For cases in which membranous glomerulonephritis is the sole kidney lesion present and TIN is not evident, avoidance of the term "IgG4-related kidney disease" is appropriate at the present time.

The membranous glomerulonephritis of IgG4-RD appears to have a different pathophysiology from the rest of IgG4-RD. The membranous glomerulonephritis of IgG4-RD is probably secondary to immune complex deposition rather than the usual destructive inflammatory process that characterizes other organ involvement by this condition. The membranous glomerulonephritis of IgG4-RD is a different disease from "idiopathic" membranous glomerulonephritis, which is characterized by antibodies to the PLA2 receptor (33). It is worth noting, however, that the anti-PLA2 receptor antibodies in idiopathic membranous glomerulonephropathy are principally of the IgG4 subclass.

Several radiological lesions within the kidney have been described in IgG4-RD, including diffuse renal enlargement, focal renal masses, and thickening of the renal pelvis. These lesions, which occur in association with other manifestations of IgG4-RD in the majority of cases, often resolve with glucocorticoid treatment and are rarely biopsied if the diagnosis has been established in another organ. We propose that such radiologically identified renal lesions also be regarded as "IgG4-related kidney disease", provided they occur in the setting of other organ involvement that has been confirmed histopathologically.

Aorta

IgG4-RD that involves the aorta has a predilection for the adventitia and peri-aortic tissues (34–36). However, the disease also involves the media, making it by definition an aortitis rather than a peri-aortitis (35). We propose the term "IgG4-related aortitis/peri-aortitis" for this condition, to reflect the anatomical extent of inflammation. IgG4-related peri-aortitis may show overlap with IgG4-related retroperitoneal fibrosis. Additional studies of medium-sized arteries and veins in IgG4-RD are needed, but the term "IgG4-related periarteritis" appears appropriate at this time.

Notes of Caution: Problems with IgG4 as a Biomarker of IgG4-RD

The adoption of "IgG4" into the name of this condition because reflects the ubiquity of IgG4-bearing plasma cells in the tissues of involved organs. It is increasingly clear, however, that serum concentrations of IgG4 are unreliable as diagnostic markers of IgG4-RD, as

indicators of disease activity, and as measures of response to treatment. Approximately 20–40% of patients with biopsy-proven IgG4-RD have normal serum IgG4 concentrations at diagnosis even before the institution of therapy (37, 38). In addition, a varying proportion (3–7%) of both healthy and disease controls have elevated serum IgG4 levels, though it is uncommon for levels in such conditions to be more than twice the upper limit of normal (39, 40).

The number of IgG4-positive plasma cells in tissues may also be misleading because the infiltration with IgG4-positive cells can be observed in conditions other than IgG4-RD (10). A consensus statement on the pathology of IgG4-RD emphasizes that certain light microscopy features, particularly storiform fibrosis, obliterative phlebitis, mild to moderate eosinophilia, and germinal center formation are also critical to the diagnosis(41). Inclusion of IgG4 in the terminology of the disease should not lead clinicians to make the diagnosis solely based on serum IgG4 concentrations or tissue-infiltrating IgG4+ plasma cells. Rather, the diagnosis of IgG4-RD must be predicated upon specific histopathologic findings and then confirmed by tissue immunostains, all in the setting of an appropriate clinical context.

Conclusion

IgG4-RD is a recently-recognized multi-organ system condition with pathological features that are consistent across a wide range of organ systems. This condition unifies a large number of medical diagnoses previously regarded as confined to single organ systems. The precise links between the full histopathological picture of IgG4-RD, the frequent serum elevations of IgG4, and the finding of increased IgG4-bearing plasma cells in tissue remain to be ascertained fully. The use of a shared nomenclature will facilitate efforts to understand better this emerging condition and its larger implications for the immune system.

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Table 1

Different Names Employed to Refer to IgG4-Related Disease

IgG4-related disease (25)
IgG4-associated disease (23)
IgG4-related systemic disease (26)
IgG4-related sclerosing disease (16)
IgG4-related systemic sclerosing disease (42)
IgG4-related autoimmune disease (4)
Hyper-IgG4 disease (43)
IgG4-positive multi-organ lymphoproliferative syndrome (44)
Systemic IgG4-related plasmacytic syndrome (SIPS)(45)
IgG4 syndrome (46)

Table 2

Names of Previously-Recognized Conditions That Comprise Or May Comprise Parts of the IgG4-Related Disease Spectrum.

Mikulicz's disease	
Küttner's tumor	
Riedel's thyroiditis	
Eosinophilic angiocentric fibrosis	
Multifocal fibrosclerosis	
Lymphoplasmacytic sclerosing pancreatitis / autoimmune pancreatitis	
Inflammatory pseudotumor	
Fibrosing mediastinitis	
Sclerosing mesenteritis	
Retroperitoneal fibrosis (Ormond's disease)	
Periaortitis /periarteritis	
Inflammatory aortic aneurysm	
Cutaneous pseudolymphoma	
Idiopathic hypertrophic pachymeningitis	
Idiopathic tubulointerstitial nephritis	
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits	
Idiopathic cervical fibrosis	
Proposed Names for Commonly-Used Eponyms and Other Terms Frequently Employed in the Description of IgG4-Related Disease	
Mikulicz's disease	IgG4-related dacryoadenitis and sialadenitis
Küttner's tumor	IgG4-related submandibular gland disease
Multifocal fibrosclerosis	IgG4-related disease
Ormond's disease	IgG4-related retroperitoneal fibrosis
Riedel's thyroiditis	IgG4-related thyroid disease

Table 3

Preferred Nomenclature for Individual Organ Manifestations of IgG4-Related Disease.

Organ System/Tissue	Preferred Name
Pancreas	Type 1 autoimmune pancreatitis (IgG4-related pancreatitis)
Eye	IgG4-related ophthalmic disease is the general term for the peri-ocular manifestations of this disease. There are several subsets, outlined below.
Lacrimal glands	IgG4-related dacryoadenitis
Orbital soft tissue (orbital inflammatory pseudotumor)	IgG4-related orbital inflammation (or IgG4-related orbital inflammatory pseudotumor)
Extra-ocular muscle disease	IgG4-related orbital myositis
Orbit with involvement of multiple anatomic structures	IgG4-related pan-orbital inflammation (includes lacrimal gland disease, extra-ocular muscle involvement, and other potential intra-orbital complications)
Salivary glands (parotid and submandibular glands)	IgG4-related sialadenitis or, more specifically, IgG4-related parotitis or IgG4-related submandibular gland disease
Pachymeninges	IgG4-related pachymeningitis
Hypophysis	IgG4-related hypophysitis
Thyroid (Riedel's thyroiditis)	IgG4-related thyroiditis
Aorta	IgG4-related aortitis/periaortitis
Arteries	IgG4-related periarteritis
Mediastinum	IgG4-related mediastinitis
Retroperitoneum	IgG4-related retroperitoneal fibrosis
Mesentery	IgG4-related mesenteritis
Skin	IgG4-related skin disease
Lymph node	IgG4-related lymphadenopathy
Bile ducts	IgG4-related sclerosing cholangitis
Gallbladder	IgG4-related cholecystitis
Liver	IgG4-related hepatopathy (refers to liver involvement that is distinct from biliary tract involvement)
Lung	IgG4-related lung disease
Pleura	IgG4-related pleuritis
Pericardium	IgG4-related pericarditis
Kidney	IgG4-related kidney disease. The specific renal complications should be termed tubulointerstitial nephritis secondary to IgG4-RD and membranous glomerulonephritis secondary to IgG4-RD. Involvement of the renal pelvis should be termed IgG4-related renal pyelitis.
Breast	IgG4-related mastitis
Prostate	IgG4-related prostatitis