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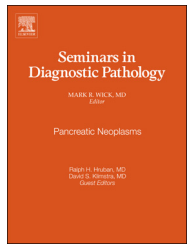

Ophthalmic immunoglobulin G4-related disease IgG4-RD Current concepts

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ABSTRACT

IgG4-related disease (IgG4-RD) is a distinct entity that frequently occurs in an ophthalmic location. As such, IgG4-RD is not limited to the orbit but may also involve other anatomical structures in and around the eye. Hence, the term 'ophthalmic IgG4-RD' is preferred over 'orbital IgG4-RD.' A high level of suspicion for the diagnosis can be derived from careful clinicoradiologic examination; the use of immunohistochemical staining for IgG4 in the context of characteristic histopathologic features is needed to reach a correct diagnosis. Recently described diagnostic criteria for ophthalmic IgG4-RD address subtle, yet significant, differences from IgG4-RD as seen in other systemic sites. Serum IgG4 titers are neither sensitive nor specific for the diagnosis of IgG4-RD and should not relied upon solely. Although most cases respond well to therapy with glucocorticoids, refractoriness to treatment and relapses are common. They necessitate the use of additional immunotherapy in such patients.

Immunoglobulin G4-related disease (IgG4-RD) is a distinctive, and relatively newly described, mass-forming, and fibroinflammatory condition. It is characterized histopathologically by storiform fibrosis and a lymphoplasmacytic infiltrate that is rich in IgG4-producing plasma cells. The diagnosis of IgG4-RD is not always straightforward, and relies heavily on the integration of clinical, histopathologic, and laboratory findings, none of which are pathognomonic of the disease. Ophthalmic IgG4-RD is not rare, and may affect any anatomic structure in and around the globe.[1] Several orbital lesions that were previously interpreted as idiopathic orbital inflammation (IOI) have now been reclassified as IgG4-RD.[2] Although most patients with ophthalmic IgG4-RD respond to glucocorticoid therapy, relapses and refractoriness are not uncommon.[3–6] This manuscript will review our current understanding of this entity.

Historical aspects and nomenclature

IgG4 is the least abundant subclass of immunoglobulin-G (IgG) accounting for 4–6% of total IgG in serum. At the beginning of this century, a group of Japanese researchers observed elevated levels of serum IgG4 in patients with sclerosing (autoimmune, type I) pancreatitis, the prototype for this group of disorders.[7] Since then, other studies have reported the presence of IgG4-RD in several other organs. Previously-characterized pathologic entities with a variety of site-specific designations are now considered to be a part of the IgG4-RD disease spectrum (Table 1). Indeed, in 2003, IgG4-RD was recognized as a systemic disease.[8] The multisystem nature of the disorder has engendered various terminologies for this disease (Table 2), the most well-recognized being 'IgG4-related disease.'[9] That term was proposed at an

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Table 1 – Previously known entities which comprise or may comprise part of the IgG4-RD disease spectrum.[8]

Mikulicz 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

international symposium on the topic.[10] Table 3 presents the terminology used for ophthalmic involvement by IgG4-RD.

Definition

IgG4-RD may be defined generically as a localized or multisystem, fibroinflammatory, mass-forming disease characterized by distinctive histopathologic features of storiform fibrosis, obliterative phlebitis, and infiltration of the affected organ(s) by a lymphoplasmacytic infiltrate that is rich in IgG4-producing plasma cells, which may be associated with elevated titers of serum IgG4.

Epidemiology

Ophthalmic IgG4-RD is regularly seen in clinical practice. Since the first report of ophthalmic involvement in 2009, many more such cases have been seen worldwide.[20] However, the true incidence of this entity is still unknown. Some investigators have estimated that it affects 0.28–1.08 persons per 1,000,000 individuals.[21] Ophthalmic IgG4-RD is generally a disease of the elderly and it usually presents in the 5th and 6th decades of life.[3,22–24] That age of presentation is slightly less than that of patients who have the disease elsewhere in the body.[25] Rare cases of ophthalmic involvement in pediatric patients also have been encountered.[26–28] Some authors have reported a male predominance, but that observation is by no means uniform.[3,22,29] Most publications have described an equal gender distribution.[30,31]

Pathogenesis

Detailed pathogenetic mechanisms in IgG4-RD remain unclear, and several hypotheses have been proposed. One of these concerns genetic predisposition through expression of the HLA-DRB1*0405 and DQB1*0401 alleles.[32] Umehara et al.[9] suggested a possible role for single nucleotide polymorphisms in immune-related genes such as cytotoxic T-lymphocyte-associated antigen-4 and tumor necrosis factor-alpha (TNFα). Molecular mimicry and aberrant immune responses have also been proposed mechanistically.[25]

A role for T-cell-derived cytokines and possible autoantibodies has likewise been studied.[33] Some have proposed a biphasic pathogenetic mechanism involving T-helper type 1 (T_H1) and T-helper type 2 (T_H2) lymphocytes.[25,34] In that construct, an initial induction phase is characterized by a decrease in naive regulatory T-cells (T-regs) with a resultant T_H1-immune response that causes release of pro-inflammatory cytokines. That is followed by upregulation of T_H2 and memory T-regs and, finally, by B-cell proliferation and maturation.[34] An expansion of IgG4-producing plasma cells and increased production of transforming growth factor-β (TGF-β)—secondary to interleukin-10-production by T_H2 cells—results in fibrosis during the progressive phase of the disease.[34] Also, interleukins 4 and 13, which are produced by T_H2 cells, induce B-cells to switch classes of immunoglobulin production to IgE and IgG4.[35] The presence of interleukins 10, 12 and 21 tilt the response towards IgG4 rather than IgE.[35]

Clinical and radiological features

Clinical features of ophthalmic IgG4-RD are not specific, and they overlap with those seen in a variety of other diseases. Most patients present with painless and gradually-progressive proptosis, and both eyes are often affected (Fig. 1).[3,5,26] Other problems can include swelling, ptosis, and chemosis, but inflammation and pain are usually

Table 2 – Terminologies which have been used for IgG4-RD.

References	Terminology
Kamisawa et al.[11]	IgG4-related autoimmune disease
van der Vliet et al.[12]	IgG4-associated multifocal systemic fibrosis
Kamisawa et al.[13]	IgG4-related systemic disease
Kamisawa et al.[14]	IgG4-related sclerosing disease
Neild et al.[15]	Hyper-IgG4 disease
Zen et al.[16]	IgG4-related disease (IgG4-RD)
Yamamoto et al.[17]	Systemic IgG4 plasmacytic syndrome (SIPS)
Masaki et al.[18]	IgG4-related multi-organ lymphoproliferative syndrome (IgG4-MOLPS)
Geyer et al.[19]	IgG4-associated disease
Umehara et al.[10]	IgG4-related disease (IgG4-RD)