PG Snippet

Ophthalmic Manifestations of Immunoglobulin G4-Related Disease (IgG4-RD)

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Abstract

Immunoglobulin-G4 related disease (IgG4-RD) is an inflammatory disorder of unknown etiology that comprises a wide spectrum of presentation, involving nearly all the bodily systems. A number of clinical conditions which were previously identified as distinct entities, such as autoimmune pancreatitis, Reidel thyroiditis, and Mikulicz syndrome, have now come within the purview of this disease. The clinical expression of IgG4-RD varies depending upon the organ involved. The authors in this article aim to highlight the various ophthalmic manifestations of IgG4-RD.

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Introduction

First identified in 2001 as an extra-pancreatic manifestation of type 1 auto-immune pancreatitis (AIP), IgG4-related disease (IgG4-RD) is a novel fibroinflammatory disorder of unknown etiology.[1] Presence of one or more ophthalmic features along with the distinct histopathological appearance is termed as IgG4-related ophthalmic disease (IgG4-ROD) (Table 1). Approximately 5% - 35% cases of IgG4-RD possess one or more ophthalmic manifestations, which can be broadly classified as:

Table 1. Ophthalmic manifestations of IgG4-RD

Orbit and Adnexa	Uvea
Lacrimal gland lesions, including dacryoadenitis	
Enlarged orbital nerves	Anterior uveitis
Extraocular muscle enlargement/ Myositis	Pan-uveitis
Lacrimal sac lesions like diverticulitis	Intermediate uveitis
Lacrimal drainage apparatus lesions	
Orbital mass	Intraocular mass (simulating uveal melanomas)
Medial canthal swelling	
Eyelid involvement, ptosis	
Orbital fat and bone involvement	
Vitreo-Retina	**Cornea, Sclera and Conjunctiva**
Exudative Retinal Detachment	Diffuse scleritis, Nodular scleritis, posterior scleritis, necrotizing scleritis
Retinal vasculitis	
Neural	Dry eye
Enlarged orbital nerves	Corneal ulcer
Optic nerve mass lesion	Peripheral Ulcerative Keratitis
Optic neuropathy	Conjunctivitis

Orbital And Adnexal IgG4-ROD

Lacrimal gland involvement, the commonest ophthalmic feature of IgG4-RD, manifests as painless, bilateral (more commonly) or unilateral dacryoadenitis. Mikulicz syndrome refers to bilateral salivary gland enlargement in presence of bilateral dacryoadenitis (Figure 1). Enlargement of orbital nerves, most commonly infra-orbital nerve followed by frontal nerve, is highly suggestive of IgG4-ROD, especially when bilateral. This may or may not be associated with adjacent bony remodeling. Histologically, the perineurium is the primary site of involvement accompanied by the absence of fibrosis.

Figure 1: *IgG4-ROD presenting as bilateral painless dacryoadenitis. Note the bilateral S-shaped lids.*

Enlargement of Extra-Ocular Muscles (EOMs), most commonly inferior rectus, followed by superior rectus, lateral rectus, medial rectus, inferior oblique, and superior oblique, presents as myositis and may be confused with myopathy associated with Thyroid Eye Disease (TED). Unlike IgG4-ROD, thyroid-associated myopathy is characterized by involvement of muscle belly with relative sparing of tendinous insertion.

IgG4-ROD may manifest as painless orbital mass, clinically presenting as bilateral or unilateral proptosis, medial canthal swelling, or even ptosis. Not only does IgG4-ROD simulates orbital lymphoma, it is also associated with an increased risk of developing lymphoma.[2] On Magnetic Resonance Imaging (MRI), adnexal IgG4-ROD typically appears isointense on T1-weighted Imaging (T1WI) and hyperintense on T2-WI with homogenous contrast enhancement.[3]

Involvement of orbital fat as well as bone has also been reported. Fibrosclerosis of the surrounding soft tissue as well as the lacrimal drainage apparatus fall within the spectrum of IgG4-ROD.

Corneoscleral IgG4-ROD (Outer Coat)[4]

Scleral involvement in the form of anterior diffuse scleritis, nodular scleritis, necrotizing scleritis, and posterior scleritis has been documented in literature (Figure 2). Corneal

and ocular surface manifestations include corneal ulcer, peripheral ulcerative keratitis, and dry eye which is partly attributed to involvement of lacrimal gland and decrease in the sub basal nerve plexus number as well as density, leading to tear film alterations. Conjunctivitis may be an associated feature.

Uveal IgG4-ROD (Middle Coat)

Occasionally, IgG4-ROD may present as an elevated intraocular mass lesion and simulate uveal neoplasms such as choroidal melanoma, and ciliary body tumor.[5-7] Anterior uveitis, vitritis, or pan-uveitis are the other associated manifestations of IgG4-ROD (Figure 3).

Figure 2: *IgG4-ROD presenting as left-sided sclero-uveitis.*

Retinal IgG4-ROD (Inner Coat)

Retinal involvement in IgG4-RD is usually secondary. Exudative retinal detachment, associated with an intraocular mass and ocular inflammation, is not uncommon. IgG4-ROD may clinically present as retinal vasculitis, masquerading autoimmune conditions such as granulomatosis with polyangiitis.[8]

Neural IgG4-ROD

Besides the involvement of the orbital nerves, IgG4-ROD may also present as an optic nerve mass lesion, mimicking a meningioma. Compressive effects due to expansion of an orbital IgG4-related mass may lead to optic neuropathy.[9]

A high index of suspicion for IgG4-ROD must be maintained in any case with the above enumerated clinical features, with or without systemic disease. The diagnosis is extremely challenging and must be confirmed by integrating clinico-radiological features with laboratory findings and histopathological examination. Recurrences and relapses are not uncommon and thus, close monitoring and long-term follow-up is recommended in all cases.

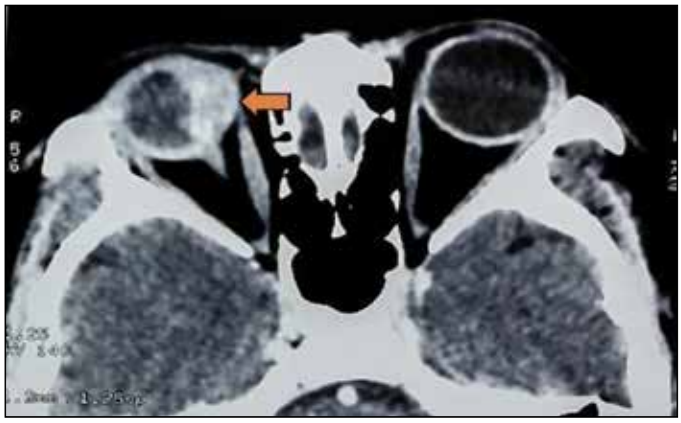

Figure 3: *Non-Contrast Computed Tomography (NCCT) scan, axial view, showing a right-sided heterogeneously enhancing hyperdense intra-ocular lesion. The patient was diagnosed as IgG4-ROD on tissue analysis.*

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