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Immunoglobulin G4(IgG4)-Related Orbital Disease – An overview

Abin Holla[1], Upender Wali[2], Abdullah Al-Mujaini[3,*]

[1,2,3]Dept. of Ophthalmology, College of Medicine & Health Sciences, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman

***Corresponding Author:**
Email: abdullah.almujaini@gmail.com

Abstract

Immunoglobulin G4 related orbital disease is a systemic fibro-inflammatory disorders with a generalized form of clinical manifestations. Although it has a wide spectrum of various pathologies that may affect distant organs as well, there is no single clinical or pathological feature which can be diagnostic. Careful clinicopathological correlation is probably the mainstay of early diagnosis which is so important in preventing severe organ damage. Steroid is effective in managing these cases, but for those patients who are steroid resistant or dependent rituximab appears to be very efficient.

Introduction

Immunoglobulin G4 related orbital disease (IgG4-ROD) is one of the manifestations of a generalized pathological process involving a wide spectrum of various disorders that may affect distant organs as well. Its features include tumor forming lesions, IgG4-positive plasma cell infiltration, elevated serum IgG4 in some cases, and a variable degree of fibrosis that has a characteristic "storiform" pattern. Eosinophilia and obliterative phlebitis are other features of systemic involvement.[1] Orbital disease may occur alone, or with systemic involvement like autoimmune pancreatitis, that was initially found to be associated with elevated serum titers of IgG4.[2] Immunoglobulin G4 related disease (IgG4-ROD) has also been described in several organs of the human body such as lymph nodes, lungs, skin, aorta, biliary tract, salivary glands, thyroid etc. IgG4-related orbital disease is the preferred terminology for this disease.[3]

Epidemiology

IgG4-ROD affects both sexes more or less equally among adults (1.3:1) with a mean age of onset being 55.5 years.[4] Children are also affected.[5,6] Many patients have a history of allergic diseases such as asthma and allergic rhinitis.[7]

Clinical Features

IgG4-ROD may present as proptosis or eyelid swelling, either unilateral or bilateral, which may be slowly progressive and often painless.[8,9]

Visual disturbances can occur if lesions are apical or in neurological involvement such as pachymeningitis.[10] The disease can involve ocular adnexae, lacrimal gland, orbital fat, extraocular muscles, eyelids, nasolacrimal duct, lacrimal sac, trigeminal nerve branch, infraorbital nerve and the periorbita.[8,9]

In a study by Sogabe et al of the 65 patients, LG enlargement was seen in 57 patients (87.7%), trigeminal nerve branch enlargement in 25 (38.5%), extraocular muscle enlargement in 16 (24.6%), diffuse orbital fat lesions in 15 (23.1%), orbital mass lesions in 11 (16.9%), eyelid lesions in eight (12.3%), and nasolacrimal duct lesion in one (1.5%). Six patients (9.2%) presented with visual disturbance due to optic nerve disturbance, eight (12.3%) with a restriction of ocular movement, and 19 (29.2%) with exophthalmos.[11]

Systemic Associations

Multiple organ involvement such as salivary glands, lymph nodes, lungs, kidney, para-aorta, and pancreas has been found in association with orbital IgG4-RD.[12,13]

Immunoglobulin G4-ROD is frequently associated with allergic conditions such as atopic dermatitis and asthma.[7,9,14]

Investigations

Laboratory Findings: The majority of patients with IgG4-ROD have elevated titers of IgG4 in the serum. About 40% have a normal serum IgG4 titer. Serum IgE titers may be low, normal, or elevated.

It must be noted that neither elevated serum IgG4 titers nor increased IgG4-positive plasma cells in tissue are specific for this condition.[8,9,14]

Hypergammaglobulinemia, elevated soluble interleukin 2 levels in association with elevated IgG4 levels, and hypocomplementemia are other features.

Radiological Findings: Computed tomography (CT) images of IgG4-ROD tumors appear as diffuse and heterogeneous masses, which may be hypointense, isointense, or hyperintense on T2- weighted magnetic resonance imaging.[8,15]

Positron emission tomography (PET) images of these lesions appear to be hypermetabolic and can also show demineralization of the orbital wall.

Tiegs-Heiden et al in their study found extraocular muscles were enlarged in 24 of 27 (89%) patients, 21 (88%) bilaterally. In 32 of 45 (71%) affected orbits, the lateral rectus was the most enlarged muscle. In 26

(96%) patients, the tendons of the extraocular muscles were spared. Nineteen (70%) patients had lacrimal gland enlargement. Twelve (44%) patients had an infiltrative process within the orbital fat. Infraorbital nerve enlargement was seen in 8 (30%) patients. Twenty-four (89%) patients had sinus disease. Cavernous sinus or Meckel cave extension was seen in 3 (11%) patients.[16]

In another study, Infraorbital nerve enlargement (IONE) was present in 53% of IgG4-ROD cases whereas it was never present in cases of non-IgG4-ROD ($P < 0.0001$). IONE was only present in cases where, on MRI, the inflammation of the inferior quadrant was present and in direct contact with the ION canal.[17]

Histology

The characteristic features of IgG4-ROD are lymphoplasmacytic infiltration of varying degrees associated with dominant sclerosing lesions or reactive lymphoid follicle (reactive lymphoid hyperplasia). Other features include fibrosis that has a storiform pattern at least focally, Eosinophilic infiltrations, and rarely, an infiltration by lymphoplasmacytic cells and macrophages containing eosinophilic material. [18] Obliterative phlebitis, a feature of systemic IgG4-ROD is rarely seen in orbital disease. [5]

Differential Diagnosis

The differential diagnosis for IgG4-ROD include idiopathic orbital inflammation, idiopathic orbital myositis, marginal zone B-cell lymphoma, antineutrophil cytoplasmic antibody (ANCA) mediated systemic vasculitis, and reactive lymphoid hyperplasia.

The hallmark of nonspecific orbital inflammatory disease and idiopathic myositis is inflammation presenting with acute onset swelling, pain, redness, and restriction of ocular motility, while Ig G4-ROD is usually chronic, painless with mild or no signs of inflammation. Tissue biopsy of the involved structure and histopathological examination will allow differentiating the cause.

Ocular adnexal marginal zone B-cell lymphomas, composed of reactive follicles, sclerosis, and plasma cells , share these histological features with that of orbital IgG4-ROD.[19]

Immunohistochemistry analysis showed expression of CD25 and CD19 was higher in patients with orbital MALT lymphoma than those with IgG4-ROD. CD3, CD4, and CD23 was higher in patients with orbital IgG4-ROD.[20]

ANCA-related vasculitis and other conditions presenting with granulomatosis with polyangiitis (Wegener's xanthogranulomatosis) can present as nonspecific inflammatory lesions and abundant IgG4-positive plasma cells. Thorough systemic investigations will be needed to differentiate it from IgG-ROD.[21,22]

Treatment

IgG4-ROD responds well to systemic glucocorticoids. Prednisolone in low doses have been used although relapse may occur after discontinuation. It may not respond in some cases. Some centers have recommended a starting dose of 40 mg/day of prednisolone for 30 days followed by gradual decrease of the dose by 5 mg for next 2 months and ending the treatment after 11-12 weeks.[23]

Intraorbital injection of corticosteroid also is an option for IgG4-ROD. However, most cases require repeat injections due to incomplete response and relapse along with its complications.[24]

Other immunosuppressants such as azathioprine, methotrexate, cyclophosphamide, and mycophenolate have also been used.

Radiotherapy can be recommended in patients not responding to steroids or in patients where these medications cannot be used.[25]

Rituximab has been shown to be effective in patients with refractory, steroid dependent or steroid intolerant disease, although recurrence is also observed after rituximab treatment ends in some patients Rituximab is a monoclonal antibody against CD20. The long-term efficacy of rituximab in IgG4-ROD is not known.[26]

Conclusion

IgG4-ROD is an underdiagnosed and increasingly recognized orbitopathy, affecting middle aged individuals. It often presents as a chronic progressive proptosis, and must be kept in mind as a differential diagnosis. Histopathology and immunohistochemistry help in diagnosing this unique disease. It responds well to corticosteroids, although some refractory cases may require a more aggressive approach.

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