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IgG4 - related orbital disease: concept and pathogenesis

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The concept and recognition of Immunoglobulin G4-related disease (IgG4-RD), an immune disregulation disorder and a minor component of four subsets of IgG, was introduced in 2003.(1) IgG4-RD often has multiple-organ involvement and some of the classical manifestations include autoimmune pancreatitis (AIP) type 1, involvement of the major salivary glands, proptosis due to orbital and lacrimal pathology, dacryoadenitis, myositis, inflammatory disorders of orbit, orbital pseudotumor, hypophysiitis, meningitis and involvement of one or more cranial nerves and retroperitoneal fibrosis. IgG4-related orbital disease is a general term for the pathologies of the orbital region. IgG4-RD Is characterized by mixed infiltrate of lymphoid cells (T cells, B cells and plasma cells), storiform fibrosis, obliterative phlebitis and mild to moderate tissue eosinophilia. The B cells are typically organized in germinal centers but T- cells-the predominant cell type- are distributed diffusely throughout the lesion. The ratio of IgG4 to IgG-bearing plasma cells (determined by semi quantitative immunohistochemistry) is typically equal to or greater than 50%.

The ocular-orbital manifestations include idiopathic orbital inflammation (pseudotumor), pachymeningitis and sclero-uveitis. The lacrimal gland involvement has been recognized as IgG4-related dacryoadenitis, while orbital lesions predominantly present in the role of orbital pseudotumors. However, recent involvement of conjunctiva and sclera have been reported.(2)

The hypothesized concept of pathogenesis in IgG4-RD involves upregulation in the expression of T-helper 2 cells, cytokines such as interleukins and transforming growth factor-beta. The mechanism of upregulation could be due to repeated and prolonged exposure to specific antigens. Interestingly, 40% of patients with IgG4-RD have concomitant allergic disorders like asthma or sinusitis.(3) IgG4-related inflammation affects many different organs, the histopathology, typically fibroinflammatory, remains the same in most cases, including the orbits. The association between IgG4 and granulomatous inflammatory diseases is now being recognized sizably, based on case reports. This includes IgG4-orbital/ocular lesions as well.

IgG4-RD is a group of immune-mediated diseases which have certain common clinical, serological and pathological similarities. This group is gaining an increasing recognition in the field of medicine. The common features in IgG-RD include involvement of almost any organ which has swellings resembling tumors, lymphoplasmacytic and fibrosis tissue infiltrates which are positive for IgG4 positive plasma cells, and a classical pathological form of storiform lesions.(4)

The exact pathophysiology of IgG4-RD is not yet clear. IgG4-RD seems to be placed between different inflammatory markers and is most likely driven by an underlying autoimmune mechanism but no precipitating factors have been identified yet. There is higher risk for IgG4-RD in certain genotypes and there is immune complex deposition and increase in regulatory CD25 T cells. Production of inflammatory tissue T-cell cytokines by Mast cells suggests their role in pathogenesis. There are conflicting reports in literature about histopathological features of IgG4-related orbital disease. Deshpande et al quoting worldwide literature say IgG4-related orbital disease is rarely associated with lymphoplasmacytic infiltration and eosinophilic material-containing macrophages.(4) Others have reported lymphoplasmacytic infiltration with predominant fibrosis, reactive lymphoid hyperplasia, macrophages and eosinophils as common features. However, a characteristic feature of IgG4-related orbital disease is very rare presence of thromboangiitis obliterans in its pathology. When IgG4-related orbital disease occurs along with other extraorbital organs it is considered as a generalized disorder and treated as such. Most common extraorbital organs involved are parotid glands and lymph nodes. Positron emission tomography (PET) scan is an excellent imaging modality to diagnose both IgG4-related orbital disease and distant lesions.(5)

For an ophthalmologist, IgG4-related orbital disease has emerged as an interesting and challenging entity. IgG4-related orbital disease is a general term for

the pathologies of the orbital region. Its protean manifestations can include eye lid swelling, ocular surface changes, infraorbital nerve involvement, conjunctival inflammation, thyroid-associated orbital disease, idiopathic sclerosing orbital inflammation, masquerading orbital lesions, etc. Orbital IgG4-related disorders are common in adults and have three classical features: The ocular adnexal tissues show typical lymphoplasmacytic infiltrations which are IgG4-positive, elevated serum levels of IgG4 and IgE and hypergammaglobulinemia Two entities which need to be differentiated from orbital IgG4 RD include idiopathic orbital inflammation and marginal zone B-cell lymphoma of orbital adnexal tissues because the treatment profiles of the diseases are different. Orbital IgG4-RD differs from other IgG4-RD in the body in that it arises from non-glandular lesions and is not associated histologically with obliterative phlebitis.

The diagnosis of IgG4-related orbital disease is based on the criteria proposed by Umihara et al.[6] Usually patients with orbital IgG4-RD present with chronic symptoms like lid swelling, proptosis usually mild or no signs of inflammation or periocular pain. Ocular motility is restricted mildly if at all despite the presence of one or more enlargements of the large extraocular muscles. There are generally no visual disturbances although they may occur due to apical orbital lesions. Imaging studies show infiltrative lesions in ocular adnexal tissues such as the lacrimal glands, extraocular muscles, infraorbital nerves, optic nerve sheath, lacrimal sac, and even cavernous sinus or the intracranial extension. Plaza et al have studied a series of patients with orbital IgG4 disorders and found bilateral orbital lesions in 62% cases and bilateral lacrimal gland involvement in 48% cases.[7] It is important to differentiate Idiopathic orbital inflammations and idiopathic orbital myositis from orbital IgG4-RD. The former two have unknown etiology and are associated with acute onset of signs and symptoms of orbital inflammation like periocular pain, swelling and redness of the eyelids, proptosis, ptosis, and ocular motility restrictions. These differ from the signs and symptoms of orbital IgG4-RD which overall has chronic course. However, some cases of idiopathic orbital inflammation may have atypical presentation without acute onset and minimal signs of inflammation.

Since the pathophysiology of IgG4-related orbital disease is yet to be explored in full, the treatment is based on empirical and institutional experiences. Corticosteroids, monoclonal anti-CD20 antibody (rituximab), anti-tumor necrosis factor drugs (infliximab), chemotherapeutic agents like borezumib form the main line of treatment, which is grossly symptomatic.

B-cell depletion is an effective and most-tried therapy in IgG4-related disease including orbital variant. Since Rituximab effectively depletes CD20-positive cells which in turn differentiate into plasma cells that produce IgG4, it supports the logic of its use in this disease. Future holds Rituximab as first line of therapy in the treatment of IgG4-related disease, replacing corticosteroids.[8]

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