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Immunoglobulin G4-Related Orbital Disease With Asymmetrical Orbital Infiltration In A 65 Years Old Male – A Case Report.

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Abstract: *Immunoglobulin G4-related disease is a systemic disease in which there is infiltration of multiple organ tissues by IgG4+ plasma cells resulting fibro-inflammatory lesion. In the region ofthehead, the disease affects the orbits, lacrimal glands, nasolacrimal duct system, extra-ocular muscles, nerves, orbital fat, meninges and pituitary. Imaging* ***(CT, MRI, PET CT)*** *along with serum biochemical investigations are extremely useful in disease detection, differentiation from other orbitopathies,treatment response monitoring and follow up.*

Keywords:

- *Immunoglobulins (MeSH unique ID: D007136).*
- *Orbit (MeSH unique ID: D009915).*
- *Lacrimal Apparatus (MeSH unique ID: D007765).*
- *Oculomotor Muscles (MeSH unique ID: D009801).*
- *Optic Nerve (MeSH unique ID: D009900).*

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I. Introduction

Immunoglobulin G4 related disease is a systemic inflammatory disease of unknown etiology, consisting of infiltration of tissues by IgG4 plasma cells and sclerosing inflammation.[1]

It has been found to affect multiple organs in the body, including pancreas, gall bladder, bile ducts, lymph nodes, mesentery, retroperitoneum, kidneys, breasts, lungs, prostate, head, neck, thyroid, pituitary, orbits, meninges and skin.[2]

II. Case Report

A 65 years old male patient presented with pain in both eyes and swelling in the region of both eyes (periorbital region) since several months. On local examination, proptosis of the eyeball was found. No complaints regarding the reduced visual acuity were given by the patient. Magnetic resonance imaging of the brain with orbit was performed which revealedgross diffuse enlargement of lacrimal glands on both sides**(Figure 1)**, diffuse enlargement of infra-orbital nerves with smooth scalloping of the roof of maxillary sinus on both sides**(Figure 2, 3, 4)**, diffuse enlargement of inferior rectus muscle on the right side**(Figure 2, 3)**, and proptosis of both eye balls (more on the right side). Based on the imaging findings and further laboratory work up including thyroid function testsand serum Ig G4 levels (conclusive of elevated IgG4 levels), a diagnosis of Ig G4-related orbital disease was given.

Figure 1: Coronal T1WI

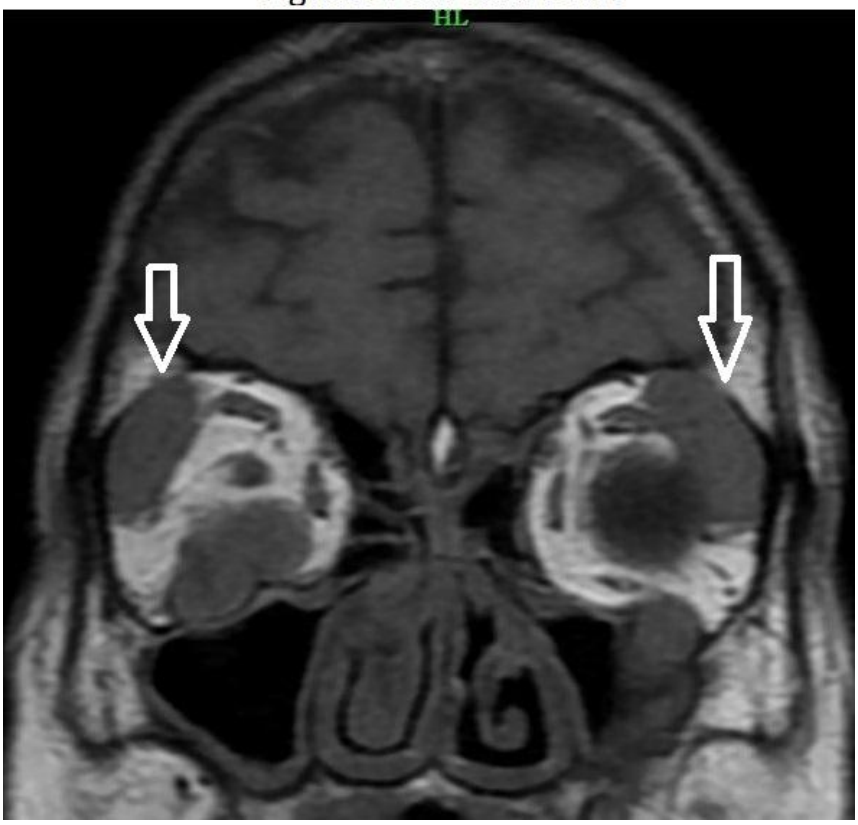

Figure 1: Coronal T2WI showing gross diffuse enlargement of lacrimal glands (arrows) on both sides.

Figure 2: Coronal T1WI

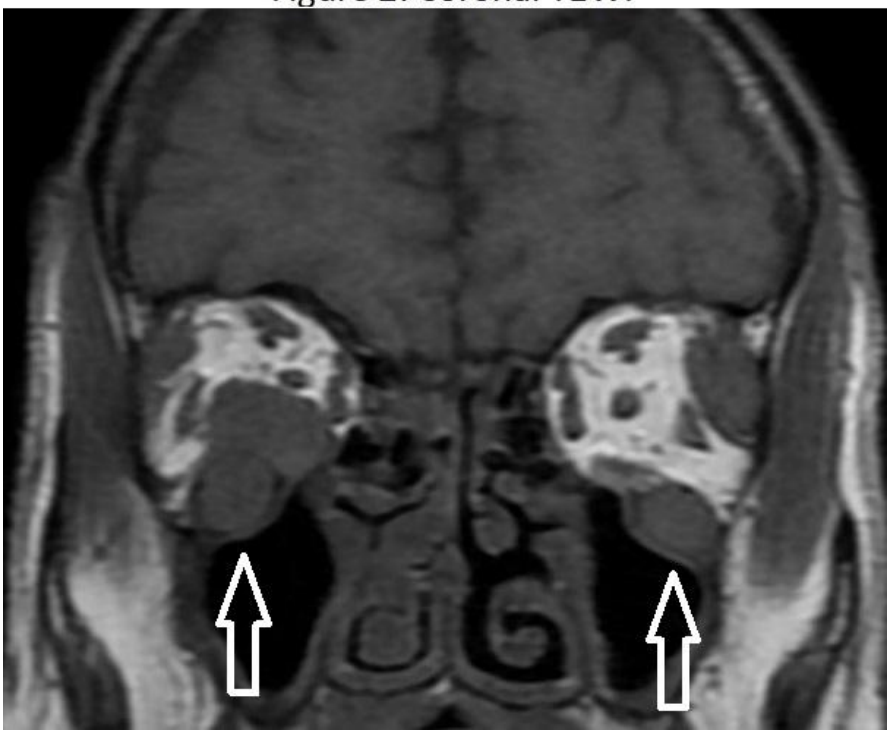

Figure 2: Coronal T1WI showing diffuse enlargement of infra-orbital nerves (arrows) with smooth scalloping of roof of maxillary sinus on both sides.

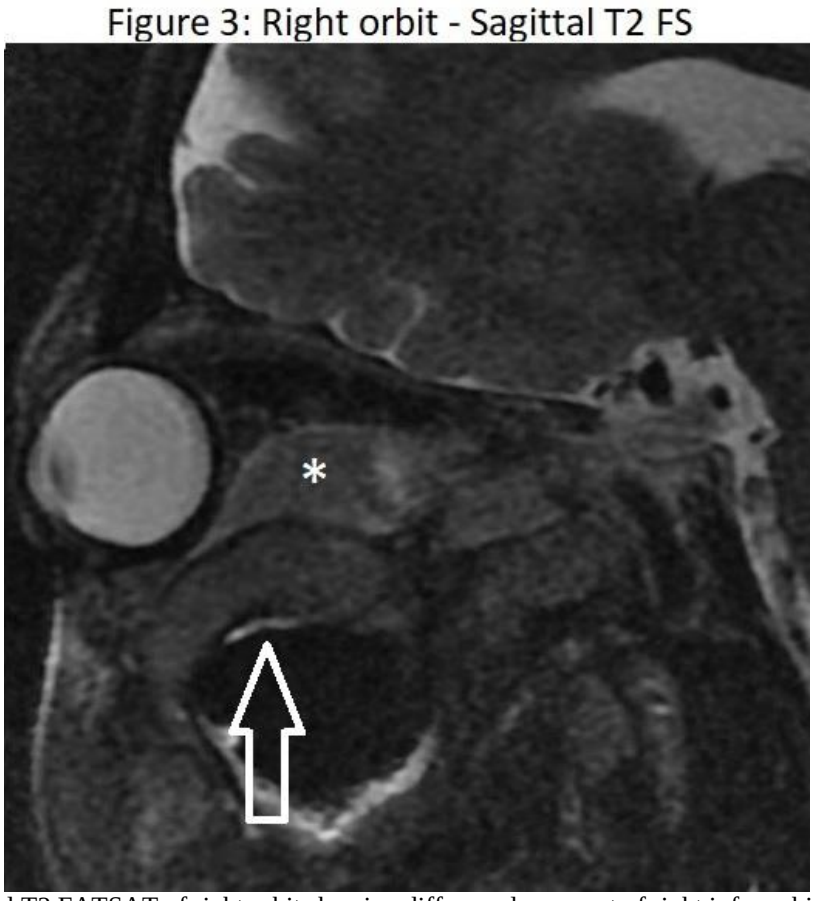

Figure 3: Sagittal T2 FATSAT of right orbit showing diffuse enlargement of right infra-orbital nerve (arrow) with diffuse enlargement of right sided inferior rectus muscle (* asterisk).

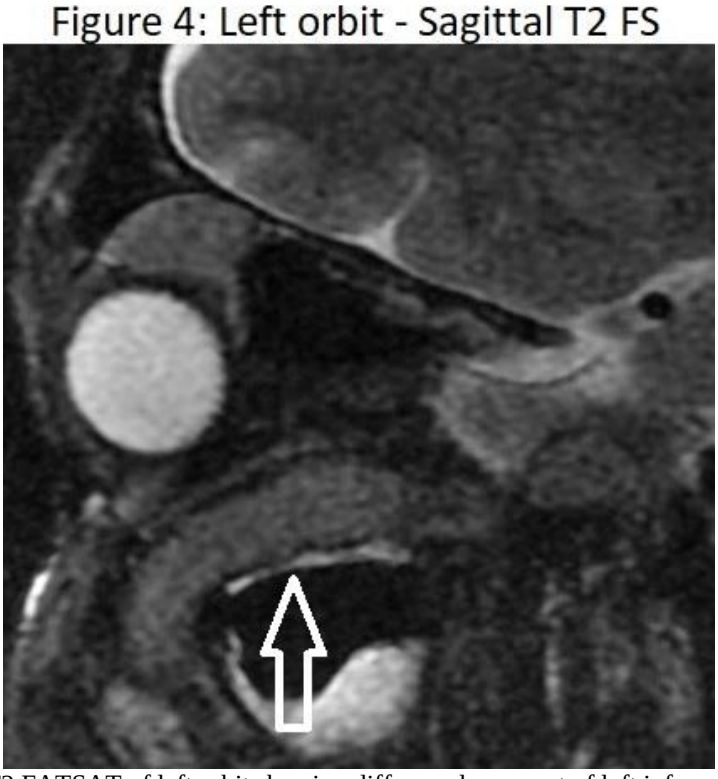

Figure 4: Sagittal T2 FATSAT of left orbit showing diffuse enlargement of left infra-orbital nerve (arrow).

III. Discussion

Immunoglobulin G4 (IgG4)-related disease is a distinct clinical-pathological systemic disease that can affect different parts of the body. In this disease, there is profuse infiltration of IgG4-positive plasma cells and lymphocytes with fibrosis. In some studies, it has been predominantly found in elderly men and associated with increased serum IgG4 levels.[3]

According to sum total of 95 patients from seven studies conducted in Taiwan, Korea, Japan, and America, mean age of onset of the IgG4-related orbital disease was 56.3 years and male to female ratio was 1.1 to 1.[4]

Approximately 20% patients show head and neck region involvement in IgG4-related disease. In these proportion of cases, approximately 40% patients show orbital involvement.[5]

Clinical features: patients with IgG4-related orbital disease present with painless, enlarging swelling over lacrimal gland region with or without proptosis. Bilateral involvement is present, however, it can be asymmetrical. Visual acuity is not impaired in majority of cases but blindness has been found in some cases whereintheoptic nerve compression was present.[4]

Primary involvement of lacrimal gland is seen in patients with IgG4-related ophthalmic disease. Inflammation of lacrimal glands i.e. dacryoadenitis is usually bilateral in IgG4 related disease and simultaneous enlargement of the salivary gland is common.[2]

Differential diagnosis of isolated involvement of lacrimal gland in IgG4-related orbital disease are: Sjogren's syndrome, extranodal marginal zone lymphoma, non-Hodgkin's lymphoma and primary pleomorphic adenoma.[2]

Unilateral acute inflammatory type onset consisting of pain, erythema, proptosis and ocular motility restriction is classical differentiating feature of many cases of idiopathic orbital inflammation, which helps in disregarding the diagnostic possibility of IgG4 related orbital disease.[6]

In Mikulicz disease, there is similar painless bilateral and symmetrical enlargement of salivary and lacrimal glands. [3]

Lesions of the orbit may be bilateral or unilateral and entire orbit or individual parts including the optic nerves, extraocular muscles and lacrimal glands can be affected.[2]

Extra-ocular muscle involvement is seen in IgG4 related orbital disease and thyroid associated orbitopathy. However, inferior and medial recti muscles are affected in the latter condition, whereas lateral rectus muscle is more commonly affected in IgG4 related orbital disease.[6]

In the region of the orbit, perineural involvement of IgG4-related disease has been found. Branches of trigeminal nerve including infra-orbital and frontal nerves are affected in this disease. Differential diagnosis for perineural spread are lymphoma, squamous cell carcinoma and adenoid cystic carcinoma. [3, 5]

Diffuse infra-orbital nerve thickening is considered specific for IgG4 related orbital disease.[7]

IgG4 related orbital disease can affect all orbital tissues, including lacrimal sac, eyelids and nasolacrimal duct.[6]

Lymphoma can originate as a complication of IgG4-related orbital disease.[5]

Unknown antigenic immunological response stimulates mature plasma cell production of IgG4, assisted by cytokines secreted by activated type 2 helper T cells, which induce fibrotic reaction. Circulating B lymphocytes and plasmablasts may be a biomarker for active disease and are found to be elevated in IgG4 related disease.[6]

Specificity of 82.6 % and a sensitivity of 87.2 % has been shown by serum IgG4 levels to screen IgG4-related disease. Approximately 5 % patients of IgG4-related orbital disease show normal serum levels of IgG4 at the time of presentation.[4]

Variations in serum levels of IgG4 are useful in analysis of the progression or regression of the disease in the majority of patients. Post steroid treatment follow up of IgG4-related disease patients showing persistently increased serum IgG4 levels is essential as there may be chances of relapse in these cases.[4]

Imaging: Magnetic resonance imaging or computed tomography demonstrate focal mass or mass-like lesions showing diffuse infiltration. CT is beneficial for assessment of osseous involvement in the region of the head and orbit. MRI offers superior soft tissue contrast with tissue characterization, demonstrating hypointense to intermediate signal intensity lesions on T2W images. [6]

The lesions show hypointense signal intensity on T1W images and relatively hypointense signal intensity on T2W images due to fibrosis and increased cellularity. On CT, the lesions show intermediate soft tissue density.[3]

Instead of bony destruction, smooth infra-orbital canal enlargement and simultaneous affection of nerves are likely indicative of a diagnosis of IgG4-related disease.[5]

Positron emission tomography with 2-[18 F]-fluoro-2-deoxy-D-glucose (FDG) shows avidly enhancing lesions in IgG4-related disease and hence can be used to detect asymptomatic cases of the disease, plan minimally invasive tissue sampling and for treatment response monitoring.[6]

Commonly used first line treatment for IgG4-related orbital disease is glucocorticoids. Initial phase of treatment consists of systemic corticosteroid administered orally for 2-4 weeks and tapered every 2-4 weeks with doses as per clinical profile, biophysical and lab parameters of the patient.[4]

Patients at the chronic disease stage and with more fibrotic changes may show poor response to glucocorticoids. Low serum IgG4 levels at the time of presentation is considered a poor prognostic factor for treatment with glucocorticoids.[4]

Approximately 17 to 50 % of relapse rate has been noted in the patients suffering with this disease. Retreatment and maintenance therapy with glucocorticoids has been found to be beneficial in some cases of recurrent IgG4 related orbital disease.[4]

In relapse cases or those refractory to steroids, Rituximab (monoclonal anti-CD20 antibody) is an effective mode of treatment. Untreated cases of IgG4 related disease are likely to become non-responsive to treatment due to extensive fibrotic changes in tissues. [6]

Current role of orbital radiotherapy is under research analysis and at present is considered as adjunctive to medical treatment for IgG4- related orbital disease. [4]

IV. Conclusion

In patients presenting with peri-orbital swelling and proptosis, imaging plays an essential role in narrowing down the differential possibilities from a broad spectrum of orbitopathies to a limited number of conditions. When certain features like symmetrical or asymmetrical involvement of extra-ocular muscles, lacrimal glands, and nerves in the periorbital region (infraorbital) present in a patient complaining of painless periorbital swelling, IgG4-related disease should be one of the differential diagnosis to be considered and evaluated further with serum biochemical investigations.

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