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IgG4-Related Orbital Disease: An Analysis of Patient Profiles, Clinical Presentation, And Histopathological Features

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Abstract

Objective: To study various presentations of patients with a histopathologically confirmed diagnosis of IgG4 disease.
Methods: This study is a retrospective review of medical records from the IgG4-RD registry at the Al-Shifa Trust Eye Hospital. Nine patients with orbital manifestations were identified. All had histopathologically confirmed diagnoses of IgG4-RD. Data obtained from the medical records included patient demographic information (name, age, gender), brief patient history, clinical presentation, histopathology reports, and diagnoses.
Results: Most patients presented with proptosis and swelling in various parts of the orbital area. Some patients also presented with pain and diplopia. The most common orbital structures involved were the lacrimal gland and the extraocular muscles, with some patients also having soft tissue involvement. 4(44%) patients had bilateral orbital involvement, while the remaining 5(55%) had unilateral disease.
Conclusion: Ophthalmic involvement is a feature of IgG4-RD and has significant implications regarding the diagnosis, prognosis, and treatment of patients with IgG4 disease.
Keywords: IgG4, Autoimmune Disease, Sclerosing, Orbit inflammation.

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1. Introduction

IgG4-related disease (IgG4-RD) is an inflammatory disorder with systemic involvement that is known to cause tumefactive lesions.[1] These lesions have been identified in almost every organ system, with certain organs being more frequently affected. The disease was initially described as "lymphoplasmacytic sclerosing pancreatitis," involving the pancreas. It is renamed type 1 (IgG4-related) autoimmune pancreatitis.[2] The disease can involve various organs, including the liver, bile ducts, thyroid gland, aorta, lymph nodes, and retroperitoneum.[3] Within the head and neck region, the middle ear, pituitary gland, meninges, salivary glands, and sinuses have been affected.[4]

IgG4-ROD appears to affect men and women equally.[5] Due to the relatively recent recognition of IgG4-RD, there are many ongoing challenges regarding its diagnosis, and the disease's epidemiology still needs to be described. Guma and Firestein reported the incidence of IgG4-related pancreatitis. They quoted the incidence as 0.28–1.08/100,000.[6] Among manifestations of IgG4-RD, orbital involvement is extensively researched and ranks the fifth most prevalent extra pancreatic site, occurring in 3.6% to 12.5% of cases.[5] Hence, the true prevalence and incidence are likely to be higher.

The diverse clinical presentation of IgG4-related disease (IgG4-RD) encompasses symptoms like organ dysfunction, swelling, and pain. Asymptomatic cases are common, often discovered incidentally during routine physical exams or imaging studies.[7] Patients may display involvement of single or multiple organs, either concurrently (synchronous organ participation) or sequentially (metachronous disease).[8] IgG4-related orbital disease (IgG4-ROD) typically presents as lacrimal gland swelling or proptosis. This clinical profile frequently results in an initial misdiagnosis, often confusing it with a malignant condition.[9]

Conditions like sarcoidosis, Wegener's granulomatosis (now known as granulomatosis with polyangiitis), and idiopathic orbital inflammatory disease are known to affect orbital structures.[10] As understanding of IgG4-RD has grown, mounting evidence indicates that many IOI cases represent ocular manifestations of IgG4-RD.[11] Like Idiopathic Orbital Inflammatory Disease (IOID), IgG4 orbital disease can also affect one or more than one structure in the orbit.[5]

The IgG4-RD can affect various orbital and ocular tissues. The most frequent sites of involvement are the lacrimal gland and lacrimal duct, extraocular muscles,

orbital soft tissue, sclera, and the cranial nerves and their branches. We aim to review the cases of IgG4-RD from an ophthalmologist's perspective and share our centre's experience with this condition, now called IgG4-related ophthalmic disease (IgG4-ROD).

2. Materials & Methods

In this study, we did a retrospective review of medical records from the IgG4-RD registry at the Al-Shifa Trust Eye Hospital. We found 09 patients with orbital manifestations, all with histopathologically confirmed diagnoses of IgG4-RD. Data obtained from the medical records included patient demographic information (name, age, gender), brief patient history, clinical presentation, histopathology reports, and diagnoses.

Only one patient in the study with systemic involvement met the diagnostic criteria. The rest of the patients have normal serum IgG4 levels with positive clinical and histopathological findings. The diagnostic criteria of IgG4-related disease,[12] include three main aspects:

1. Clinical examination revealing characteristic swelling or masses in one or more organs.
2. Hematological examination showing high levels of IgG4 in the blood (>135 mg/dl).
3. Histopathologic examination indicating either significant infiltration of lymphocytes and plasma cells with fibrosis or the presence of IgG4+ plasma cells (with a ratio of IgG4+/IgG+ cells greater than 40% and more than 10 IgG4+ plasma cells per high-power field).

If patients with IgG4-RD showed any ophthalmic involvement based on symptoms, signs, physical exams, or imaging tests like ultrasound, CT scan, MRI, or PET/CT, they were considered to have IgG4-related orbital disease (IgG4-ROD). Additionally, we carried out a literature review on IgG4-ROD using MEDLINE and PubMed databases.

3. Results

Nine cases included in this study are presented in Table 1. Of these 9 patients, 6(66%) were men and 3(33%) were women. The overall mean age was 35.7 years (17-56). Most patients presented with proptosis and swelling in various parts of the orbital area. Some patients also presented with pain and diplopia. The lacrimal gland and the extraocular extraocular muscles were the most common structures involved, with some patients also having soft tissue involvement. 4(44%) patients had bilateral orbital involvement, while the remaining 5(55%) had unilateral disease. All patients had a histopathologically confirmed diagnosis of IgG4-ROD. Seven out of nine (77%) patients had extra-orbital manifestations of IgG4-RD, with two (22%) patients having IgG4-ROD in isolation. The extra-orbital manifestations were not part of this study's scope.

A detailed breakdown of each patient's clinical presentation is as follows:

Table 1: Clinical Features of the selected patients

Case	Age/ Gender	Orbital Manifestation	Extra-orbital Manifestation	Bilateral Disease
1	40/M	Superomedial periorbital and orbital swelling	None Reported	Not reported
2	21/F	Right proptosis and a firm palpable tumour along the superolateral orbit and adjoining roof	None Reported	Not reported
3	53/M	Bilateral proptosis, generalized pallor, edema	None Reported	Yes
4	32/M	Left forward and outward mildly painful displacement	None Reported	Not reported
5	56/M	Left marked proptosis and outwards displaced globe	None Reported	Not reported
6	17/F	Painful forward proptosis	None Reported	Not reported
7	25/M	Right very dense growth along the floor of the orbit concealed by ocular prosthesis	None Reported	Not reported
8	48/F	Severe, shooting pain in the orbit	None Reported	Not reported
9	45/M	Bilateral proptosis	IgG4-related GIT disease, as well as diabetes inspires due to pituitary hypophysitis	Yes

Patient 1: A 40-year-old male patient initially presented with mild left dystopia inferolateral and annoying diplopia persisting for three months. Post-surgery, he experienced recurrent superomedial periorbital and orbital swelling. The histopathology report confirmed a diagnosis of nonspecific sclerosing inflammation and IgG4-ROD.

Patient 2: A 21-year-old female patient presented with right proptosis and a firm palpable tumour along the superolateral orbit and adjoining roof. She was diagnosed with IgG4-ROD of the lacrimal gland.

Patient 3: A 53-year-old male patient presented with bilateral proptosis, marked cachexia, anorexia, weakness, generalized pallor, oedema, and evening

temperature with rigours over one year. Lab work found hypergammaglobulinemia. His diagnosis was IgG4-ROD.
Patient 4: A 32-year-old male patient presented with left forward and outward mildly painful displacement over six months. He was diagnosed with IgG4-ROD.
Patient 5: A 56-year-old male patient presented with left marked proptosis and outwards displaced globe. He was diagnosed with IgG4-ROD.
Patient 6: A 17-year-old female patient had a gradual, painful forward proptosis over six months. She was diagnosed with IgG4-ROD.
Patient 7: A 25-year-old male patient presented with a right very dense growth along the floor of the orbit, concealed by an ocular prosthesis that he had been using for a few years. The diagnosis was IgG4-ROD.
Patient 8: A 48-year-old female patient presented with severe shooting pain in the orbit for the last three years, and the vision was completely lost. The diagnosis was IgG4-ROD.
Patient 9: A 45-year-old male patient presented with bilateral proptosis over three months. He was earlier diagnosed with IgG4-related GIT disease as well as diabetes insipidus due to pituitary hypophysitis. His diagnosis was IgG4-ROD and GIT disease with Diabetes Insipidus.

Pathology: Most biopsy specimens demonstrated nonspecific inflammation; all cases were confirmed as IgG4-ROD.

Table 2: Hematological and Histopathological features of selected patients

Case	Bx Site	Infiltrate	Fibrosis	Obliterative Phleb	Non-Obliterative-Phleb	Eos	IgG4+ cells
1	Superomedial	Yes	Yes	Yes	Yes	No	Positive in plasma cells
2	Lacrimal	Yes	Yes	No	Not Reported	No	positive
3	Lacrimal	Yes	Yes	No	Not Reported	No	Positive in plasma cells >10/hpf
4	Superomedial	Yes	Yes	No	Not Reported	Yes	positive
5	Superomedial	Yes	Yes	No	Yes	No	positive
6	Scleral	Yes	Yes	No	Not Reported	No	positive
7	Orbit Floor	Yes	Yes	No	Not Reported	No	Positive in 40% cells
8	Roof	Yes	Yes	Yes	Yes	Yes	Positive
9	Not Biopsied	IgG4-related GIT disease	IgG4-related GIT disease	IgG4-related GIT disease	IgG4-related GIT disease	IgG4-related GIT disease	IgG4-related GIT disease

4. Discussion

This discussion presents a series of 9 patients representing a diverse range of manifestations of IgG4-Related Ophthalmic Disease (IgG4-ROD)). The ocular expressions of IgG4-Related Disease (IgG4-RD) are numerous, and those of the orbit are among the most common aspects of the condition. This series from our centre, Al-Shifa Trust Eye Hospital, represents the largest single-institution patient series reported thus far.
Our patients' disease is histopathologically proven, but serum IgG4 levels were within normal range. Elevated serum IgG4 levels are not necessarily raised in all IgG4 disease cases and are insufficient for diagnosing the disease. Serum IgG4 levels are more significantly raised in patients with systemic involvement. If raised serum IgG4 levels are found, they are a good indicator of treatment response. Serum IgG4 levels significantly decrease after steroid therapy.
Previously, a literature review analyzed 21 definitive cases of IgG4-RD. In their analysis, lacrimal gland swelling was the most common site, and women were more frequently affected than men. Most cases were bilateral; salivary gland involvement was the most common systemic manifestation.
Our cases generally agree with these findings, although the gender distribution differs, and we highlight some unique manifestations.
Lacrimal gland involvement (dacryoadenitis):
In our study, we observed that the lacrimal gland was frequently affected in the orbit. During a physical examination, patients typically exhibited signs of the disease in both eyes. In IgG4-related ophthalmic disease (IgG4-ROD), orbital involvement is prevalent independently or as part of a larger systemic disease.[13]

The lacrimal glands were among the first areas outside the pancreas to display signs of IgG4-R.

IgG4-ROD and Sjögren syndrome (SjS):

Before identifying IgG4-RD as a unique entity affecting multiple organ systems, "Mikulicz's disease" was typically referred to as a diagnosis whenever there is bilateral lacrimal gland enlargement with salivary gland enlargement. This was misclassified as a subset of Sjögren syndrome (SjS). However, unlike SjS, "Mikulicz's disease" is not associated with positive anti-nuclear antibodies (ANA) or anti-Ro or anti-La antibodies. It is now recognized as a manifestation of IgG4-RD. IgG4-ROD and Mikulicz's disease are part of the spectrum of IgG4-RD.[2]

Extraocular muscle involvement (orbital myositis):

IgG4-related ophthalmic disease causes a condition known as orbital myositis. The extraocular extraocular muscles may significantly enlarge in individuals with IgG4-ROD. Interestingly, most patients maintain normal ocular motility despite the muscle enlargement. In certain cases, patients may experience symptoms like exotropia (outward deviation of the eye) or hypertropia (upward deviation of the eye).[14]

Our study identified patients with extraocular extraocular muscle (EOM) involvement, all of whom had additional ocular adnexal involvement. EOM involvement can present with proptosis, associated with diplopia and pain. Diagnosis can be challenging due to the inaccessibility of EOMs for biopsy and the risk associated with the procedure.

Nasolacrimal duct involvement:

The disease can affect the nasolacrimal duct, although this is relatively uncommon. In certain instances, IgG4-related inflammation may result in acquired nasolacrimal duct obstruction, causing symptoms such as mucoid discharge and proptosis.[15] Our series identified two cases with nasolacrimal duct involvement, both presented with epiphora.

Orbital soft tissue involvement:

In IgG4-related ophthalmic disease (IgG4-ROD), the involvement of orbital soft tissues can present as swelling, inflammation, and thickening of the tissues. This manifestation may impact various structures in orbit, including the extraocular extraocular muscles, orbital fat, and other soft tissue components.[5] In our study, six patients had orbital soft tissue involvement. They had no extra-orbital disease, and biopsies of the soft tissue behind the eye confirmed their diagnoses.

Scleritis:

IgG4-related ophthalmic disease (IgG4-ROD) may exhibit scleritis, characterized by inflammation of the sclera, the outer white layer of the eye. While scleritis associated with IgG4-ROD is rare, it has been documented in several cases. Ocular symptoms may involve scleral injection, bilateral conjunctival congestion, intermittent blurred vision, and painful downward gaze.[16] One patient in our study was thought to have scleritis related to IgG4-RD.

Xanthogranuloma:

Xanthogranuloma is an orbital disease characterised by the existence of foamy macrophages and Touton giant cells. Although there have been infrequent instances of both IgG4 disease and xanthogranuloma occurring simultaneously, such cases are rare.[17,18] In our study, there was one case with orbital xanthogranulomatous disease.

Features of IgG4-ROD not identified in our study but described elsewhere:

In IgG4-related ophthalmic disease (IgG4-ROD), various nerves in the orbit can be involved. The infraorbital nerve is frequently affected, leading to its enlargement.[19] Other nerves that may be affected include the trigeminal nerve,[20] and optic nerve.[21] The involvement of these nerves can result in symptoms such as blurred vision, vision loss, and facial numbness. In Literature, a patient presented with bony involvement. The nature of the lesion was described as osteo-destructive.[22]

This study presents several limitations, given its retrospective nature. Firstly, the predominant involvement of the lacrimal gland, orbital soft tissue, and extraocular muscles in our study population limits the generalizability of our findings, leaving gaps in understanding rarer manifestations in the orbital bones, nasolacrimal duct, and eyelid.

Secondly, with only a small number of patients with disease confined solely to the ocular region, our study may need more comprehensive insights into the significance of serum IgG4 levels, especially compared to those with extraocular involvement.

Thirdly, the retrospective nature of our study raises uncertainties about the necessity of screening patients diagnosed with IgG4-RD for ocular involvement during the initial stages, introducing complexity in interpreting results due to potential undiagnosed ocular disease lacking symptoms or specific imaging findings.

Fourthly, the varied follow-up durations among patients present challenges in assessing the natural progression

of IgG4-Related Ophthalmic Disease, as diverse follow-up times hinder our ability to draw comprehensive conclusions about disease evolution over time.

5. Conclusion

Ophthalmic involvement is a feature of IgG4-RD and has significant implications regarding diagnosis, prognosis, and treatment. Given the complexities in clinical presentation and similarities with other disorders, accurate diagnosis through biopsy is vital in managing this condition effectively. Our study highlights the need for further research to improve diagnosis and treatment protocols for IgG4-ROD.

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