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OCULOPLASTICS AND ORBIT

Clinicopathologic features of orbital immunoglobulin G4-related disease (IgG4-RD): a case series and literature review

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Abstract
Background Involvement of orbital structures by immunoglobulin G4-related disease (IgG4-RD) is not uncommon. We conducted this study to evaluate the clinicopathologic features of orbital IgG4-RD.
Material/Methods This was a retrospective, clinicopathologic study. Clinical records, light microscopic features, results of immunostaining with IgG & IgG4 and laboratory findings were reviewed in 16 patients diagnosed with orbital IgG4-RD.
Results Eleven patients had a bilateral disease, and the lacrimal gland was involved in 14. Dense sclerosis, plasma cell aggregates and dense lymphoplasmacytic infiltrate were seen in all patients. Serum IgG4 titre was elevated in 12 patients. Nine patients responded completely to glucocorticoid treatment. Five patients had a relapse on discontinuation of treatment.
Conclusion Orbital IgG4-RD is a distinct clinicopathologic entity requiring increased awareness and needs to be differentiated from other orbital lymphoproliferative lesions.

Keywords Orbit · Lacrimal gland · Immunoglobulin · IgG4 · Inflammation · Myositis

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently described entity characterised by a diffuse or mass forming inflammatory reaction with tissue infiltration by IgG4+ plasma cells. Several synonyms have been previously used for this disease, such as IgG4-related autoimmune disease, IgG4-associated multifocal systemic fibrosis, IgG4-related disease, IgG4-related multiorgan lymphoproliferative syndrome, and IgG4-related sclerosing disease [1–5]. Debate still exists which of these terminologies should be used. However, the term "IgG4-related disease" is agreed upon at the moment [6]. Autoimmune pancreatitis, which is considered to be the prototype of this disease, was associated with elevated serum titres of IgG4 at the beginning of this century [7]. Since then, several organs have been reported to be affected by IgG4-RD. Some of these are lymph nodes, hepatobiliary tract, salivary gland, lung, skin, pituitary, urinary tract, thyroid, etc. [8–13]. Orbital involvement is not uncommon. In the orbit, IgG4-RD involves not only the lacrimal gland, but also other tissues such as the lacrimal sac, extraocular muscles (EOM), orbital adipose tissue, periorbital membrane, and the eyelids [14–17]. Although IgG4-RD is a distinct group of diseases, questions regarding its pathogenesis, diagnostic criteria, and the role of IgG4 still need to be elucidated. Because of its distinct pattern of tissue involvement and prognosis, it is important to identify

and differentiate this entity from its mimics. The present study was aimed at documenting the clinicopathologic and laboratory features of orbital IgG4-RD which would help differentiating this disease from its mimics.

Material and methods

This retrospective clinicopathologic study included patients diagnosed with orbital IgG4-related disease at the Centre For Sight Super specialty Eye Hospital, Hyderabad and L.V.Prasad Eye Institute, Hyderabad between February 2012 and July 2013. The study was approved by the Institutional Review Board and was performed in accordance with the tenets of the Declaration of Helsinki. Sixteen cases were retrieved from the archives of the National Reporting Centre for Ophthalmic Pathology (Centre For Sight) and Ocular Pathology Service (L.V.Prasad Eye Institute).

Clinical evaluation

Medical records of all patients were reviewed for age, gender, location, duration of symptoms, treatment, and clinical outcomes. All patients were evaluated for systemic involvement and associated systemic autoimmune diseases.

Microscopic examination

Hematoxylin and eosin stained sections of the tissues were reviewed for presence of sclerosis, lymphoplasmacytic infiltrate, type of lymphoid follicles, plasma cell aggregates, obliterative & non-obliterative phlebitis, eosinophils, and multinucleate giant cells.

Immunohistochemical staining

Immunohistochemical staining with IgG4 (MRQ-44, Cell Marque, Rocklin, CA, USA), IgG (269A-17, Cell Marque), CD3 (MRQ-39, Cell Marque), CD20 (SP32, Cell Marque), Kappa light chains (L1C1, Cell Marque) and lambda light chains (Lamb14, Cell Marque) was performed. The number of IgG4+ plasma cells per high power field (HPF) and the IgG4+ to IgG+ plasma cell ratio was determined using a 40× objective (Nikon eclipse Ci microscope, Tokyo, Japan). Five HPF with maximum density of IgG4+ plasma cells were used for this purpose. For determining the T- to B-cell ratio, lymphocytes were counted in ten successive HPFs.

Laboratory investigations

Serum IgG4 titre was evaluated in all patients using peripheral blood before initiation of treatment.

Diagnostic criteria

The study included cases classified as IgG4-RD using the criteria proposed by Umehara et al. [18] as below:

1. Clinical examination showing characteristic diffuse/localised swelling or masses in single or multiple organs.
2. Haematological examination shows elevated serum IgG4 concentration (≥135 mg/dl).
3. Histopathological examination shows:
   A. Marked lymphocyte and plasma cell infiltration and fibrosis
   B. Infiltration of IgG4+ plasma cells: ratio of IgG4+ to IgG+ cells >40 % and >10 IgG4+ plasma cells/high power field (HPF)

$$\text{Definite}: (1)+(2)+(3);\ \text{probable}: (1)+(3);\ \text{possible}: (1)+(2)$$

Results

As seen from Tables 1 and 2, 12 cases were ‘definite’ IgG4-RD and four were ‘probable’ IgG4-RD.

Clinical features

Clinical profiles and outcomes are shown in Table 1. All patients presented with a painless and gradually developing proptosis of the affected eye (Fig. 1a, c, and e). In 13 patients, this was accompanied by swelling of the eyelid and by chemosis of the conjunctiva in three patients. Eleven patients had a bilateral disease. The lacrimal gland was the most frequently involved orbital structure (n=14/16). Case 13 and case 16 had a lacrimal gland-sparing IgG4-RD which involved the orbital soft tissue and EOM. The mass appeared homogenous and diffuse on computed tomography (Fig. 1b, d, and f). Although EOM involvement was present in six patients (Fig. 1f), none of them had an isolated muscle disease. Restriction of ocular movements was less frequent in patients with an isolated lacrimal gland disease (one of five) as compared to those with additional or only soft tissue and/or EOM involvement (11 of 11). Systemic involvement was seen in four patients; bilateral parotid gland enlargement in two, cervical lymphadenopathy in one and Hashimoto’s thyroiditis in one. Whilst parotid

Table 1 Clinical features and outcomes in patients with orbital IgG4-related disease

Case no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Age (years)	51	46	39	54	47	7	45	62	51	72	50	64	58	58	35	64
Gender	F	M	M	M	F	M	F	F	F	F	F	F	M	M	F	M
Laterality	B	B	B	U	B	B	B	B	U	U	U	B	B	B	B	U
Presenting symptoms																
- Painless proptosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
- Eyelid swelling	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+
- Conjunctival chemosis	−	−	−	−	−	+	−	+	−	+	−	−	−	−	−	−
Duration of symptoms (months)	3	7	10	4	21	9	7	8	13	6	10	6	12	7	6	9
Structures involved																
- Lacrimal gland	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−
- Extra-ocular muscles	−	−	−	+	−	+	−	−	+	−	−	+	+	−	−	+
- Soft tissue	+	−	+	+	−	+	−	+	+	−	−	+	+	+	+	+
Systemic involvement	+	−	+	−	−	−	−	−	−	−	−	+	+	−	−	−
Associated diseases																
- Asthma	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
- Atopic dermatitis	−	−	−	−	+	−	−	−	−	−	−	+	−	−	−	−
- Diabetes mellitus	−	−	−	−	+	−	−	+	−	−	−	−	−	−	−	−
- Hypertension	−	−	−	−	−	−	−	+	−	+	−	−	−	−	−	−
Response to prednisolone (complete, partial, refractory)	C	P	C	P	C	C	R	P	C	R	C	C	C	P	C	P
Relapse on discontinuation of treatment	+	−	−	+	−	+	−	+	−	−	−	−	−	−	−	+

M Male, *F* Female, *B* Bilateral, *U* Unilateral, *C* Complete, *P* Partial, *R* Refractory

involvement was seen in both patients concurrent to the orbital disease, cervical lymphadenopathy and Hashimoto's thyroiditis occurred subsequent to the orbital disease. Other associated systemic manifestations included asthma ($n=1$) and atopic dermatitis ($n=2$).

Histopathologic & laboratory features

The average number of IgG4+ plasma cells per HPF varied from 13 to 58 (mean 27.3) and the IgG4+ to IgG+ plasma cell ratio varied from 42 to 75 % (mean 55.8 %) (Fig. 2f).

Table 2 Pathologic & laboratory features in patients of orbital IgG4-related disease

Case no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Dense fibrosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Storiform fibrosis	−	−	−	−	+	−	−	+	−	−	−	−	−	−	−	+
Dense lympho–plasmacytic infiltrate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Obliterative phlebitis	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Non–obliterative phlebitis	−	−	−	+	−	−	−	−	−	+	−	−	−	−	−	−
Primary lymphoid follicles	+	−	+	+	+	+	−	+	−	+	−	−	+	+	+	−
Secondary lymphoid follicles	+	−	−	+	−	+	−	+	−	−	−	−	−	−	−	−
Eosinophils	+	−	+	−	+	+	+	−	+	−	−	+	+	−	+	−
Multinucleate giant cells	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−
Plasma cell aggregates	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
IgG4-positive plasma cells per HPF	21	13	36	19	31	25	26	37	18	22	27	32	15	42	58	14
IgG4/IgG-positive plasma cells (%)	51	42	64	52	58	59	62	73	46	49	56	54	49	59	75	43
T-/B-cell ratio	19:1	23:1	15:1	21:1	31:1	18:1	30:1	22:1	21:1	15:1	23:1	25:1	28:1	13:1	16:1	12:1
Serum IgG4 (mg/dl)	655	120	436	332	260	1093	890	3216	510	105	112	560	96	3368	3739	190

HPF High power field, (+) present, (−) absent

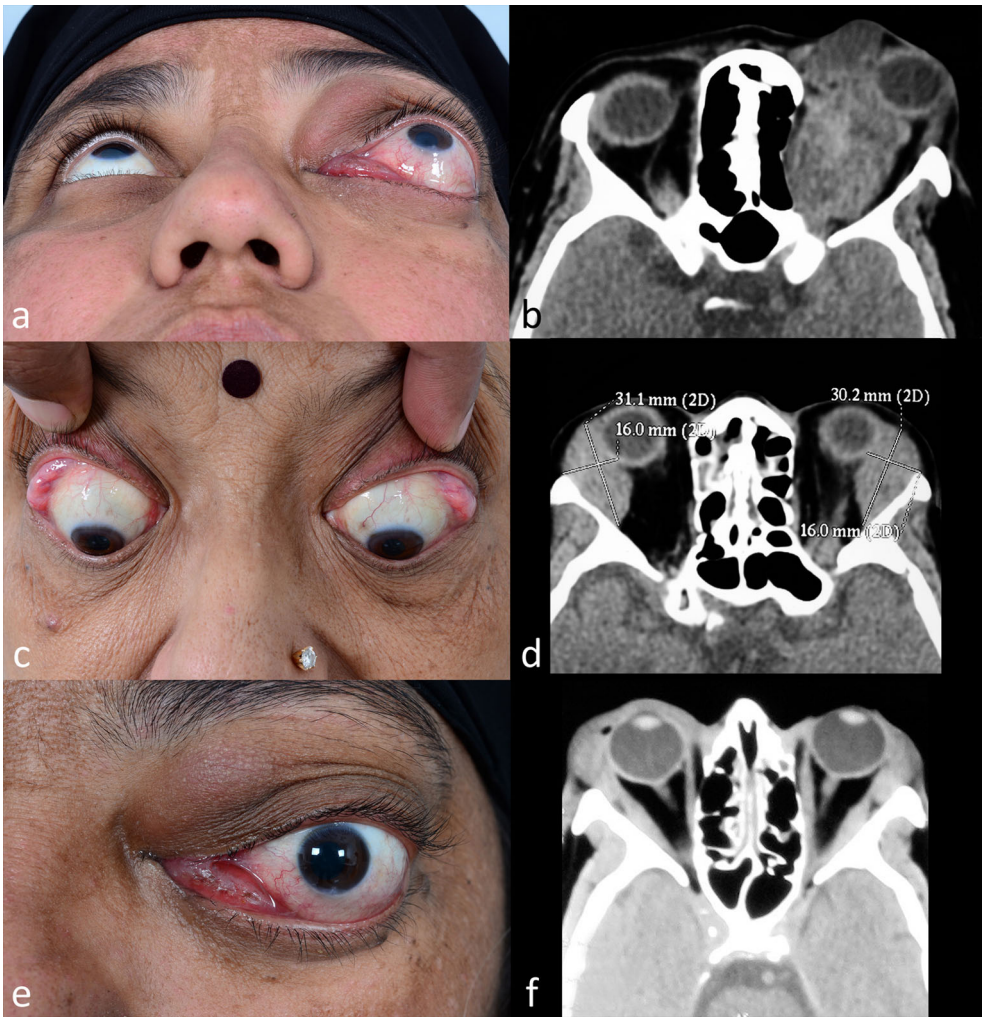

Fig. 1 Clinico-radiological features of orbital IgG4-related disease. **a** A 50-year-old female with chronic axial proptosis of the left eye. **b** Computed tomography (CT scan) of the same patient showing a diffuse & heterogenous mass in the left orbit with displacement of the globe. **c** A 62-year-old female with bilateral IgG4-related dacryoadenitis. **d** CT scan of the same patient showing a bilateral lacrimal gland enlargement. **e** A 50-year-old female with eyelid swelling. **f** CT scan showing a homogenous mass involving the lacrimal gland and adjacent orbital soft tissue bilaterally

Although dense sclerosis (Fig. 2c) was seen in all cases, a storiform pattern was present in only three (Fig. 2a). In all cases, the lymphoid infiltrate was predominantly of T-cell type with few interspersed B-lymphocytes. Immunostaining with kappa and lambda light chains did not reveal light chain restriction in any of the cases. Primary and secondary lymphoid follicles were seen in ten and four cases respectively (Fig. 2a and b). Plasma cell aggregates (cluster of ten or more plasma cells in at least two foci) were present in all and seen at the periphery of lymphoid follicles and in the fibrous stroma (Fig. 2d). The intermittent stroma showed lymphocytes and plasma cells in addition to eosinophils (n=9/16) and multinucleate cells (n=1/16). Touton giant cells were rare (n=1). Obliterative (n=1) and non-obliterative phlebitis (n=2) were seen. Neutrophils or granulomas were not seen in any case.

Treatment and follow-up

All patients were treated with intravenous (IV) methyl predinisolone (500 mg on 3 consecutive days as an initial dose, followed by 500 mg as IV bolus every 3 weeks for six courses). The dosage was tapered based on the patient's response. In patients who were refractory to treatment (n=2) or in those who responded only partially (n=5) to glucocorticoid therapy, immunosuppressants were administered (cyclophosphamide in two, azathioprine in four and methotrexate in one). These patients continue to be free of disease at the time of their last follow-up.

Discussion

Immunoglobulin G4-related disease (IgG4-RD) is a novel fibroinflammatory disease characterised by mass lesions in the affected organ, lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, storiform fibrosis, and often elevated serum IgG4 concentration [19]. The term 'IgG4-related disease' was agreed upon in 2011, and since been the preferred name for this condition [6]. The eye and periocular structures are commonly involved by IgG4-RD [20]. The preferred nomenclature for orbital involvement includes IgG4-related

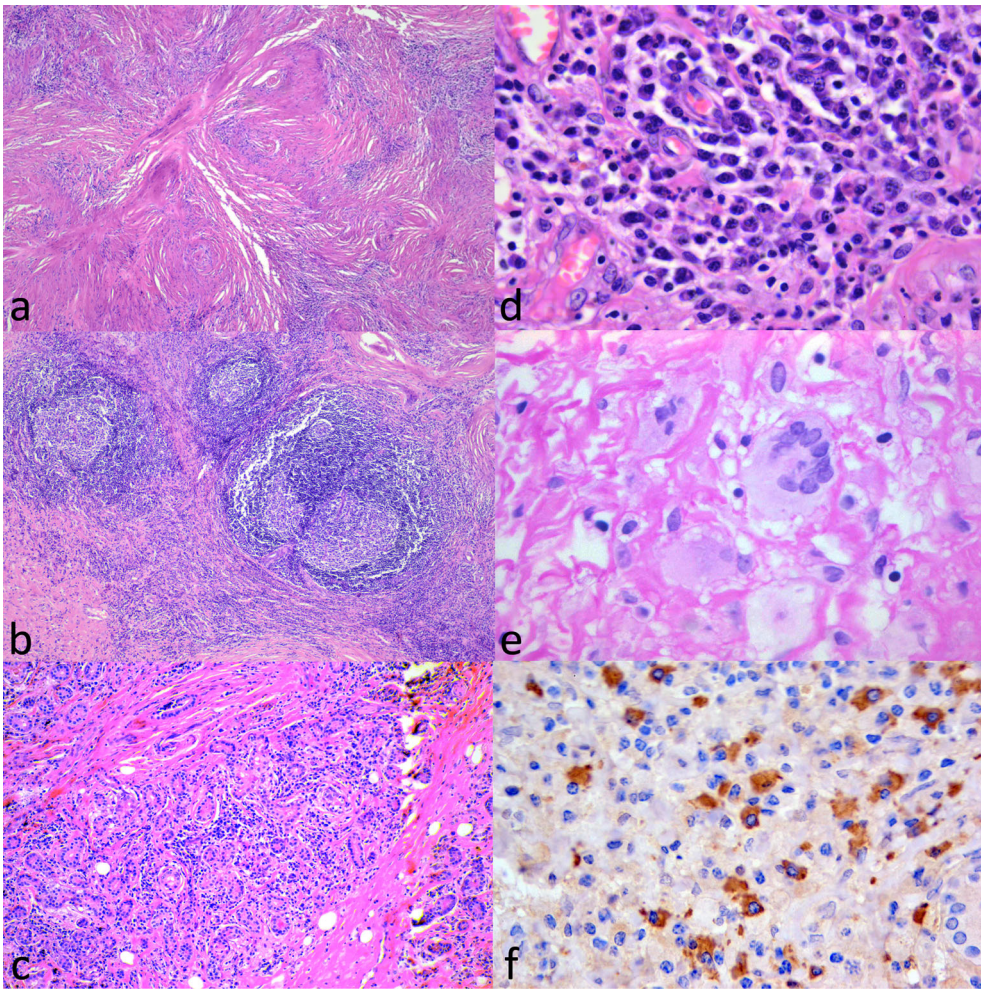

Fig. 2 Histopathological features of orbital IgG4-related disease. **a** Storiform fibrosis and lymphoplasmacytic infiltrate (H & E, ×40). **b** Secondary lymphoid follicles (H & E, ×40). **c** Lacrimal gland involvement by fibrosis and lymphoplasmacytic infiltrate (H & E, ×100). **d** Plasma cell aggregates (H & E, ×400). **e** Touton-like and multinucleate giant cells (H & E, ×400). **f** IgG4+ plasma cells (×400)

dacryoadenitis (lacrimal gland), IgG4-related orbital inflammation (orbital soft tissue), IgG4-related orbital myositis (extraocular muscles), and IgG4-related pan-orbital inflammation (orbit with involvement of multiple anatomical structures) [20]. Although orbital IgG4-RD is a disease predominantly affecting the adults (mean = 50 years), children in the paediatric age-group may also be affected [21, 22]. The present study included 15 adults and one child. No gender predominance has been documented in literature, as was observed in the present study (M:F+1:1.3) [22–24]. Similarly to Mikulicz's disease, a 1:3 bilaterality for lacrimal lesions has been reported in IgG4-RD [24, 25]. The results of the present study were in agreement with these reports. As observed by us and reported by a recent study, patients of orbital IgG4-RD usually present with a painless, progressive proptosis and/or swelling of the eyelids on the affected side [24]. Visual disturbances are not a feature of IgG4-RD unless it is complicated by neural involvement [26]. Although lacrimal glands are frequently involved (69 %), lacrimal gland-sparing IgG4-RD has been recently reported [24, 26]. Fourteen of 16 patients in the present study had lacrimal gland involvement. Orbital soft tissue (n=10) and extra-ocular muscles (n=5) were less frequently affected. Systemic involvement and associated allergic conditions such as atopic dermatitis or asthma have been reported in association with orbital IgG4-RD [24, 27, 28]. Four patients in the present study had systemic lesions. Atopic dermatitis was seen in two patients, while asthma was present in one.

Elevated serum IgG4 titres are suggestive of but not specific to or a pre-requisite for IgG4-RD [20]. In 20–40 % of patients, the serum IgG4 may be normal [29, 30]. On the other hand, serum IgG4 titres can be elevated in healthy individuals, and in conditions such as multicentric Castleman's disease and Wegener's granulomatosis [31, 32]. Four patients in the present study had normal serum IgG4 titre. In the remaining 12, serum IgG4 ranged from 260 to 3,739 mg/dl. Serum IgE titres can be low, normal, or elevated in patients with ocular IgG4-RD [24, 25, 27]. Serum IgE level was evaluated in one patient (case 6) of the present study and was found to be elevated (688 mg/dl, normal 0–248). Hypergammaglobulinemia and elevated serum interleukin 2 levels have also been described [24, 25, 27].

Characteristic histopathologic features and increased number of IgG4+ plasma cells are peculiar to IgG4-RD. According to the consensus diagnostic criteria laid down by Deshpande

et al., major histopathologic features associated with IgG4-RD include a dense lymphoplasmacytic infiltrate, fibrosis (usually storiform), and obliterative phlebitis, of which at least two are required for the diagnosis of IgG4-RD [33]. Exceptions to this rule include lymph nodes, lungs, lacrimal glands, and minor salivary glands where storiform fibrosis and obliterative phlebitis can be inconspicuous or absent [33]. Presence of eosinophils and phlebitis without obliteration are other associated features. Although all patients in the present study showed dense fibrosis, a storiform pattern was seen in only three. Obliterative phlebitis and non-obliterative phlebitis were seen in one and two patients respectively.

Treatment protocols for IgG4-RD are not established. Glucocorticoids are the first line of management in IgG4-RD. The suggested dosage of glucocorticoids is 0.6 mg/kg of body weight per day for 2 to 4 weeks, then tapered over a period of 3 to 6 months to 5 mg/day, and then continued at a dose of 2.5–5.0 mg/day for 3 years [31]. Glucocorticoids were the primary treatment of choice in all our patients. Complete and partial response was seen in nine and five patients respectively. Two patients were refractory to glucocorticoid therapy. A recent study reported a higher relapse rate in patients of IgG4-RD who were rheumatoid factor (RF)-positive [34]. None of our patients were RF-positive. Prednisolone combined with an immunosuppressant such as azathioprine is a good treatment of choice in patients with steroid-dependant IgG4-RD [30]. Additional immunosuppressant therapy was beneficial in five patients of the present study who were initially partially responsive or refractory to glucocorticoids. Five patients in the present study had a relapse after discontinuation of treatment. These patients were administered a combined glucocorticoid and cyclophosphamide regimen, and are in complete remission at 12-month follow-up. Rituximab can be used in patients who are refractory to conventional immunosuppressive therapy [35]. However, recurrence has been reported in patients of orbital IgG4-RD after discontinuation of Rituximab [28]. Recent literature describes the beneficial role of mycophenolate in IgG4-RD [36].

IgG4-RD must be differentiated from non-specific orbital inflammatory disease (NSOID), reactive lymphoid hyperplasia without IgG4+ plasma cells, extranodal marginal zone lymphomas of B-cell type (EMZL), and idiopathic myositis. Unlike IgG4-RD, idiopathic myositis and NSOID present with sudden onset of inflammation, pain, redness of eyelids, and ocular motility restrictions, in addition to proptosis, lid swelling, or ptosis [37]. EMZL may show reactive follicles in 64 % of cases, sclerosis in 20 % of cases and plasma cells in 35 % of cases [38]. Elevated serum IgG4 tires and infiltration by IgG4+ plasma cells have also been reported in 9 % of patients with EMZL [39, 40]. The majority of ocular adnexal lymphomas are of B-cell type. As observed in the present study, in all cases, the T-lymphocytes greatly outnumber the B-lymphocytes in IgG4-RD, and the lymphoid infiltrate was polyclonal in nature. This observation, along with demonstration of light-chain restriction and immunoglobulin gene (IGH) rearrangement, would help differentiate the two entities because the majority of ocular adnexal lymphomas are of B-cell type, thus comprising of predominantly B-lymphocytes, show light-chain restriction and IGH gene rearrangement [41].

To conclude, IgG4-related disease is a novel, rapidly emerging, and distinct clinicopathologic entity which may involve the orbit either in isolation or as a part of a systemic process. It is quintessential that IgG4-related disease be included in the differential diagnosis of orbital lesions, and the diagnosis ascertained with a biopsy. Although corticosteroids are helpful in managing these patients, addition of immunosuppressants to the treatment regimen may be required. Finally, the diagnosis of IgG4-RD warrants a long-term follow-up, as these patients are at a risk of relapse or evolution into a lymphoma. Since all cases included in the present study were from centres catering to an Indian population, and as the geographic and racial variations in IgG4-RD have not been thoroughly investigated in literature to date, the characteristics of orbital IgG4-RD described in the present study may not be the same in patient populations elsewhere. A multi-centre study involving patients from different geographic locations would help analyze this aspect of the disease.

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Conflict of interest All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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