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IgG4-related disease presenting with profound bilateral orbital and adnexal inflammation

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ABSTRACT

Purpose: IgG4-related disease is an immune-mediated fibroinflammatory condition that can affect almost every major organ system. Orbital and adnexal involvement in IgG4-related disease though not uncommon can be varied depending on the site of the lymphoplasmacytic infiltration. This case of profound bilateral orbital inflammation is presented to demonstrate the significant clinical manifestations of IgG4-related ophthalmic disease.

Observations: A 52-year-old man with a remote and seemingly unrelated history of lymphadenopathy presented to the Oculoplastics clinic with massive bilateral upper and lower lid swelling and induration. Hematologic testing demonstrated an elevation in serum IgG4 - a non-specific finding seen in various infectious, inflammatory, and malignant processes. Imaging demonstrated diffuse enlargement of orbital structures, including the lacrimal glands and extraocular muscles, as well as inflammatory changes of the adnexal and retrobulbar soft tissue. Orbital biopsy was required to confirm the diagnosis of IgG4-related ophthalmic disease.

Conclusions and Importance: IgG4-related ophthalmic disease presents with various non-specific clinical signs and symptoms. The most common presentations include dacryoadenitis, enlarged orbital nerves, and orbital fat involvement; however, the extent of involvement both locally and systemically varies greatly. Clinical findings and imaging are helpful in narrowing the differential diagnosis; however, biopsy for histopathologic examination is essential to confirm IgG4-related disease. Physicians must maintain a high level of suspicion for the disease for proper management.

1. Introduction

IgG4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition that can affect one or more organ systems. It is characterized by sclerotic, tumefactive lesions with marked lymphoplasmacytic infiltration rich in IgG4-positive plasma cells. First recognized as a distinct disease in 2003 among patients with autoimmune pancreatitis,[1] the characteristic lesions of this systemic disease have been described in almost every major organ system of the body. Orbital and adnexal involvement in IgG4-related disease is common; more specifically, it is referred to as IgG4-related ophthalmic disease (IgG4-ROD). IgG4-ROD manifests with varying clinical presentations, symptoms and disease severity. The lacrimal gland is the most frequently involved ocular structure in IgG4-ROD, though lymphoplasmacytic infiltration can occur in almost any tissue of the orbit and adnexa including the trigeminal nerve, extraocular muscles, orbital fat, eyelid, and, less frequently, the nasolacrimal duct.[2,3] Diagnosis of the disease requires correlation between the clinical features, imaging studies, and histopathology results. Given the relatively recent recognition of IgG4-related disease as its own clinical entity, the scientific community's awareness of the condition, understanding of the pathophysiology, diagnostic criteria, and management options for IgG4-related disease continues to evolve. This case of profound bilateral orbital inflammation is presented to further demonstrate the many clinical manifestations of IgG4-ROD and to maintain a heightened awareness of the disease among providers.

2. Case report

A 52-year-old man presented in the Oculoplastics clinic in May 2022 with a chief complaint of "bulging eyes." He reported significant swelling of both eyelids over the past year, which had progressively

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worsened despite several courses of oral steroids. Past medical history was significant for type II diabetes mellitus, and a recent hemoglobin A1C of 5.9. He endorsed chronic rhinosinusitis, as well as a history of enlarged lymph nodes. In 2014, the patient underwent fine needle aspiration of an enlarged left submandibular gland; the findings were most consistent with a reactive lymph node without cytological evidence for lymphoma or malignancy. The patient reported good health without other known medical conditions.

Initial clinical exam was notable for proptosis and 4+ bilateral upper and lower lid swelling and induration. Focal masses of the left eyelids were notably larger compared to the right eyelids. The extensive lid fullness resulted in mechanical ptosis, with an MRD1 of 0 in each eye (Fig. 1). The patient demonstrated a nontender, enlarged left submandibular lymph node. His pupillary response and extraocular movements were unremarkable.

Laboratory evaluation was notable for elevation in serum immunoglobulin G (2149; reference range 603–1613 mg/dL) as well as total immunoglobulin E (1026; reference range 6–495). Further evaluation of IgG subclasses revealed significantly elevated serum IgG4 (621; reference range 2–96 mg/dL). Of note, results were not consistent with thyroid disease, ANCA-vasculitides, sarcoidosis, necrotizing myopathy, nor infection. The patient's complete blood count and complement factors were within normal limits.

MRI brain/orbits with contrast was obtained. Imaging demonstrated severe proptosis of the bilateral globes with associated straightening of the optic nerves. There was diffuse enlargement of the lacrimal glands as well as the extraocular muscles bilaterally. Inflammatory changes were seen in the eyelid and retrobulbar fat bilaterally, with associated stranding within the bilateral orbital fat and crowding of the orbital apex. Additionally, imaging showed diffuse sinus inflammatory disease, most severe within the bilateral ethmoid air cells and sphenoid sinuses

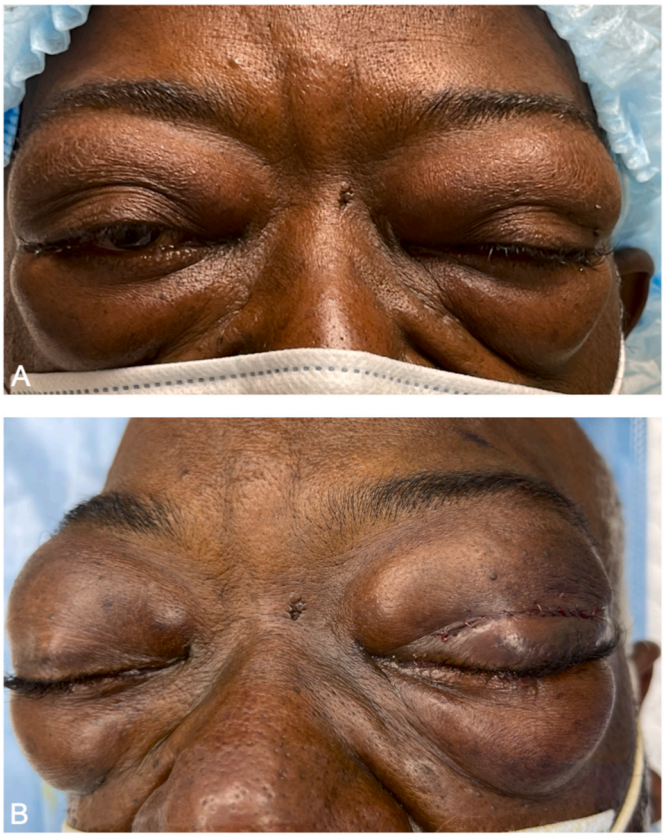

Fig. 1. Peri-operative external photographs. **A)** Pre-operative diffuse bilateral periorbital swelling with mechanical ptosis. **B)** Bilateral lid fullness and proptosis following diagnostic left orbital biopsy.

(Fig. 2).

The patient underwent a diagnostic left anterior orbitotomy with biopsy of the left orbital fat and left orbital lobe of the lacrimal gland for histopathologic assessment (Fig. 3).

Flow cytometry of the specimens did not demonstrate a monoclonal B-cell population or immunophenotypically abnormal T-cell population. Histopathology of the orbital fat and lacrimal gland biopsies did demonstrate a prominent lymphoplasmacytic infiltrate, including follicle formation, in the background of fibrosis. Immunohistochemical stains for IgG4 highlighted a significant subset of plasma cells, >400 cells per single high-power field on both samples. IgG4: IgG ratio estimated 50–60% on both. No well-formed granulomas were identified. Neither specimen demonstrated obliterative thrombophlebitis. Overall, the pathology revealed a pattern of chronic inflammation and fibrosis histologically highly suggestive of IgG4-related disease using consensus criteria[4] and were consistent with definite IgG4-related disease using comprehensive and organ specific criteria[5] (Fig. 4).

Re-examination of the fine needle aspiration of the left submandibular node biopsy from 2014 was inconclusive. This may be related to extent of disease at the time, or insufficient tissue to draw a conclusion.

Together, the clinical findings, imaging, and histopathology were compatible with IgG4-ROD. The patient was referred to a rheumatologist for further work-up and assistance with systemic management. Initiation of oral corticosteroid induction therapy resulted in a dramatic improvement in his clinical appearance (Fig. 5).

3. Discussion

IgG-RD is now recognized as a distinct entity with a multitude of clinical manifestations depending on the organ system or systems affected. The orbit is a frequent site of involvement; however, IgG-ROD alone can present in a variety of ways. Prior reports have recognized the following patterns as the most common manifestations of IgG-ROD.

- Sclerosing dacryoadenitis: the lacrimal gland is the most common site involved in IgG-ROD. This frequently presents as unilateral or bilateral eyelid swelling and may be associated with salivary gland swelling. This pattern, previously known as "Mikulicz's disease," was described in the literature long before the recognition of IgG-RD as a unique clinical entity. Patients may experience dry eye symptoms from lacrimal gland dysfunction.
- Enlargement of the trigeminal nerve: enlargement of multiple branches of the trigeminal nerve (particularly the infraorbital nerve) is frequently associated with enlargement of the lacrimal glands and extraocular muscles. Peripheral eosinophilia and paranasal sinusitis are often present as well.
- Orbital fat infiltration: Patients may present with proptosis in the setting of orbital fat enlargement. Orbital fat infiltration is usually associated with lacrimal gland enlargement and can be associated extraocular muscle changes resulting in motility issues.

Less commonly, IgG4-ROD may involve the lacrimal drainage system, sclera, and conjunctiva. In rare, severe cases, vision loss can occur due to optic nerve compression at the orbital apex.[3]

Given the diversity of disease manifestations and the clinically ambiguous signs and symptoms of IgG-ROD, providers must maintain a high level of suspicion of the disease and actively pursue targeted diagnostic measures to arrive at the accurate diagnosis. Diagnosis of IgG4-ROD requires integration of clinical signs, laboratory results, orbital imaging, and histopathologic findings. In order to make a definitive diagnosis, biopsy for histopathologic examination is essential. Compared to needle biopsy, surgical biopsy is superior in histologically identifying IgG4-RD.[4,5] This may have contributed to the inability to diagnose this patient from the submandibular node fine needle biopsy years earlier.

Multiple criteria for diagnosis of systemic IgG4-RD have been

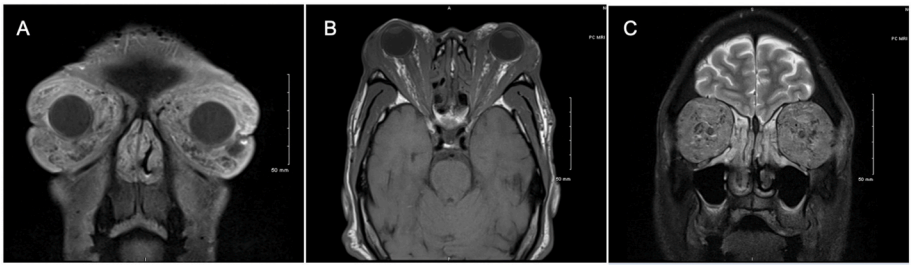

Fig. 2. Contrast enhanced magnetic resonance imaging of the brain and orbits. **A)** T1-weighted coronal scan demonstrates inflammatory changes and expansion of the adnexal fat bilaterally. **B)** T1-weighted axial scan shows enlargement of the bilateral lacrimal glands and extraocular muscles as well severe proptosis of bilateral globes with associated straightening of the optic nerves. **C)** T2-weighted coronal scan through the mid orbits displays inflammatory changes of the retrobulbar fat.

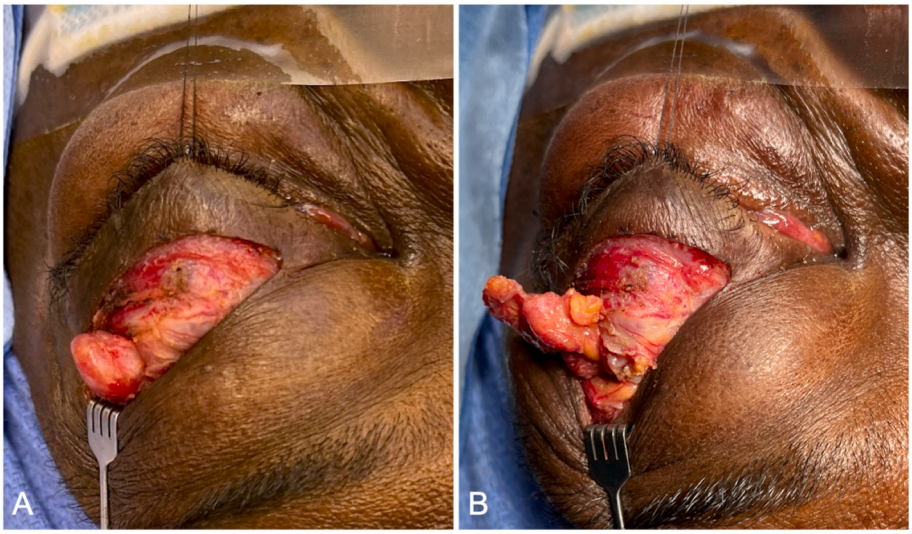

Fig. 3. Intra-operative photographs. **A)** Enlargement of the orbital lobe of the left lacrimal gland before biopsy. **B)** Fibrotic changes and abnormal appearance of the left orbital fat.

proposed.[4,6,7,] Of these, the most recent IgG4-RD classification criteria, proposed and validated in 2019, incorporates a series of both exclusion and weighted inclusion criteria to identify IgG4-RD with excellent sensitivity and specificity.[7] Organ specific criteria have additionally been published. For orbital disease specifically, Goto et al. developed the following diagnostic criteria for IgG4-ROD in 2015.

1. Imaging studies show enlargement of the lacrimal gland, trigeminal nerve, or extraocular muscle as well as masses, enlargement, or hypertrophic lesions in various ophthalmic tissues.
2. Histopathologic examination shows marked lymphocyte and plasmacyte infiltration, and sometimes fibrosis. A germinal center is frequently observed. IgG4+ plasmacytes are found and satisfy the following criteria: Ratio of IgG4+ cells to IgG + cells of >40%, *or* >50 IgG4+ cells per high-power field (x400).
3. Blood test shows elevated serum IgG4 (>135 mg/dl)

Diagnosis is classified as "definitive" when (1), (2), and (3) are satisfied; "probable" when (1) and (2) are satisfied; and "possible" when (1) and (3) are satisfied.[8]

In order to diagnose IgG4-ROD, alternative diagnoses must be ruled out. The differential diagnosis of IgG4-ROD includes: Sjögren syndrome, lymphoma, sarcoidosis, ANCA-associated vasculitides, thyroid-related orbitopathy, infection, and idiopathic orbital inflammation. In multiple studies, retrospective review of histopathology slides showed that a significant portion of cases initially diagnosed as idiopathic orbital inflammation or reactive lymphoid hyperplasia were in fact IgG4-ROD.[9,10] Many alternative diseases also contain a high number of IgG4+ cells; therefore, the ratio of IgG4 to IgG may be of greater importance. Of note, mucosa-associated lymphoid tissue (MALT) lymphoma can also contain IgG4+ cells. Differentiating between these two prevalent lymphoproliferative diseases of the orbit is critical.[8]

Despite its inclusion in the majority of proposed diagnostic criteria of both IgG4-RD and IgG4-ROD, elevation of serum IgG4 is neither necessary nor specific to the disease. On average, patients with IgG4-RD have a significantly higher serum IgG4 level compared to those without the disease. However, the range in levels is broad, and research supports that patients with biopsy-proven IgG4-RD can have normal levels of serum IgG4.[11,12] Therefore, the diagnostic criteria proposed by Goto et al., which requires elevation in serum IgG4 levels to meet criteria for "definitive" IgG4-ROD, may be misleading at this time. When used in isolation, elevated serum IgG4 is of limited diagnostic utility; however, serum IgG4 levels may be helpful during disease work-up and while monitoring the response to treatment.[13] Similarly, serum IgE concentrations on average are elevated in patients diagnosed with IgG4-RD. The significance of this laboratory abnormality in the diagnosis and management of IgG4-RD remains an active area of research.[15–17] Among patients with IgG4-RD, elevation in serum IgE concentration at baseline is associated with increased risk of IgG4-RD relapse; therefore, IgE levels at the time of diagnosis can serve as a predictor for the disease trajectory.[15,17,18]

The majority of patients with IgG4-ROD will have systemic disease with additional organs affected by IgG4-RD.[3,19] Common organ systems involved in IgG4-RD include the pancreas/biliary tree, salivary glands, lymph nodes, retroperitoneum, aorta, kidney, and lungs.[14] Given the high probability of systemic disease, referral to a rheumatologist to

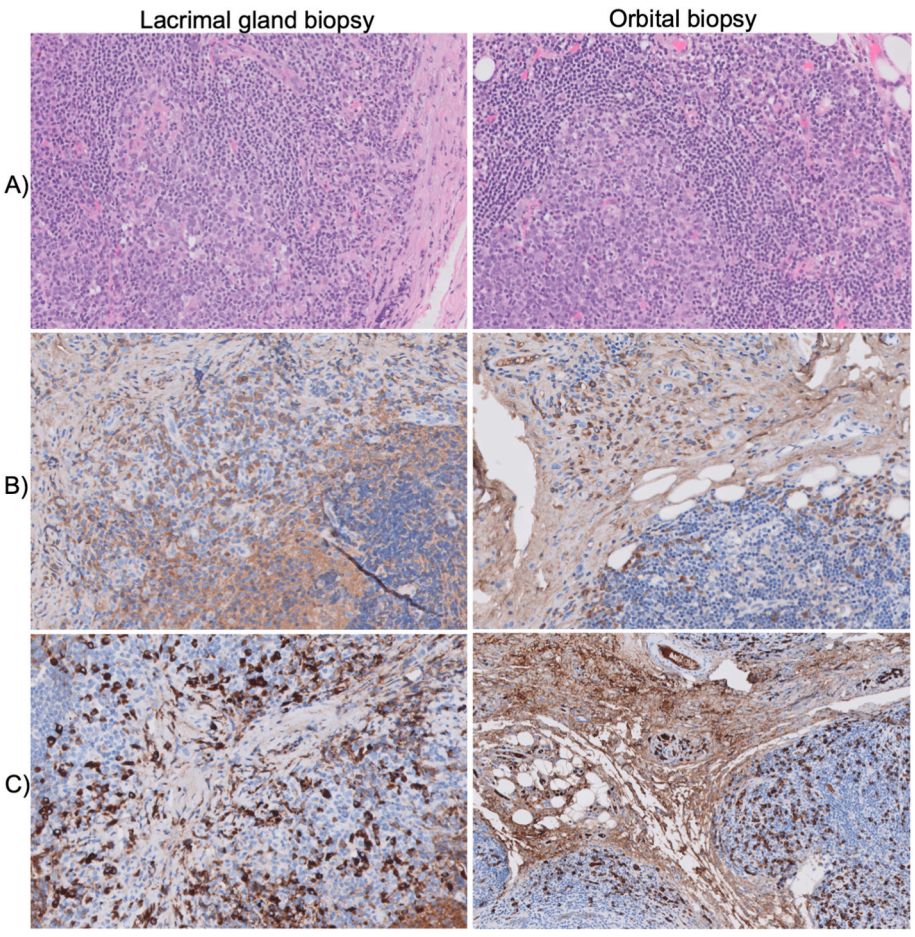

Fig. 4. Biopsies of the orbit and lacrimal gland showing chronic inflammation and fibrosis histologically suggestive of IgG4-related disease. **A)** Prominent lymphoplasmacytic infiltrate, including follicle formation, in the background of fibrosis (hematoxylin and eosin stain, original magnification ×20); **B)** Large subset of IgG-positive plasma cells (IgG immunohistochemical stain, magnification ×20); **C)** Significant subset of IgG4-positive plasma cells, >400 cells per high-power field, seen in each biopsy [IgG4 immunohistochemical stain, magnification ×20 (left) and magnification ×10 (right)].

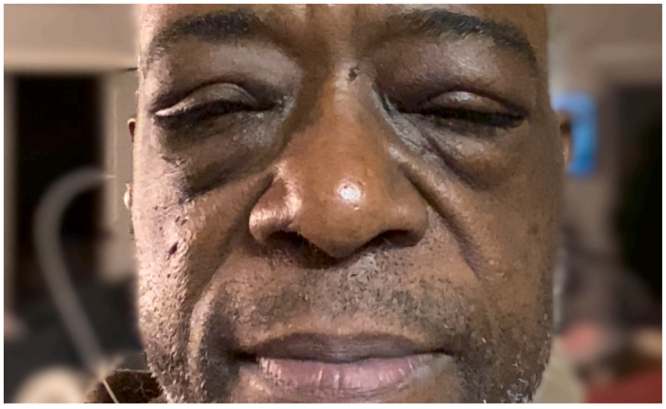

Fig. 5. Clinical photograph demonstrating significant improvement in periorbital edema following corticosteroid induction therapy.

further investigate involvement of other organs is essential. Oral corticosteroids remain the mainstay of initial treatment for active disease, with an induction course followed by a slow taper.[19] Patients may require maintenance dosing to prevent disease relapse. Consistent with prior reports, this case demonstrates that an excellent response to steroid induction therapy is possible even in long-standing disease.[20,21] However, while the majority of IgG4-ROD cases show a therapeutic response to induction therapy, relapse rates remain high and disease remission off medication is rare.[19,22] In cases of recalcitrant or recurrent disease, various steroid-sparing immunosuppressants have been utilized, of which Rituximab has shown the most promising therapeutic effects.[19] Rituximab, a chimeric monoclonal antibody that targets CD20, reduces the circulating IgG4-producing memory B cells and related CD20-positive precursors, thereby decreasing the level of plasmablasts and serum IgG4.[23] Rituximab maintenance therapy has also shown to reduce circulating biomarkers of fibrosis and tissue myofibroblast activation.[24]Other emerging biologics, such as FcRn inhibitors, additionally demonstrate promising therapeutic potential. The neonatal fragment crystallizable (Fc) receptor (FcRn) is involved in the recycling pathway of IgG, functioning to return intact IgG back into the circulation by preventing lysosomal degradation.[23] FcRn inhibition, therefore, selectively leads to increased catabolism of each IgG subclasses. While ongoing trials suggest promising potential, further studies are needed to better understand the role of biologics, both established and emerging, in the treatment paradigm for IgG4-ROD.[23,25]

4. Conclusions

IgG4-ROD is a fibroinflammatory condition that clinically presents in a myriad of ways. Elevated serum IgG4 is not a unique biomarker for the disease, and mimickers of IgG4-ROD must be ruled out. Ultimately, surgical biopsy for histopathology is crucial to establish the correct diagnosis. Needle biopsy can yield insufficient tissue to histologically recognize IgG4-RD, which may lead to a delay in diagnosis. Ophthalmologists must maintain a high level of suspicion for IgG4-ROD when a patient presents with an inflammatory orbital process of unclear etiology. IgG4-ROD may be one manifestation of a systemic condition. Timely diagnosis and prompt referral for thorough work-up and targeted management is a critical part of providing comprehensive care for the patient. Though corticosteroids are the current mainstay of treatment, biologics such as anti-CD20 monoclonal antibodies and FcRn inhibitors

may prove effective therapeutic alternatives.

Patient consent

The patient consented to publication of the case in writing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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