



Rituximab for relapsing IgG4-related ophthalmic disease resistant to corticosteroids: Literature review and a case report

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Keywords

Ophthalmic Disease; Orbital Pseudotumor; Rituximab; Corticosteroids

Abstract

Background: Immunoglobulin G4 (IgG4)-related ophthalmic disease (IgG4-ROD) is a newly recognized term for patients with IgG4-related disease (IgG4-RD) with ocular adnexal involvement. It primarily affects the orbit, lacrimal glands, extraocular muscles, and other periocular structures, leading to orbital masses, proptosis, and potential vision impairment. This study aims to present a case of bilateral IgG4-ROD to highlight its diagnostic approaches and therapeutic options.

Case Report: We report a case of 34-year-old woman presenting with bilateral proptosis. Imaging revealed involvement of lacrimal glands as well as a right retrobulbar mass encasing ocular muscles. Despite having a normal serum IgG4 level (28 mg/dl), the diagnosis of IgG4-ROD was made based on presence of ophthalmic tissue mass and IgG4-positive plasma cells in histopathology (> 40%). Recurrence of periorbital symptoms occurred five months after initial remission

while being on glucocorticoids (GCs) and azathioprine (AZA).

Conclusion: Symptoms improved after being switched to rituximab (RTX), and the patient remained symptom-free during a one-year follow-up. IgG4-ROD can manifest as a pseudotumor with involvement of adjacent tissues and should be considered in approaching ocular lesions. Appropriate workup to detect multi-organ involvement is essential.

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Refractory or recurrent IgG4-ROD is not unusual, and therefore maintenance or intensifying treatment can prevent irreversible organ damage. RTX is a promising treatment option for corticosteroid-resistant cases.

Introduction

Immunoglobulin G4 (IgG4)-related disease

(IgG4-RD) is a rare and relatively underrecognized disorder characterized by systemic immune-mediated inflammation and lymphoplasmacytic infiltrates with abundance of IgG4+ plasma cells and tumor-like lesions that can be found in virtually every organ.¹ Key pathologic landmarks of IgG4-RD are lymphoplasmacytic infiltration, obliterative phlebitis, and storiform fibrosis.² IgG4-related ophthalmic disease (IgG4-ROD) has now become a variant of IgG4-RD³ with the reported prevalence of between 17%-34%.^{4,6} Various ophthalmic structures may be involved in IgG4-ROD with the most common sites being the lacrimal gland, extraocular muscles, and orbital soft tissue.⁷ Other involvements such as eyelid, trigeminal nerve branch, optic nerve, and conjunctiva have also been reported.⁸⁻¹⁰ Treatment is indicated in symptomatic active disease with corticosteroids being the first-line agent of choice.¹¹ We report a case of IgG4-ROD who experienced relapse while on combined treatment with prednisolone (PDN) and

azathioprine (AZA) but was managed successfully with rituximab (RTX) and has remained disease-free during 1 year of follow-up. This case contributes to the current understanding of IgG4-RD by underscoring the limitations of serum IgG4 as a diagnostic marker and the importance of individualized treatment strategies. This research adhered to the tenets of the Declaration of Helsinki. Informed and written consent to publish the photographs was signed by the patient.

Case Report

Herein, we present the case of a 34-year-old woman who was admitted to emergency department (ED) of Imam-Khomeini Hospital, Tehran, Iran, in January 2023, with the aggravation of periorbital swelling (predominantly in right eye), proptosis, and redness since six months ago which has worsened in the past few days. Bilateral retrobulbar pain was also noted (Figure 1).

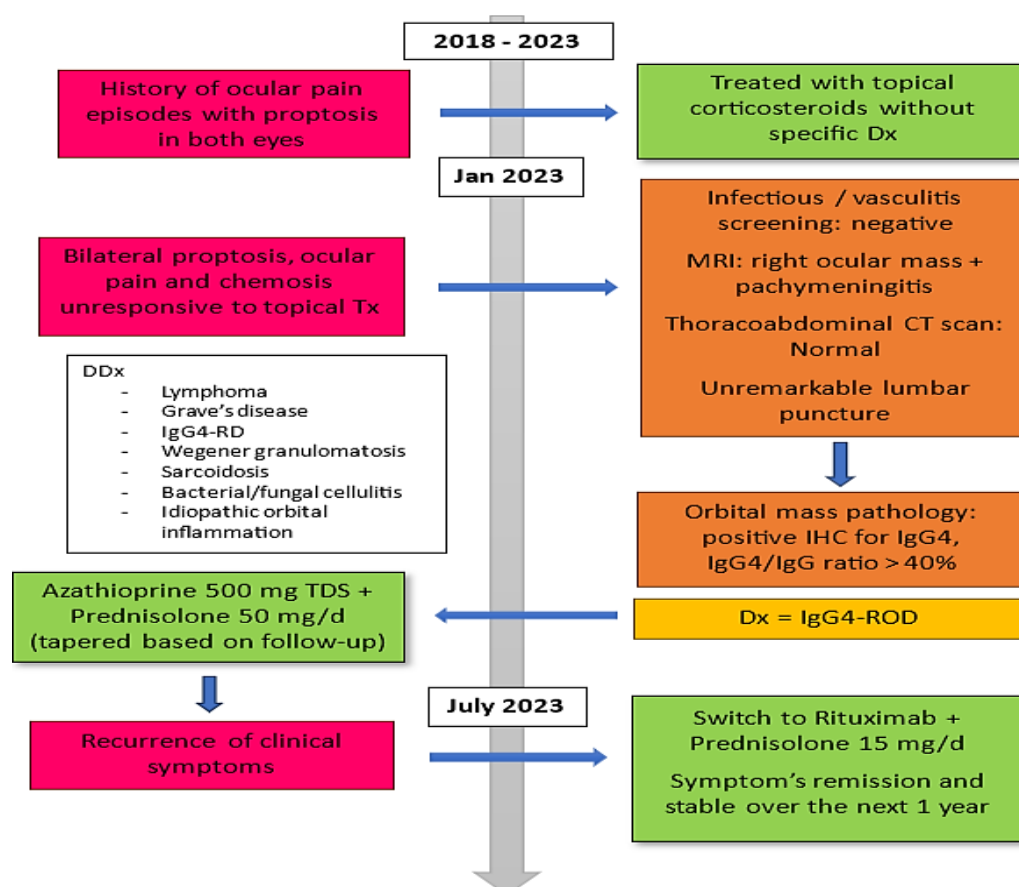


Figure 1. Case report timeline

No diplopia, visual deficit, ocular movement restriction, or headache was present at the time. She had a 5-year history of fluctuating bilateral

periorbital swelling. During past visits to different ophthalmologists, an inflammatory process was suspected; however, a comprehensive diagnostic

evaluation was not undertaken. Often, short-term corticosteroid drops were given which alleviated her swelling and symptoms.

She was a nulligravid woman with a past medical history significant for beta-thalassemia minor and Chiari-malformation type I (CM-1) for which she underwent two surgeries three years ago. She took baclofen and carbamazepine due to a right-sided neuralgic pain in the maxillomandibular region of her face which occurred occasionally in the past years. Other drugs included folic acid and atorvastatin. Family history was notable for type 2 diabetes in father and hypothyroidism plus hypertension (HTN) in her mother.

On arrival at the ED, bilateral proptosis and periorbital edema were noted, along with chemosis of the right eye (Figure 2). Visual acuity was 10/10 in both eyes and eye movements were not limited or associated with pain. Fundoscopy revealed temporal pallor of the right optic nerve head. No afferent pupillary defect was seen, and there were no other contributory neurologic findings at examination. Moreover, no signs or symptoms of hyperthyroidism or systemic illness were present.



Figure 2. Ocular findings of patient at presentation (upper panel) and 6 months after rituximab (RTX) induction treatment (lower panel). Marked proptosis and chemosis was present in the right eye at initial presentation. No clinical symptoms were present at follow-up.

Initial evaluations, including imaging and laboratory evaluations, were undertaken based on primary suspicion of the following differential diagnoses: malignancies (e.g., lymphoma), autoimmune conditions (e.g., granulomatosis with polyangiitis, sarcoidosis, IgG4-RD, thyroid eye

disease), idiopathic orbital inflammatory syndrome (IOI) (orbital pseudotumor), and infectious etiologies (e.g., tuberculosis, syphilis, brucellosis). Nasal endoscopy was done which ruled out mucosal damage typical of Wegener's granulomatosis. Laboratory results showed normal complete blood count (CBC) with the exception of microcytic anemia. Additional serum laboratory results are summarized in table 1.

Table 1. Relevant laboratory results on admission

Laboratory parameter	Result	Normal range
IgG4 (mg/dl)	28.0	11-150
IgG (g/l)	2.9	0.8-1.4
TSH (mIU/l)	4.2	0.3-5.0
ACE (U/l)	22.5	1-17
Wright	Negative	Negative
Coombs Wright	Negative	Negative
2ME Wright	Negative	Negative
RPR	Non-reactive	Non-reactive
CRP (mg/l)	24	< 6
ESR (mm/h)	20	< 20 (in women of 0-50 years)
CSF appearance	Colorless, clear	
CSF WBC (cells/ μ l)	0-1	0-5
CSF RBC (cells/ μ l)	20	0
CSF protein (mg/dl)	57	15-45
CSF glucose (mg/dl)	71	50-70
CSF LDH (mg/dl)	33	< 40
CSF ACE (U/l)	1.5	Less than 2.5

All measurements were done before corticosteroid administration except serum immunoglobulin G4 (IgG4) level which was done 10 days in to the treatment.

IgG4: Immunoglobulin G4; IgG: Immunoglobulin G; TSH: Thyroid-stimulating hormone; 2ME: 2-Mercaptoethanol; ACE: Angiotensin-converting enzyme; CRP: C-reactive protein; CSF: Cerebrospinal fluid; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; RPR: Rapid plasma reagin; WBC: White blood cell; RBC: Red blood cell

Looking for infectious or malignancy-related clues, lumbar puncture was also performed; however, the results were unremarkable (Table 1). Chest computed tomography (CT) scan revealed two nodules with the diameter of 3 and 4 mm in apicoposterior of left upper lobe and right medial lobe, respectively. Additionally, small ground glass patch was seen in right lower lobe. Abdominopelvic CT scan was normal. Orbital magnetic resonance imaging (MRI) showed a

bizarre-shaped hetero-enhancing right retroglobal mass about 32×20 mm with low signal intensity on T2 (Figure 3). The mass involved rectus muscle and lacrimal glands (Figure 4).

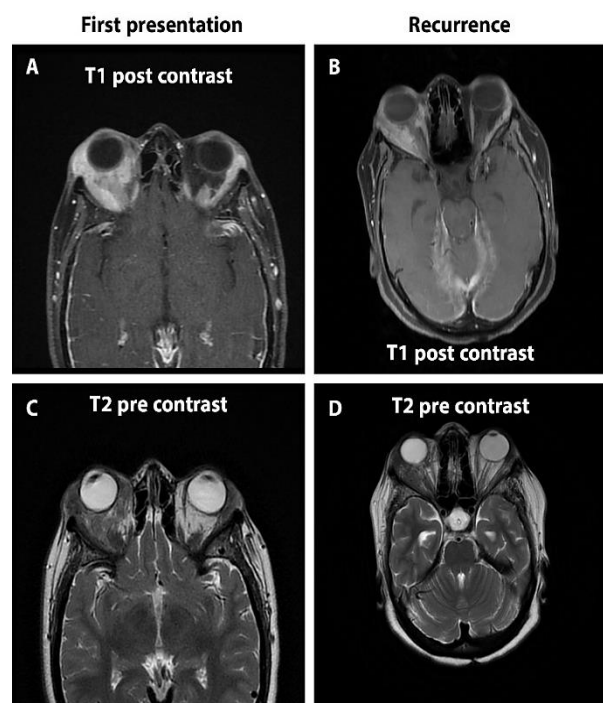


Figure 3. Axial magnetic resonance imaging (MRI) at first admission (A, C), revealing bilateral proptosis primarily in the right side with a retro-ocular soft tissue mass. During relapse (B, D) improved but partial proptosis is shown.

Based on the finding of retrobulbar mass and

possible diagnosis of lymphoproliferative diseases, orbital biopsy was planned. Pending the results of histopathology and owing to relative symptom control with corticosteroids in the past, oral PDN was initiated with the dose of 1 mg/kg pending the result of biopsy. A week later, immunohistochemistry (IHC) results revealed positive plasma cells with cluster of differentiation 138 (CD138) immunostaining and $> 40\%$ IgG4-positive plasma cells, and therefore the diagnosis of inflammatory pseudotumor related to IgG4-RD was confirmed (Figure 5). Accordingly, PDN 50 mg daily was maintained and AZA 50 mg three times a day (TDS) was warranted to be added to the treatment due to severe orbital involvement.¹²

Partial resolution of periorbital symptoms was observed in the next weeks, and she was discharged to be followed on an outpatient basis with PDN planned to being tapered over the course of months. Her symptoms steadily improved after discharge; however, she had recurrence of periorbital symptoms after 5 months while taking PDN (10 mg daily) plus AZA (50 mg TDS), and was admitted again. The retrobulbar mass was relatively shrunk in the MRI performed during the relapse compared to the initial presentation. However, the retro-global mass still remained enhanced, indicating relative disease activity. Consequently, based on IgG4-RD management algorithms, change of glucocorticoid (GC)-sparing agent was warranted, and therefore we switched to RTX treatment (two doses of 1000 mg – 2 weeks apart) and increased PDN to 15 mg daily. Her proptosis and swelling steadily decreased, and she has not had experienced any relapse during the one-year follow-up with 500 mg RTX being given every six months while tapering PDN back to 7.5 mg daily. During the follow-up period, she did not experience any adverse effects related to RTX.

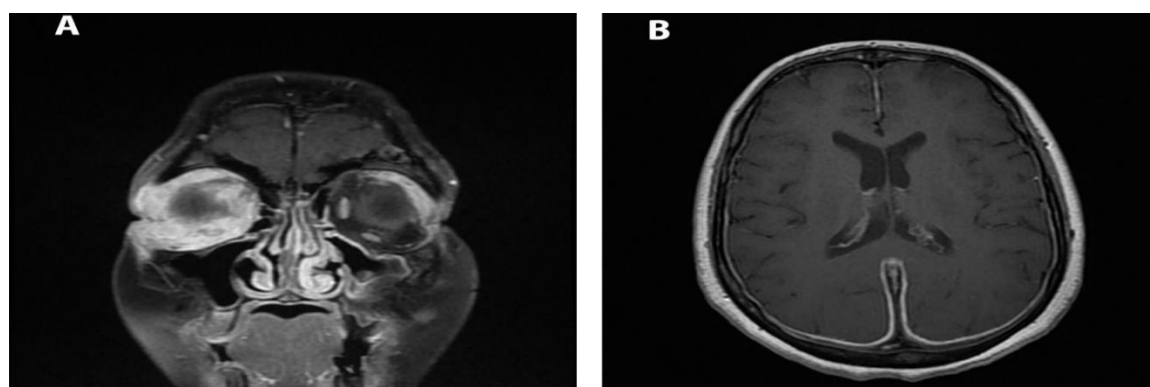


Figure 4. A) Bilateral lacrimal glands involvement at presentation; B) Persistent diffuse dural thickening and enhancement at follow-up

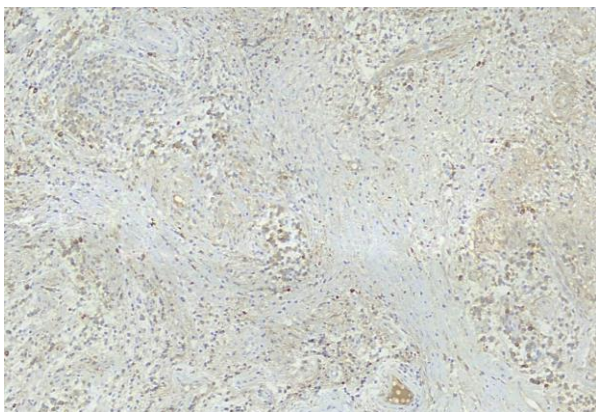


Figure 5. Immunohistochemical (IHC) staining for immunoglobulin G4 (IgG4) in an intraocular tissue sample. The section demonstrates IgG4-positive plasma cells in most plasma cells.

Discussion

IgG4-RD is a fibro-inflammatory disease which can present with tumefactive lesions. Mass lesions may involve a single organ but multi-organ involvement can be evident upon diagnosis or found during the course of the disease.¹³ Patients with IgG4-ROD typically present with painless periorbital swelling with or without proptosis, xerophthalmia, and diplopia.¹⁴ Other ocular manifestations such as ocular movement restriction, scleritis,⁵ and visual acuity impairment due to nerve compression¹⁵ are less common. Our patient reported intermittent neuralgic pain in right maxillary region of her face which could be due to trigeminal nerve branches being affected by the disease. Involvement of trigeminal nerve has been reported in up to 39% of IgG4-ROD cases in a Japanese cohort, two thirds of whom showing bilateral nerve enlargement.⁸

Diagnostic criteria and challenges

The diagnosis of IgG4-ROD is based on an appropriate clinical, histological, and serologic examination which was developed in 2014 and includes: 1) imaging studies showing 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 showing 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 immunoglobulin G (IgG)+ cells of 40% or above, or more than 50 IgG4+ cells/high power field (HPF) (x400)], and 3) blood test with elevated serum IgG4 (C135 mg/dl). If a patient

satisfies all three, diagnosis is classified as “definite”, whereas “probable” and “possible” cases are referred to patients when serologic or histopathologic criteria are not met, respectively. Our patient had elevated serum IgG level (2.9 g/l, normal range: 0.8-1.4 g/l), normal serum IgG4 level (28 mg/dl, normal range: 11-150 mg/dl), and IgG4/IgG ratio of 9%. Since the third criteria was not satisfied in our case, she would be classified as a probable IgG4-ROD case. One caveat is that serum IgG4 measurement was measured 10 days after PDN initiation which may have confounded the results.¹⁶ Although elevated serum IgG4 level ≥ 135 mg/dl has a sensitivity of 90% for the diagnosis of IgG4-RD,¹⁷ normal levels have been reported in 25%-48% of cases.^{18,19} Moreover, inflammatory conditions and malignancies especially low-grade B-cell lymphomas are also associated with elevated serum IgG4 level.²

Differential diagnosis of IgG4-ROD

It is necessary to keep in mind other inflammatory or non-inflammatory conditions associated with orbital structures involvement when evaluating a possible IgG4-ROD case. These include Graves' orbitopathy, Sjogren syndrome, granulomatosis with polyangiitis (formerly Wegener's granulomatosis), sarcoidosis, lymphoma, inflammatory myofibroblastic tumor, infection, orbital pseudotumor, and IOI.²⁰ Additional workup is, therefore, needed to rule out other possible causes and also to evaluate multi-organ involvement after the diagnosis of IgG4-RD has been made.

Involvement of organs in IgG4-RD

Single-organ involvement has been shown to be associated with lower risk of relapse rate.²¹ Multi-organ involvement is usual in patients with IgG4-ROD with salivary glands being the most common organ involved followed by lymph nodes and pancreas.²² It has also been suggested that bilateral ophthalmic involvement is associated with more likelihood of systemic IgG4-RD.²³ We also found diffuse dural thickening and enhancement which was persistent in both MRIs done at presentation and follow-up. Nevertheless, the patient had no signs of meningeal inflammation. Although rare, IgG4+ plasma cell infiltrates can also affect meninges that may lead to symptoms secondary to dural thickening, inflammation and fibrosis, or local compression.²⁴

Management and treatment response

With regard to management of IgG4-ROD, corticosteroids (0.5-0.6 mg/kg daily oral PDN for 4

weeks and tapered gradually), alone or in combination with other immunosuppressive drugs, represent the first-line of treatment.¹¹ Despite a high rate of response to GCs, relapses are not uncommon especially following tapering or withdrawal of drug.²¹ In the Chinese cohort of 132 patients with IgG-ROD with minimum follow-up of one year, 37% of patients experienced relapse. Factors associated with higher relapse rate were having multiple ocular lesions and not achieving complete response after 6 months of treatment. Moreover, combination therapy with GC and other immunosuppressive agents was associated with lower relapse rate compared to either one as monotherapy.²¹

RTX in refractory IgG4-ROD

Although the humoral immune response is not adequate to explain the pathophysiology of IgG4-RD alone, the abundance of B-cells in lymphoplasmacytic infiltrates and elevation of serum IgG4 propelled efforts to elucidate the immunologic mechanisms by which B-cells play a part in IgG4-RD pathophysiology.^{25,26} RTX is a monoclonal anti-CD20 which targets B-cells and leads to their depletion. The first experience of RTX utilization in the treatment of patients with IgG4-RD was in 2010 when four GC-resistant/dependent cases were successfully treated with RTX, and significant clinical improvements were seen.²⁷ An open-label clinical trial done in 2015 on 30 patients with active IgG4-RD showed 97% response rate with RTX treatment; 87 percent of whom did not require corticosteroid throughout the trial.²⁸

Our patient symptoms recurred despite adhering to the treatment regimen of GC plus AZA but responded well after switching to RTX. A systematic review on the efficacy of different therapeutic approaches in IgG4-ROD indicated a 90% response rate to induction treatment with

GCs, while 93% of patients responded well to RTX as a second- or third-line option, suggesting it as an efficient and favorable option in refractory cases.²² A network meta-analysis on the efficacy of different treatment approaches for IgG4-RD found that RTX maintenance therapy or combined GC + immunosuppressive [such as AZA or mycophenolate mofetil (MMF)] therapy was associated with more favorable relapse and remission rates when compared to GC or immunosuppressive monotherapy or RTX induction therapy.²⁹ RTX combined with GC has also been suggested for vision-threatening cases.²²

Conclusion

We presented a case of a 35-year-old woman with proptosis in whom diagnosis of IgG4-RD was established despite normal serum levels of IgG4. Failure of sustained remission with GC + AZA treatment imposed therapeutic challenge. However, after changing the therapeutic regimen to RTX + GC, remission was achieved, and she has stayed relapse-free for a year during follow-up. Given the possibility of normal serum IgG4 levels in a subset of patients, clinicians should not exclude IgG4-RD based solely on serologic findings. With a reasonable safety profile, RTX seems to be a valid option for IgG4-ROD cases, particularly in refractory or recurrent cases treated with conventional therapy.

Conflict of Interests

The authors declare no conflict of interest in this study.

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