Rituximab for corticosteroid-resistant relapsing IgG4-related ophthalmic disease*:* A case report and literature review

Authors

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Abstract

Background IgG4- related ophthalmic disease (IgG4-ROD) is a newly recognized term for IgG-related disease (IgG4-RD) patients with ocular adnexal involvement. This study aims to present a case of bilateral IgG4-ROD to highlight its diagnostic approaches and therapeutic options

Case presentation 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 histopathologic and radiologic findings. Remission was attained with rituximab (RTX) after a recurrence of symptoms while being on glucocorticoids (GC) and azathioprine (AZA).

Conclusions IgG4-ROD can manifest as a pseudotumor with involvement of adjacent tissues and should be considered in approaching ocular lesions. Appropriate work-up to detect multi-organ involvement is essential. Refractory or recurrent IgG4-ROD is not unusual and therefore maintenance or intensifying treatment can prevent irreversible organ damage.

Keywords: IgG4-related ophthalmic disease, orbital pseudotumor, Rituximab

Introduction

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-RD[3] 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 in who experienced relapse while on combined treatment with prednisolone and azathioprine but was managed successfully with rituximab and has remained disease-free during 6 months of follow-up. 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 presentation

Herein we present the case of 34-year-old woman with a 5-year history of fluctuating bilateral periorbital swelling. Suspecting an inflammatory process and without any diagnostic evaluations, she was given short-term corticosteroid drops by different ophthalmologists which alleviated her swelling. On January 2023, she was admitted to emergency department of Imam-Khomeini hospital, Tehran, Iran with the aggravation of periorbital swelling (predominantly in right eye), proptosis and redness from six months ago which has worsened in the past few days and was associated with retrobulbar pain. No diplopia, visual deficit, ocular movement restriction or headache were present.

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 in her mother.

On arrival at the ED, bilateral proptosis and periorbital edema were noted, along with chemosis of the right eye (Figure 1). 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 diseases were present.

Initial evaluations based on a primary suspicion on orbital tumor was conducted with imaging alongside the assessment of differential diagnoses such as Grave's orbitopathy and ANCA-associated vasculitis. Laboratory results showed normal complete blood count with the exception of microcytic anemia and ruled out infectious (namely brucellosis, syphilis, hepatitis B and C and HIV) and auto-immune causes, as well as hyperthyroidism as the possible explanation for her condition (Table 1). Orbital MRI showed a bizarre shaped hetero-enhancing right retroglobal mass about 32*20 mm with low signal intensity on T2 (Figure 2). The mass involved rectus muscle and lacrimal glands.

Based on the finding of retrobulbar mass and possible diagnosis of lymphoproliferative diseases, orbital biopsy was planned and owing to relative symptom control with corticosteroids in the past, oral prednisolone was initiated with the dose of 1mg/Kg pending the result of biopsy. A week later, immunohistochemistry (IHC) results revealed positive plasma cells with CD138 immunostaining and >40% IgG4 positive plasma cells and therefore the diagnosis of inflammatory pseudotumor related to IgG4-related disease was confirmed. Accordingly, prednisolone was maintained and azathioprine 50mg TDS was added to the treatment. Partial resolution of periorbital symptoms was observed in the next weeks and she was discharged to be followed on an outpatient basis with prednisolone being tapered over the course of months. Her symptoms steadily improved after discharge; However, she had recurrence of periorbital symptoms after 5 months despite taking PDN (10 mg daily) plus AZA (50 mg TDS) and was admitted again. The retrobulbar mass was relatively shrunk in the MRI done during the relapse compared to the one done at first presentation. Consequently, we switched to rituximab treatment (two doses of 1000mg – 2 weeks apart) and increased PDN to 15mg daily. Her proptosis and

swelling steadily decreased and she has not had experienced any relapse during the 6-months follow-up despite tapering PDN back to 7.5mg daily.

Table 1 *Table 1 Relevant laboratory results on admission*

Laboratory parameter	Result	Normal range
IgG4	28 mg/dL	11 - 150
IgG	2.9 g/L	0.8 - 1.4
ACE	22.5 U/L	1-17
Wright	Negative	Negative
Coombs wright	Negative	Negative
2ME Wright	Negative	Negative
RPR	Non-reactive	Non-reactive
CRP	24 mg/L	<6
ESR	20 mm/h	<20 (in females 0-50 yrs)

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

2ME, 2-Mercaptoethanol, ACE = angiotensin converting enzyme, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, RPR = rapid plasma reagin

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[12]. Patients with IgG4-ROD typically present with painless periorbital swelling with or without proptosis, xeropthalmia and diplopia[13]. Other ocular manifestations such as ocular movement restriction, scleritis[5] and visual acuity

impairment due to nerve compression[14] 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].

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 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 above, or more than 50 IgG4+ cells/HPF (x400), (3) Blood test shows elevated serum IgG4 (C135 mg/dl). If a patient satisfy 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%. One caveat is that serum IgG4 measurement was done about 10 days after prednisolone initiation which may have confounded the results[15]. Although elevated serum IgG4 level has a sensitivity of 90% for the diagnosis of IgG4-RD [16], normal levels have been reported in 25-48% of cases[17, 18]. Moreover, Inflammatory conditions and malignancies especially Low-grade B-cell lymphomas are also associated with elevated serum IgG4 level[2].

It's 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 idiopathic orbital inflammation (IOI)[19]. 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. In our patient, Nasal endoscopy was negative for any abnormality. Chest 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. Single organ involvement has been shown to be associated with lower risk of relapse rate[20]. Multi organ involvement is usual in IgG4-ROD patients with salivary glands being the most common organ involved followed by lymph nodes and pancreas[21]. It has also been suggested that bilateral ophthalmic involvement is associated with more likelihood of systemic IgG4-RD[22]. 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[23].

Corticosteroids (0.5-0.6 mg/Kg daily oral prednisolone 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 a response to glucocorticoids, relapses are not uncommon especially following tapering or withdrawal of drug[20]. In the Chinese cohort of 132 IgG-ROD patients 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[20].

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[24, 25]. Rituximab (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 IgG4-RD patients was in 2010 when 4 glucocorticoid resistant/dependent case were successfully treated with RTX and significant clinical improvements were seen[26]. 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 didn't require corticosteroid throughout the trial[27].

Our patient symptoms were refractory despite adhering to a month-long trial of combined glucocorticoid and azathioprine treatment 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 glucocorticoids while 93% of patients responded well to rituximab as a second- or third- line option, suggesting it as an efficient and favorable option in refractory cases[21]. 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 MMF) therapy were associated with more favorable relapse and remission rates when compared to GC or immunosuppressive monotherapy or RTX

induction therapy[28]. RTX combined with GC has also been suggested for vision-threatening cases[21].

In conclusion, we presented a case of a 35-year-old woman with unilateral proptosis in whom, diagnosis of IgG4-RD was established but normal serum levels of IgG4 and failure of remission induction with GC + AZA treatment imposed diagnostic and therapeutic challenges. After changing the therapeutic regimen to RTX + GC, remission was achieved and she has stayed relapse-free for 6 months.

Declaration Statement: Informed and written consent to publish the photographs and all other relevant data while maintaining her anonymity was signed by the patient. The authors declare that they have no competing interests.

1. Kamisawa, T., Y. Zen, S. Pillai, and J.H. Stone, *IgG4-related disease.* Lancet, 2015. **385**(9976): p. 1460-71.
2. Deshpande, V., et al., *Consensus statement on the pathology of IgG4-related disease.* Mod Pathol, 2012. **25**(9): p. 1181-92.
3. Goto, H., M. Takahira, and A. Azumi, *Diagnostic criteria for IgG4-related ophthalmic disease.* Jpn J Ophthalmol, 2015. **59**(1): p. 1-7.
4. Phaopraphat, K., et al., *Clinical manifestations, clinical course, and outcomes of immunoglobulin G4-related disease.* Int J Rheum Dis, 2020. **23**(11): p. 1468-1473.
5. Ebbo, M., et al., *Ophthalmic manifestations in IgG4-related disease: Clinical presentation and response to treatment in a French case-series.* Medicine (Baltimore), 2017. **96**(10): p. e6205.
6. *A prevalence study of IgG4-related ophthalmic disease in Japan.* Jpn J Ophthalmol, 2013. **57**(6): p. 573-9.
7. Wallace, Z.S., V. Deshpande, and J.H. Stone, *Ophthalmic manifestations of IgG4-related disease: single-center experience and literature review.* Semin Arthritis Rheum, 2014. **43**(6): p. 806-17.
8. Sogabe, Y., et al., *Location and frequency of lesions in patients with IgG4-related ophthalmic diseases.* Graefes Arch Clin Exp Ophthalmol, 2014. **252**(3): p. 531-8.
9. Zhao, Z., et al., *Clinical features and relapse risks of IgG4-related ophthalmic disease: a single-center experience in China.* Arthritis Res Ther, 2021. **23**(1): p. 98.
10. Gan, L., et al., *Ophthalmic involvement disparities in clinical characteristics of IgG4-related disease: a retrospective study of 573 patients.* BMC Ophthalmol, 2021. **21**(1): p. 447.
11. Khosroshahi, A., et al., *International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease.* Arthritis Rheumatol, 2015. **67**(7): p. 1688-99.

12. Stone, J.H., Y. Zen, and V. Deshpande, *IgG4-related disease.* N Engl J Med, 2012. **366**(6): p. 539-51.
13. Wallace, Z.S., et al., *IgG4-related systemic disease as a cause of "idiopathic" orbital inflammation, including orbital myositis, and trigeminal nerve involvement.* Surv Ophthalmol, 2012. **57**(1): p. 26-33.
14. Cheuk, W., H.K. Yuen, and J.K. Chan, *Chronic sclerosing dacryoadenitis: part of the spectrum of IgG4-related Sclerosing disease?* Am J Surg Pathol, 2007. **31**(4): p. 643-5.
15. Suzuki, D., K. Shimizu, and K. Shiratori, *EFFECT OF STEROID THERAPY ON THE SERUM IgG4 LEVELS AND THE CLINICAL MANIFESTATIONS OF AUTOIMMUNE PANCREATITIS.* Pancreas, 2008. **37**(4): p. 497.
16. Carruthers, M.N., et al., *The diagnostic utility of serum IgG4 concentrations in IgG4-related disease.* Ann Rheum Dis, 2015. **74**(1): p. 14-8.
17. Kwon, O.C., M.C. Park, and Y.G. Kim, *Correlation between serologic parameters and disease activity of IgG4-related disease: Differences between patients with normal and elevated serum IgG4 concentrations.* Front Immunol, 2022. **13**: p. 1020459.
18. Wallace, Z.S., et al., *IgG4-Related Disease: Clinical and Laboratory Features in One Hundred Twenty-Five Patients.* Arthritis Rheumatol, 2015. **67**(9): p. 2466-75.
19. Bledsoe, J.R., E. Della-Torre, L. Rovati, and V. Deshpande, *IgG4-related disease: review of the histopathologic features, differential diagnosis, and therapeutic approach.* Apmis, 2018. **126**(6): p. 459-476.
20. Gan, L., et al., *Long-Term Outcomes of IgG4-Related Ophthalmic Disease in a Chinese IgG4-Related Disease Cohort.* Front Med (Lausanne), 2021. **8**: p. 784520.
21. Detiger, S.E., et al., *The treatment outcomes in IgG4-related orbital disease: a systematic review of the literature.* Acta Ophthalmol, 2019. **97**(5): p. 451-459.
22. Wu, A., N.H. Andrew, A.A. McNab, and D. Selva, *IgG4-Related Ophthalmic Disease: Pooling of Published Cases and Literature Review.* Curr Allergy Asthma Rep, 2015. **15**(6): p. 27.
23. Baptista, B., et al., *Neurological Manifestations of IgG4-Related Disease.* Curr Treat Options Neurol, 2017. **19**(4): p. 14.
24. Liu, C., P. Zhang, and W. Zhang, *Immunological mechanism of IgG4-related disease.* J Transl Autoimmun, 2020. **3**: p. 100047.
25. Lin, W., et al., *B cell subsets and dysfunction of regulatory B cells in IgG4-related diseases and primary Sjögren's syndrome: the similarities and differences.* Arthritis Res Ther, 2014. **16**(3): p. R118.
26. Khosroshahi, A., D.B. Bloch, V. Deshpande, and J.H. Stone, *Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease.* Arthritis Rheum, 2010. **62**(6): p. 1755-62.
27. Carruthers, M.N., et al., *Rituximab for IgG4-related disease: a prospective, open-label trial.* Ann Rheum Dis, 2015. **74**(6): p. 1171-7.
28. Omar, D., Y. Chen, Y. Cong, and L. Dong, *Glucocorticoids and steroid sparing medications monotherapies or in combination for IgG4-RD: a systematic review and network meta-analysis.* Rheumatology (Oxford), 2020. **59**(4): p. 718-726.

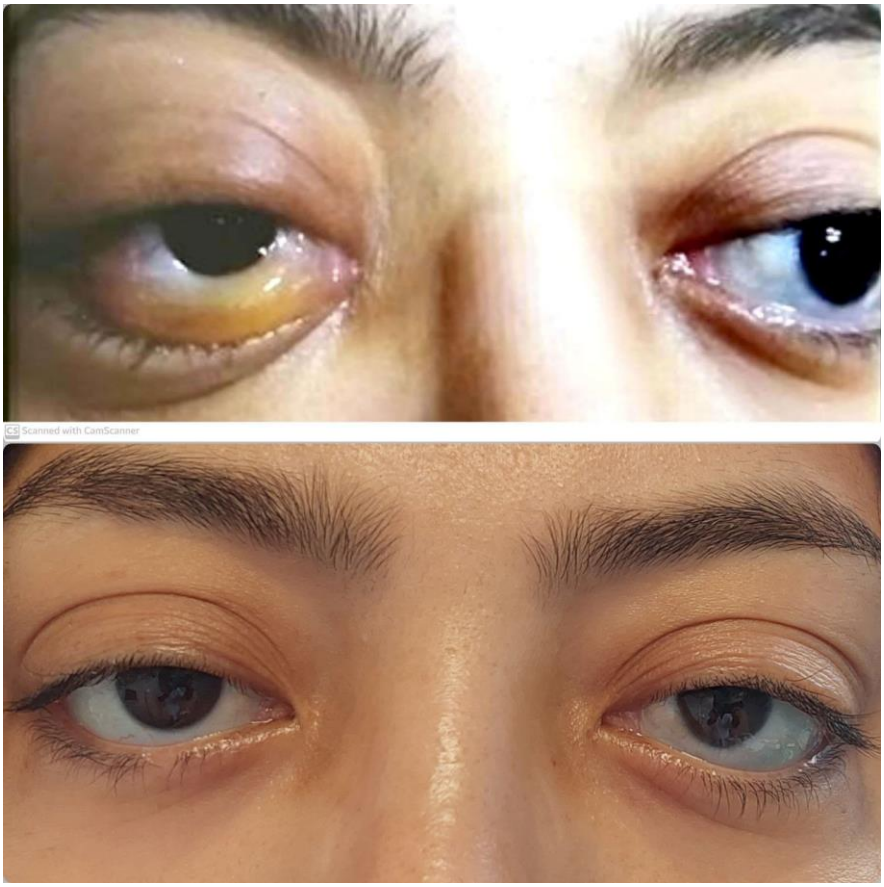

Figure 1 Ocular findings of patient at presentation (upper panel) and 6 months after RTX induction treatment(lower panel). (A) Marked proptosis and chemosis is present in the right eye. (B) No clinical symptoms were present at follow-up.

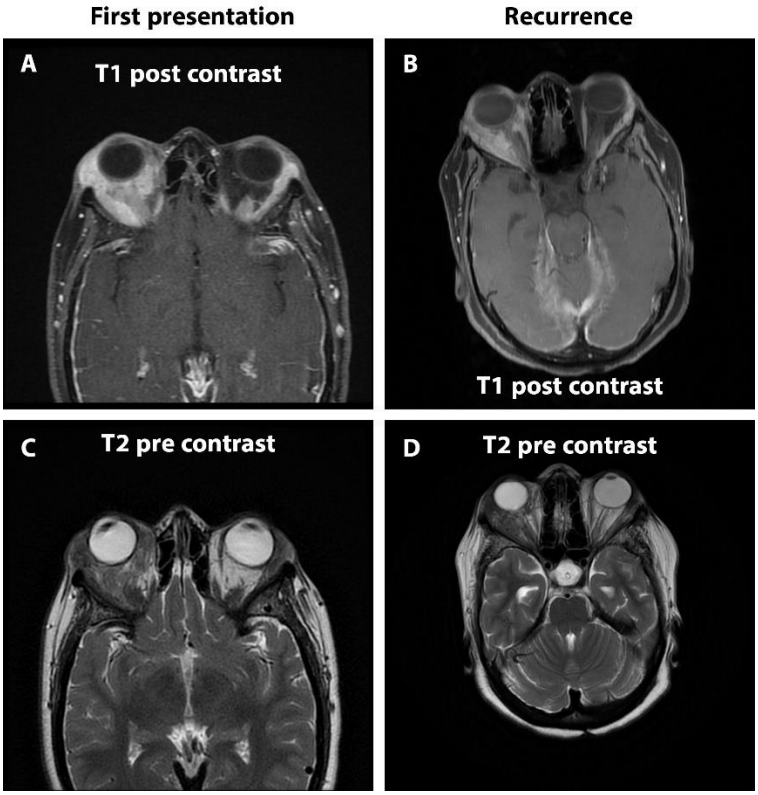

Figure 2 Axial Magnetic Resonance Imaging (MRI) at first admission (A, C), revealing bilateral proptosis primarily in the right side with a retro-ocular soft tissue mass. During relapse (B, D) improved but partial proptosis is shown.

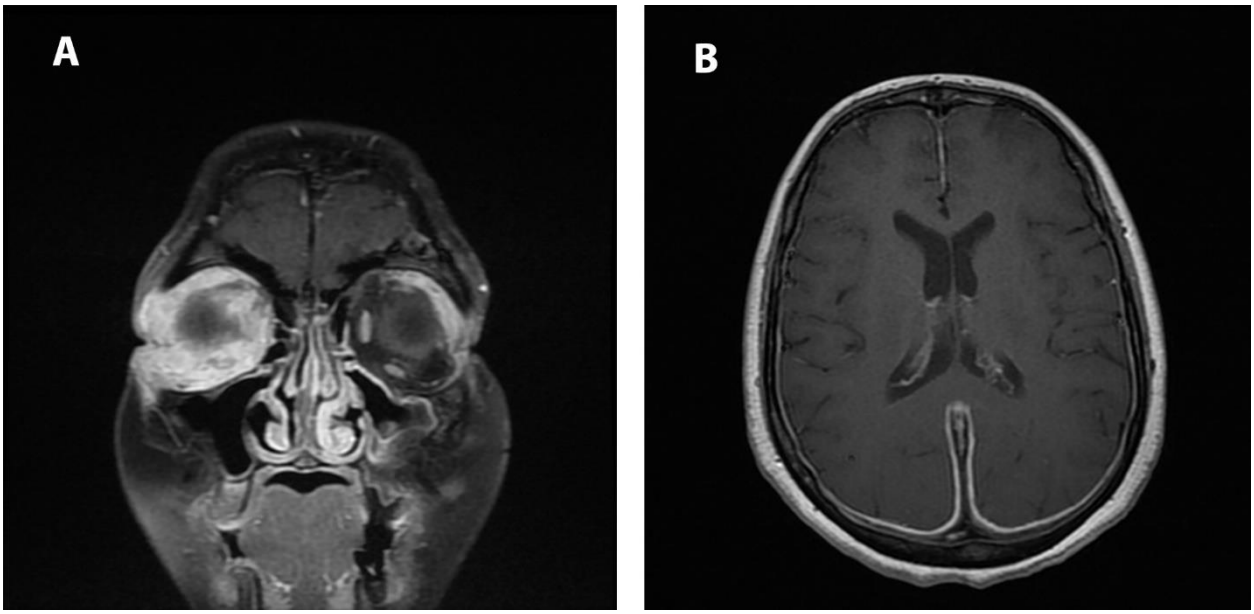

Figure 3 Bilateral lacrimal glands involvement at presentation (A) and persistent diffuse dural thickening and enhancement at follow-up (B)