CASE REPORT

Immunoglobulin G4-related ophthalmic disease presenting as a steroid-resistant choroidal mass: a case report

Cherie YK Wong[1,2], MRCSEd(Ophth); Moon-ho Leung[3], PhD(HKU), FRCP, FHKCP, FHKAM(Med); Vanissa WS Chow[1,2], FRCSEd(Ophthalmology), FCOphthHK, FHKAM(Ophth); Shaheeda Mohamed[1,2], MPH, MMed, FRCSEd(Ophth), FRCOphth, FCOphthHK, FHKAM(Ophth); NM Lam[1,2], FCOphthHK, FHKAM(Ophth); Hunter KL Yuen[1,2], FRCOphth, FRCSEd, FCOphthHK, FHKAM(Ophth); Carmen KM Chan[1,2], FRCP(Lond), FRCOphth, FRCSEd(Ophth), FCOphthHK, FHKAM(Ophth)

[1]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong*
[2]*Hong Kong Eye Hospital, Hong Kong*
[3]*Department of Medicine, Queen Elizabeth Hospital, Hong Kong*

Correspondence and reprint requests:
Dr Carmen KM Chan, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong. Email: kmcc2001@hotmail.com

Abstract

Immunoglobulin G4-related ophthalmic disease (IgG4-ROD) is a cause for orbital and ocular inflammation. Involvement of the sclera and intraocular tissues is less common, and presentation is mostly unilateral. We hereby describe a probable case of steroid-resistant intraocular IgG4-ROD presenting as a choroidal mass in the left eye, with sequential anterior uveitis and scleritis of the fellow right eye. The diagnostic path was not straightforward and included subconjunctival biopsy, blood tests, magnetic resonance imaging, positron emission tomography–computed tomography, and biopsies in two extra-ocular sites. Disease progression was rapid in the left eye despite high-dose oral steroids, while the inflammation of the fellow eye was controlled with the use of rituximab and second-line immunosuppressants. At the 3-year follow-up, the ocular inflammation was well controlled. The left eye was phthisical, but the right eye maintained a visual acuity of 20/20.

Key words: Choroid diseases; Immunoglobulin G4-related disease; Scleritis; Uveitis

Case presentation

In June 2019, a 27-year-old woman presented to Hong Kong Eye Hospital with a 4-week history of left eye redness and pain. On physical examination, she appeared to have left eye superonasal sectoral scleritis associated with 1+ anterior chamber cells (**Figure 1a**). Dilated fundal examination of the left eye showed a superonasal choroidal mass and posterior vitreous cells. (**Figure 1b**). The right eye was unremarkable. Ultrasound B-scanning showed a choroidal mass with choroidal effusion and mild vitritis in the left eye (**Figure 1c**). Magnetic resonance imaging of the orbits showed an intraocular mass in the left eye and mildly enlarged lacrimal glands bilaterally (**Figure 1d**). Blood tests for complete blood count, anti-nuclear antibody, anti-neutrophil cytoplasmic antibodies (classic and perinuclear), rheumatoid factor, syphilis, human immunodeficiency virus were all normal/negative. The erythrocyte sedimentation rate was 49 mm/hr. Chest X-ray showed multiple radiopaque masses up to 2.8 cm in both lungs non-typical of tuberculous infection, and interferon-gamma-releasing assay was negative. A non-infective inflammatory cause was suspected, and the patient was put on a therapeutic trial of oral prednisolone 50 mg daily (1 mg/kg) for 2 weeks. However, the eye symptoms and signs were progressive.

As the response to high-dose oral steroid was poor,

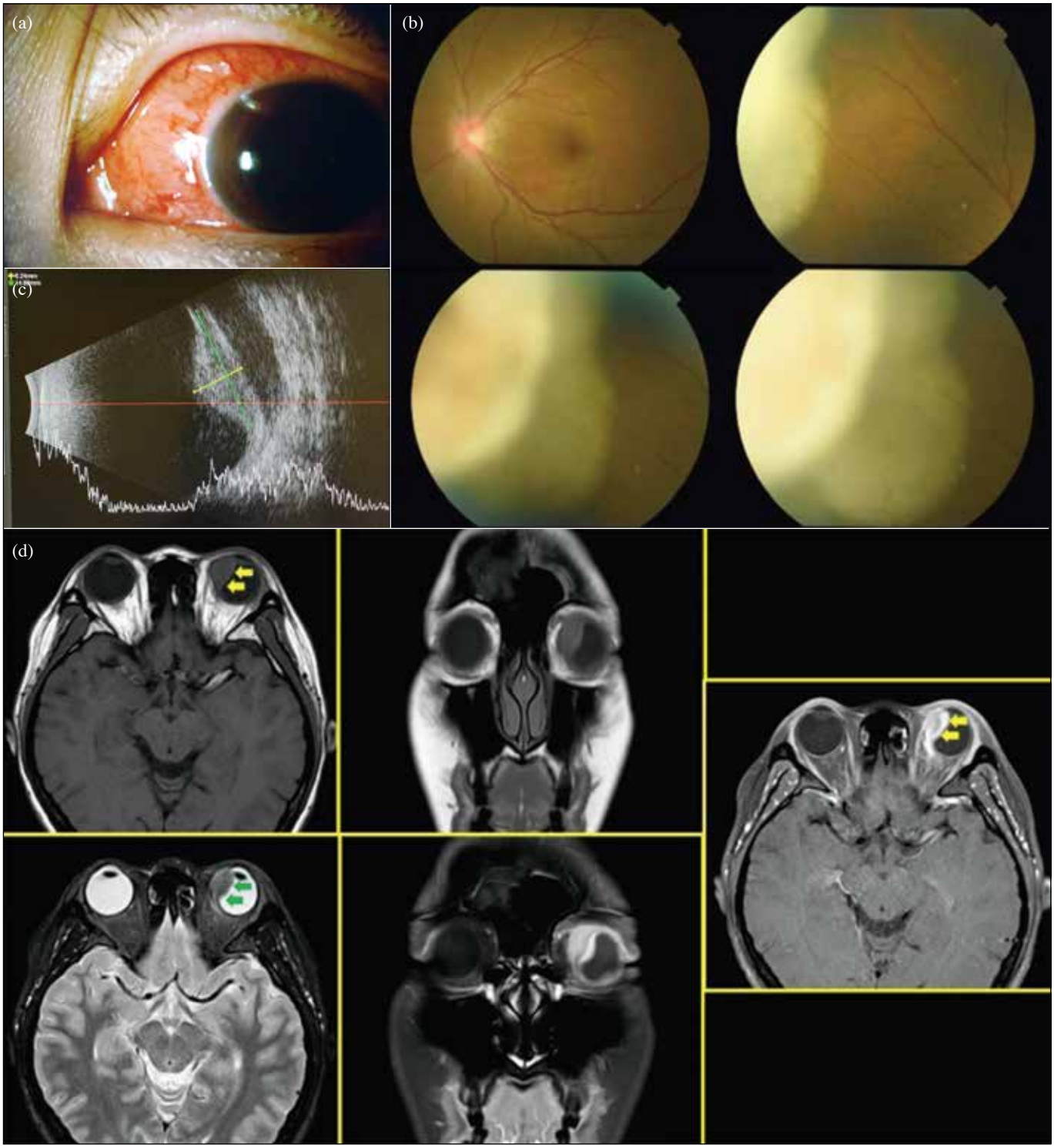

Figure 1. (a) Slit lamp photograph showing left eye sectoral scleritis, (b) dilated fundal examination showing a superonasal choroidal mass, (c) an ultrasound B-scan of the left eye showing a hyperechogenic choroidal mass with choroidal effusion, and (d) a magnetic resonance image of the orbits showing a left intraocular mass and mildly enlarged lacrimal glands bilaterally.

lymphoproliferative/neoplastic causes were suspected. Scleral biopsy (which is less invasive than intraocular biopsy) of the choroidal mass was planned after stopping oral prednisolone for 2 weeks. During the procedure, a subconjunctival (rather than scleral) mass was found and biopsied (**Figure 2a**). The specimen showed vascularized stromal tissue infiltrated by a large number of plasma cells and lymphocytes (**Figure 2b**). Immunostaining showed mixed populations of B (CD20+) and T (CD3+) cells. There were 133 immunoglobulin G4+ (IgG4+) plasma cells per high power field, but the ratio of IgG4+ cells to IgG+ cells was only 20% (**Figure 2c**). Serum IgG4 level (taken

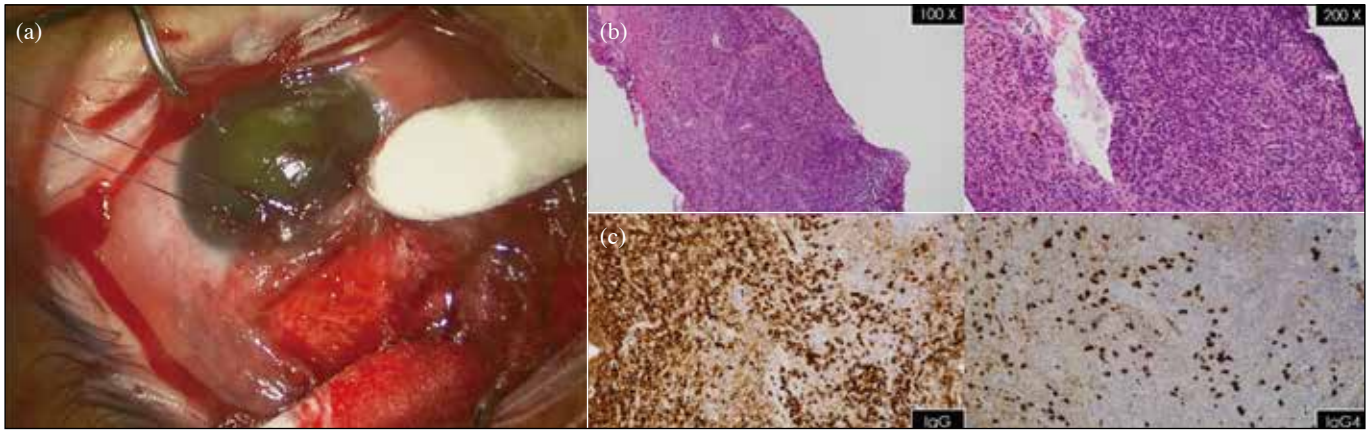

Figure 2. (a) Biopsy of the subconjunctival mass overlying the site of choroidal lesion. (b) Histology showing vascularized stromal tissue infiltrated by a large number of plasma cells and lymphocytes. There is no evidence of granulomas, vasculitis, or malignancy. (c) Immunostaining showing mixed populations of B (CD20+) and T (CD3+) cells. There are 133 IgG4+ plasma cells per high power field that constitute approximately 20% of the IgG+ cells.

after commencement of high-dose steroid) was 1.28 g/L (normal range, <0.86 g/L). These findings were suggestive of IgG4-related ophthalmic disease (IgG4-ROD) but did not completely fulfill the diagnostic criteria. Polymerase chain reaction and acid-fast bacilli culture of the specimen was negative for *Mycobacterium tuberculosis* complex.

Owing to the unusual disease presentation, abnormal chest X-ray findings, and the lack of response to high-dose oral prednisolone, positron emission tomography–computed tomography was performed and showed a hypermetabolic intraocular mass in the left eye (maximum standardized uptake value [SUVmax], 16.5), multiple pulmonary masses (SUVmax of the largest mass, 9.7), and prominent bilateral tonsillar uptake (SUVmax, 9.8 on left side and 10.5 on right side) [**Figure 3**]. Lymphoma was suspected. To delineate the nature and systemic involvement of the disease, bilateral tonsillectomy and tongue base lymphoid biopsy were performed. The specimen showed reactive lymphoid hyperplasia with a small number of IgG4+ plasma cells. Transbronchial biopsy showed no significant pathology. Polymerase chain reaction and acid-fast bacilli culture of the bronchial aspirate was negative for *M tuberculosis* complex.

Open lung biopsy was performed. The specimen showed heavy lymphoplasmacytic infiltrate, fibrosis, and obliterative vasculitis, which were suggestive of IgG4-related disease (IgG4-RD). The left eye intraocular mass continued to progress, filling and expanding the globe and causing proptosis (**Figure 4**).

A provisional diagnosis of IgG4-ROD with systemic involvement was made. The patient was started on intravenous methylprednisolone 1 g/day for 3 days followed by a course of high-dose oral prednisolone 50 mg daily. However, the patient developed anterior uveitis in the fellow right eye. Two doses of rituximab (1 g 2 weeks apart) were given as a steroid-sparing agent to reduce the adverse effects of high-dose steroids and for better disease control. However, the condition of both eyes progressed. The right eye developed scleritis with intraocular extension, whereas the left eye became phthisical with light perception only. In view of the aggressive nature of the eye and systemic conditions, mycophenolate mofetil was added at 8 weeks (up to 1000 mg twice daily) after rituximab therapy, and tacrolimus was also commenced at 12 weeks (up to 1 mg twice daily). The right eye responded well, with resolution of anterior uveitis and scleritis (**Figure 5**). IgG4 level was normalized at 0.59 g/L.

At the 3-year follow-up, the ocular inflammation was well controlled by a maintenance dose of mycophenolate mofetil 250 mg twice daily and tacrolimus 0.5 mg daily with no topical or systemic corticosteroid. The left eye was phthisical, but the right eye maintained a visual acuity of 20/20. The patient had no symptoms or signs of lymphoma or tuberculous infection, and her inflammatory markers were within normal limits.

Discussion

IgG4-RD is a multi-system fibro-inflammatory disease secondary to infiltration of IgG4+ plasma cells in various organs. It can affect the pancreas, hepatobiliary ducts, salivary glands, lungs, etc. Whereas IgG4-ROD refers to IgG4-RD targeting ocular structures including extraocular muscles, orbital soft tissue, cavernous sinus, sclera, choroid, and nasolacrimal system. IgG4-ROD was first reported to be associated with chronic sclerosing dacryoadenitis in 2007. Lacrimal gland is the most common site of ophthalmic involvement. The overall frequency of IgG4-ROD in IgG4-RD is 4% to 34%.[1]

Reports of intraocular IgG4-ROD are less common. Presenting manifestations of intraocular IgG4-ROD include unilateral scleritis, bilateral multifocal choroiditis,

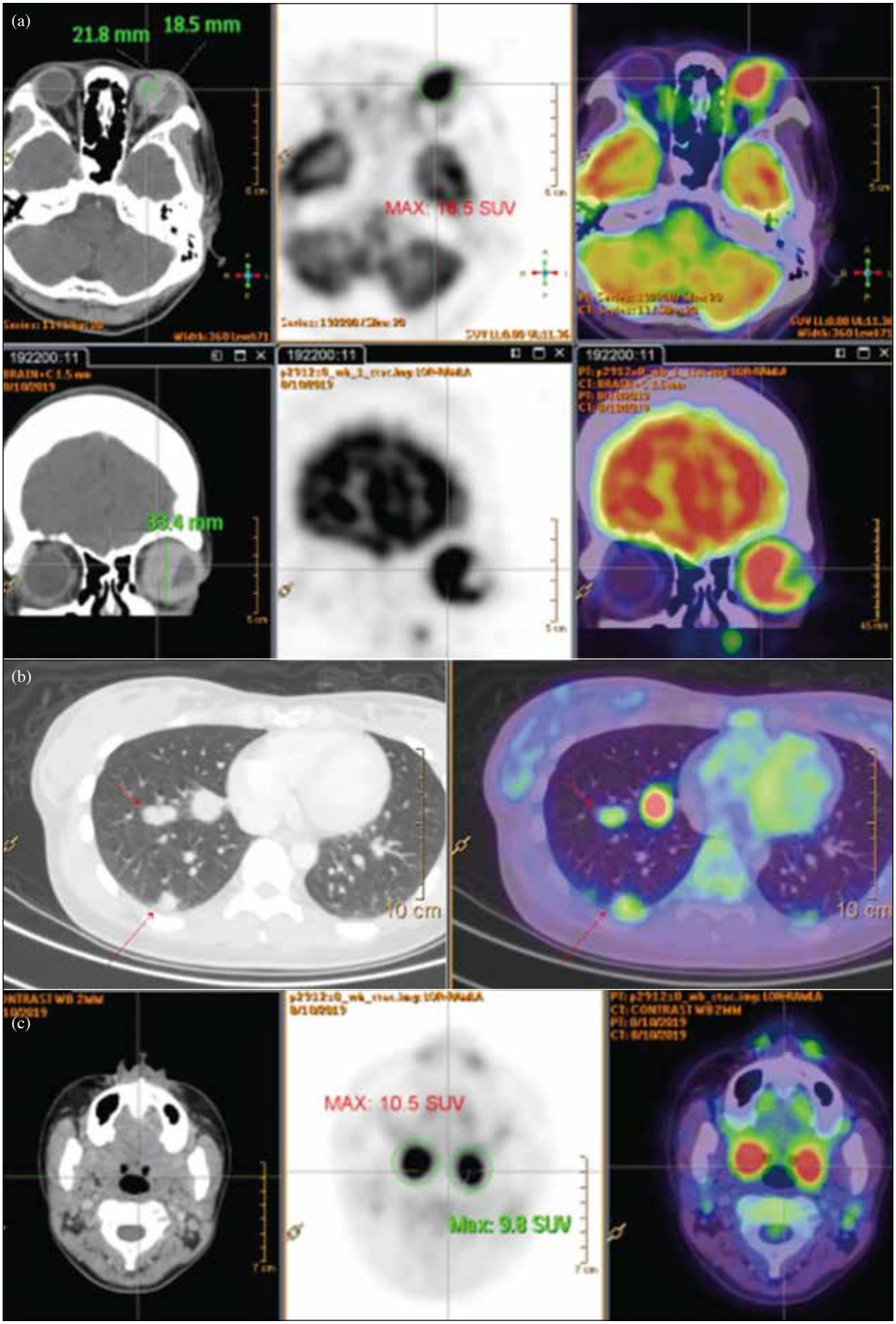

Figure 3. Positron emission tomography–computed tomography showing (a) a hypermetabolic intraocular mass in the left eye, (b) multiple pulmonary masses, and (c) prominent bilateral tonsillar uptake.

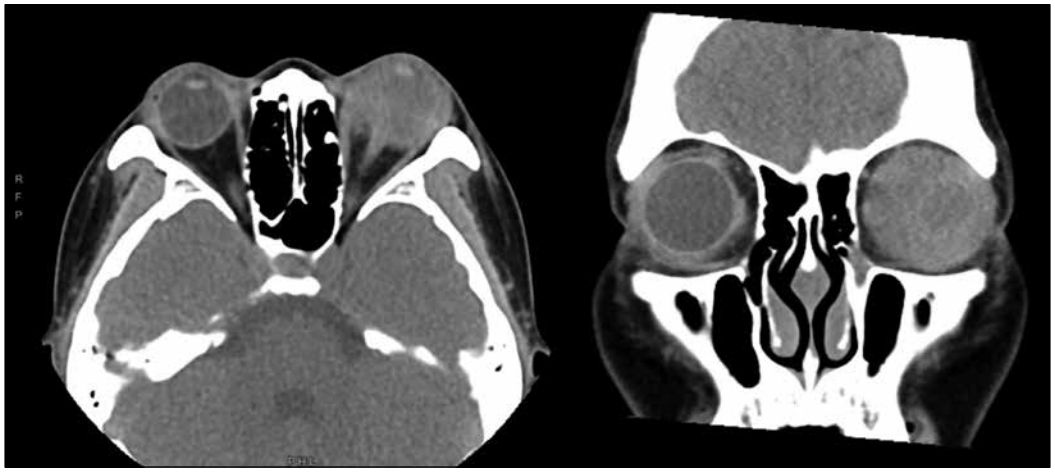

Figure 4. Computed tomography of the orbits showing progressive enlargement of the left eye intraocular mass filling and expanding the globe and causing left eye proptosis.

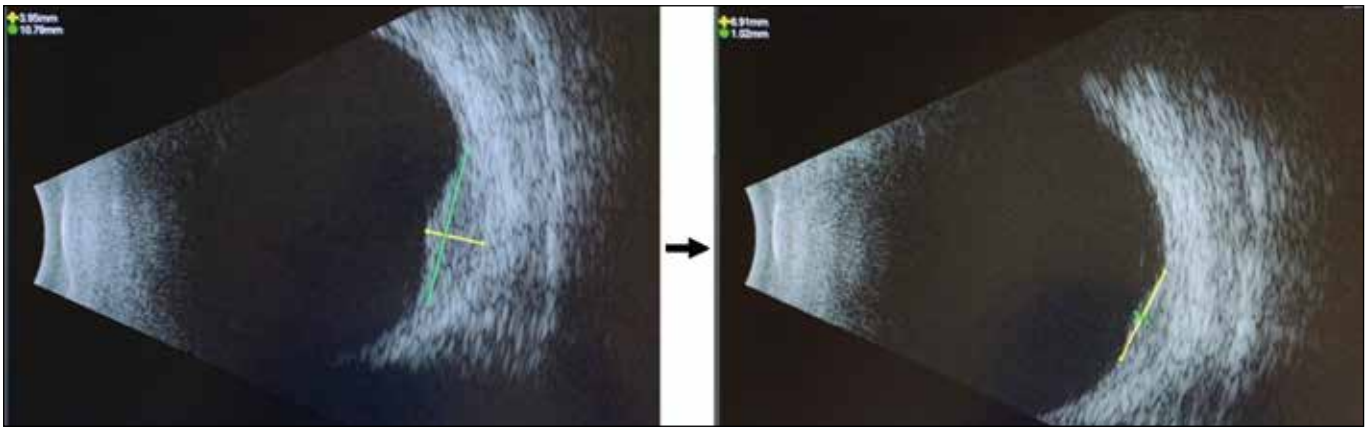

Figure 5. Resolution of the intraocular mass in the fellow right eye after treatment with mycophenolate mofetil and tacrolimus.

choroidal mass, and ciliary body mass.[1] Most reported cases of intraocular involvement were unilateral. There are six reported cases of IgG4-related choroidal mass[2-7] and one reported case of choroidal effusion.[8] Our case is the first case that demonstrates sequential but heterogeneous involvement of the fellow eye, which developed anterior uveitis while on high-dose steroids. With the prompt commencement of rituximab and second-line immunosuppressants, the condition of the fellow eye was brought under control with visual acuity preserved.

As IgG4-ROD can mimic infective, inflammatory, or malignant conditions, thorough workup and systemic examination should be performed. Malignancy such as lymphoma and choroidal melanoma must be ruled out, especially in cases with atypical presentations. Biopsy is the gold standard for diagnosing IgG4-ROD. Histopathological findings include lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, storiform fibrosis, obliterative and non-obliterative phlebitis, and frequent germinal centers.[1] Serum IgG4 level is often elevated but can be normal in 30% to 40% of patients.[5]

Diagnostic criteria for IgG4-ROD comprise radiological, histological, and serological criteria:[9] (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 geminal center is frequently observed. IgG4+ plasmacytes fulfill the following: (a) the ratio of IgG4+ cells to IgG+ cells being ≥40% or (b) >50 IgG4+ cells per high power field (x400). (3) Blood test shows elevated serum IgG4 of ≥1.35 g/L. Diagnosis is classified as definitive when (1), (2), and (3) are fulfilled, probable when (1) and (2) are fulfilled, and possible when (1) and (3) are fulfilled.

In our patient, histological findings of the subconjunctival mass showed >50 IgG4+ cells per high power field, but the ratio of IgG4+ to IgG+ cells did not reach 40%. Open lung biopsy showed heavy lymphoplasmacytic infiltrate, fibrosis, and obliterative vasculitis, which were suggestive of IgG4-RD. The serum IgG4 level was elevated to 1.28 g/L but did not reach the diagnostic criteria of ≥1.35 g/L.

Both the histology and serum IgG4 level could have been affected by prior high-dose steroid treatment. Therefore, the condition was treated as a probable IgG4-ROD. The main differential diagnoses include multicentric Castleman's disease, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and sarcoidosis, but all these were not supported by the histological and serological findings.

Corticosteroids are the mainstay of treatment for IgG4-ROD. Initial treatment response to oral prednisolone is good, but a limited window of steroid efficiency is suggested, and relapses are common. Suggested dosage is approximately 0.6 to 1 mg/kg/day, with long tapering and maintenance dose between 2.5 and 10 mg/day of prednisolone to prevent relapse and involvement of other organs.[10] Second-line treatment options include immunosuppressive agents such as azathioprine, methotrexate, mycophenolate mofetil, tacrolimus, and biologics such as infliximab and rituximab.[11,12] Rituximab, in particular, is effective as second or third-line treatment, with high rates of remission in both IgG4-RD and IgG4-ROD.[1] The optimal frequency or duration of rituximab is not known; initial treatment with two doses of rituximab separated by 15 days is suggested.[13] In our patient, mycophenolate and tacrolimus were chosen over azathioprine and methotrexate for their faster onset of action.

In our case, the diagnostic path was not straightforward and required supportive evidence from biopsies in two extra-ocular sites (lung and tonsil). Disease progression in the left eye was rapid despite high-dose oral steroid. Although malignant lymphoma was a differential diagnosis and IgG4-RD is associated with an increased risk of lymphoma,[14] the patient did not have any B symptoms (fever, night sweats, and loss of >10% of body weight over 6 months) and the diagnosis of lymphoma was not supported by histological findings. The involvement of the fellow right eye was treated promptly with rituximab and second-line immunosuppressants, which led to resolution of scleritis and choroidal mass. At the 3-year follow-up, the ocular inflammation was well controlled by a maintenance dose of low-dose mycophenolate mofetil and tacrolimus. The patient achieved disease remission in the right eye with preserved visual acuity and had no signs or symptoms of ocular or systemic lymphoma or tuberculous infection, but the left eye was phthisical.

Conclusion

IgG4-ROD is a cause for intraocular, scleral or orbital inflammation. Biopsy is the gold standard for diagnosis. Malignancy and systemic involvement should be ruled out, particularly in patients with atypical presentation and disease course. Prompt diagnosis and treatment with systemic steroids lead to better outcomes.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient provided written informed consent for all invasive procedures according to prevailing clinical guidelines, and for publication.

Acknowledgement

The authors would like to thank Dr David Liu and Dr Alex Wong for providing supplementary clinical images, and Dr Wah Cheuk for his help with histology.

References

1. *Derzko-Dzulynsky L. IgG4-related disease in the eye and ocular adnexa. Curr Opin Ophthalmol 2017;28:617-22.* Crossref
2. *Ohno K, Sato Y, Ohshima K, et al. IgG4-related disease involving the sclera. Mod Rheumatol 2014;24:195-8.* Crossref
3. *Goto H, Ueda S. Immunoglobulin G4-related ophthalmic disease involving the sclera misdiagnosed as intraocular tumor: report of one case. Ocul Oncol Pathol 2016;2:285-8.* Crossref
4. *Reynolds GL, Norris JH, Aslam S, Sharma S. IgG4-related disease presenting as posterior scleritis and vitritis, progressing to multifocal orbital involvement. BMJ Case Rep 2017;2017:bcr2017219568.* Crossref
5. *Gange WS, Holland SM, De Alba F. IgG4-related ophthalmic disease presenting as choroidal and orbital lesions. Retin Cases Brief Rep 2019;13:283-6.* Crossref

6. *Aragona E, Miserocchi E, Arrigo A, et al. Immunoglobulin G4-related ophthalmic disease mimicking intraocular lymphoma: a case report. Retin Cases Brief Rep 2022;16:32-5.* Crossref
7. *Attiku Y, Rishi P, Biswas J, Krishnakumar S. Intraocular IgG4 disease masquerading as nodular scleritis. Indian J Ophthalmol 2020;68:1935-6.* Crossref
8. *Koenigstein D, Neudorfer M, Goldenberg D, Habot-Wilner Z. Choroidal effusion as an ocular manifestation of immunoglobulin G4-related disease. Retin Cases Brief Rep 2016;10:197-200.* Crossref
9. *Goto H, Takahira M, Azumi A; Japanese Study Group for IgG4-Related Ophthalmic Disease. Diagnostic criteria for IgG4-related ophthalmic disease. Jpn J Ophthalmol 2015;59:1-7.* Crossref
10. *Philippakis E, Cassoux N, Charlotte F, et al. IgG4-related disease masquerading as recurrent scleritis and chronic conjunctivitis. Ocul Immunol Inflamm 2015;23:168-72.* Crossref
11. *Löhr JM, Beuers U, Vujasinovic M, et al. European Guideline on IgG4-related digestive disease: UEG and SGF evidence-based recommendations. United European Gastroenterol J 2020;8:637-66.* Crossref
12. *Khosroshahi A, Wallace ZS, Crowe JL, et al. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. Arthritis Rheumatol 2015;67:1688-99.* Crossref
13. *Wallace ZS, Mattoo H, Mahajan VS, et al. Predictors of disease relapse in IgG4-related disease following rituximab. Rheumatology (Oxford) 2016;55:1000-8.* Crossref
14. *Yu T, Wu Y, Liu J, Zhuang Y, Jin X, Wang L. The risk of malignancy in patients with IgG4-related disease: a systematic review and meta-analysis. Arthritis Res Ther 2022;24:14.* Crossref