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IgG4-related hypertensive granulomatous anterior uveitis

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ABSTRACT

Purpose: To report a case of hypertensive granulomatous anterior uveitis in the setting of IgG4-related disease (IgG4-RD).

Observations: A 69-year-old man presented with no light perception vision in both eyes and bilateral granulomatous anterior uveitis with iris neovascularization and hyphema in the right eye. He also demonstrated concurrent polyuria, polydipsia, and altered mental status, and was diagnosed with new-onset diabetes mellitus. MRI revealed no orbital abnormalities, but showed bilateral occipital strokes attributed to hyperglycemic hyperosmolar syndrome. Chest CT revealed pleural-based nodules and mediastinal and abdominal lymphadenopathy, and a liver biopsy confirmed fibroinflammatory nodules with increased IgG4 positive plasma cell infiltrates, diagnostic of IgG4-RD. Serum IgG4 levels were 1381 mg/dL. The patient was treated with a combination of systemic and topical steroids, and later initiated on rituximab.

Conclusion and importance: IgG4-related ophthalmic disease may present as an isolated hypertensive granulomatous anterior uveitis without associated scleral or orbital involvement.

1. Introduction

IgG4-related ophthalmic disease (IgG4-ROD) most commonly presents as inflammation of orbital and scleral tissues, but is also a rare cause of uveitis. We report a case of IgG4-related disease (IgG4-RD) presenting as a hypertensive granulomatous-appearing anterior uveitis without associated scleral or orbital involvement.

2. Case report

A 69-year-old male was referred for evaluation of decreased vision and elevated intraocular pressure (IOP) in both eyes requiring treatment with intravenous mannitol. He had been concurrently diagnosed with a granulomatous bilateral anterior uveitis, associated with iris neovascularization and hyphema in the right eye (Fig. 1A). On initial presentation, visual acuity was no light perception in both eyes, and the patient demonstrated altered mental status, polyuria, and polydipsia. Following admission to the intensive care unit, he was subsequently diagnosed with hyperosmolar hyperglycemic syndrome (HHS) secondary to new onset diabetes mellitus. An MRI was negative for orbital abnormalities but revealed bilateral occipital infarcts, attributed to hypercoagulable state from HHS.

After discharge, his vision improved to 20/100 in both eyes with improved blood sugar control. Dilated fundus examination was limited due to secluded pupil but did not reveal vitritis, chorioretinal lesions, or vasculitis, and no evidence of macular edema or vascular leakage was seen on optical coherence tomography (Fig. 1C and D) and fluorescein angiography. Laboratory work-up revealed elevated ACE to 93 (range 13–69 U/L), lysozyme to 3.99 (normal $\leq$2.75 μg/mL), and elevated liver enzymes and alkaline phosphatase. His syphilis and tuberculosis serologies were negative. Chest CT demonstrated enlarged mediastinal and abdominal lymph nodes, with diffuse ground-glass lung opacities. Several solid pleural-based nodules were also seen in the right upper lobe (Fig. 2A and B). Follow-up studies demonstrated elevated serum IgG4 levels (1381 mg/dL, normal range 1–123 mg/dL). Magnetic resonance cholangiopancreatography (MRCP) was performed, suggestive of a primary sclerosing cholangitis. A liver biopsy revealed portal fibroinflammatory nodules with increased IgG4 positive plasma cell infiltrates (>100 per high-power field), diagnostic of IgG4-related disease (Fig. 2C and D). Given that the liver biopsy was consistent with IgG4-related primary sclerosing cholangitis, a lung biopsy was deferred.

The patient was treated with a combination of systemic and topical

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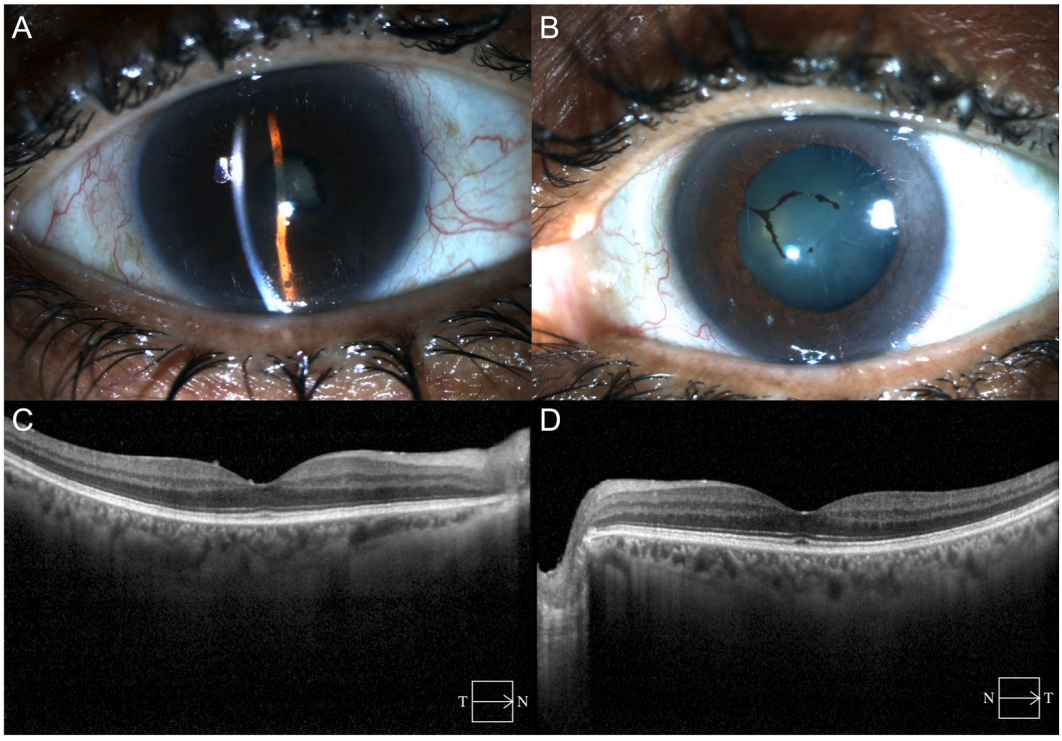

Fig. 1. Slit lamp photographs at initial presentation. Right eye demonstrates granulomatous keratic precipitates inferiorly and posterior synechiae (A). Left eye with broken posterior synechiae (B). Enhanced depth imaging optical coherence tomography (EDI-OCT) of the macula at presentation, which was within normal limits (C, right eye, D, left eye).

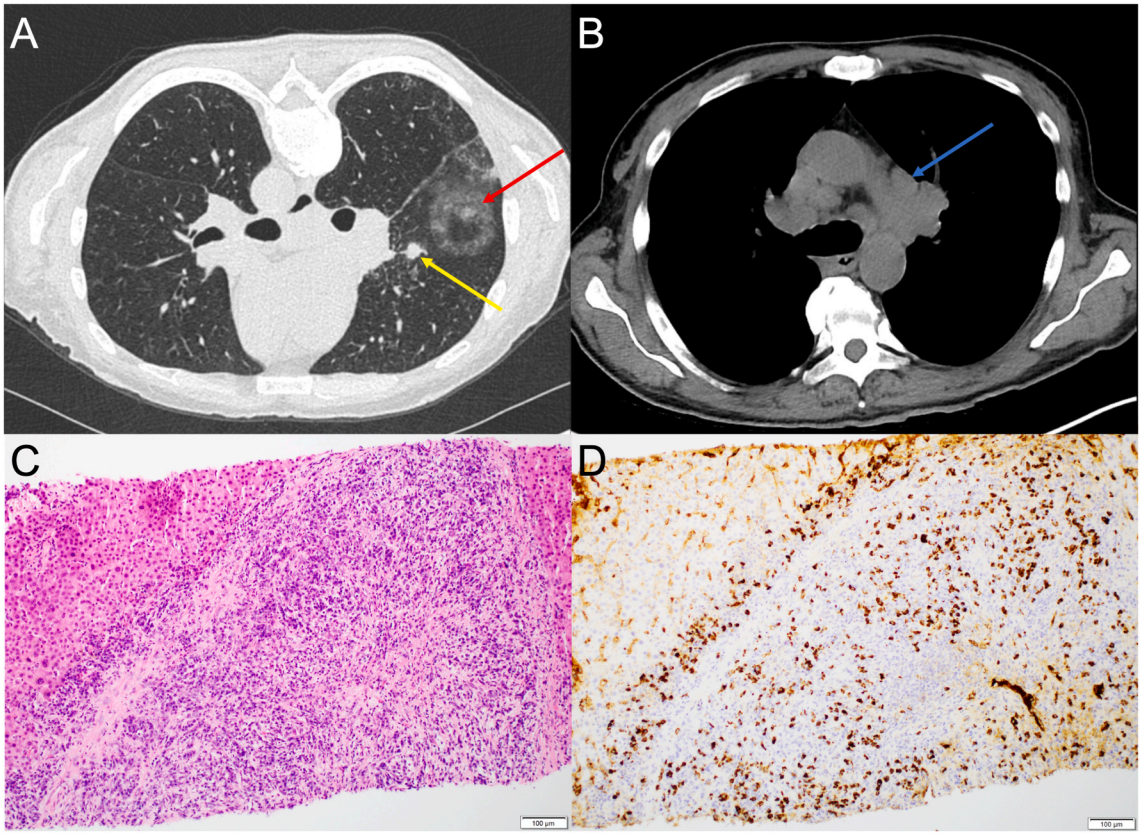

Fig. 2. Computed tomography of the chest revealed pulmonary nodules in the right upper lobe (yellow arrow) and groundglass opacities (red arrow) (A), as well as mediastinal lymphadenopathy (blue arrow) (B). Liver biopsy demonstrates portal fibroinflammatory nodules (C) with prominent IgG4-positive plasma cell infiltrates (D). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

steroids, and later initiated on rituximab. He also underwent right eye tube shunt implantation for management of secondary glaucoma. Subsequently, he also underwent cataract surgery of his right eye. At his 9-month follow-up, visual acuity was 20/25 in the right eye, 20/30 in the left eye, and IOP and ocular inflammation were well controlled.

3. Discussion

Systemic IgG4-related disease is a fibro-inflammatory disorder of unknown etiology that can affect multiple organs throughout the body, and is characterized by infiltration of organs with IgG4-positive plasma cells. The most common tissues involved are the pancreas and salivary glands, with the development of diabetes, as observed in our patient, thought to be related to infiltration and alteration of pancreatic beta cells in autoimmune pancreatitis (AIP).[1] Ophthalmic involvement has been noted in up to 19.2% of IgG4-RD patients, with orbital and orbital adnexal structures such as the lacrimal glands and extraocular muscles being most frequently affected.[2,3] A definitive diagnosis of IgG4-ROD requires fulfillment of 3 criteria: enlargement of or hypertrophic lesions within ophthalmic tissues, elevated serum IgG4 levels $\geq$135 mg/dL, and histopathology demonstrating lymphoplasmacytic infiltration of IgG4+ plasma cells with a high IgG4+ to IgG + plasma cell ratio.[4]

Uveitis in the setting of IgG4-ROD is rarely reported, and our patient demonstrated several unique clinical features. Prior cases have described findings of optic nerve head edema, exudative retinal detachments, hypopyon, and multifocal as well as solitary choroidal lesions.[5,6] All cases have also been associated with scleral and/or orbital inflammation, with the exception of one patient who presented with an isolated panuveitis.[7] Additional investigations to consider in future cases would be indocyanine green angiography, which could reveal potential choroidal involvement that would otherwise not observed on clinical examination.

The presence of mediastinal lymphadenopathy in our patient raises the possibility of concurrent ocular sarcoidosis, though he does not meet criteria for the diagnosis of definitive ocular sarcoidosis as his biopsy was negative for noncaseating granulomas. Michel et al. previously reported a patient who presented with AIP and elevated serum IgG4 levels, whose biopsy of salivary glands and celiac lymph nodes demonstrated noncaseating granulomas, consistent with a diagnosis of sarcoidosis; however, it was indeterminate whether this was a manifestation of IgG4-related disease with systemic granulomatous lesions, or a true association of AIP with sarcoidosis.[8] Our patient did not undergo a lung biopsy as his liver biopsy was consistent with IgG4-RD, and he did not manifest dyspnea or other pulmonary symptoms. Additional histopathologic and radiologic examination may help further distinguish between the entities of sarcoidosis and IgG4-RD. A study by Tsushima et al. comparing the clinical and pathological features of pulmonary lesions in patients with AIP versus those with sarcoidosis found that AIP patients demonstrated significantly elevated serum IgG and IgG4 levels, as well as infiltration of lymphocytes and IgG4-positive plasma cells in transbronchial lung biopsies.[9] In a study comparing patients with sarcoidosis and those with IgG4-RD, Hanaoka et al. identified C–C chemokine ligand 1 (CCL1) as a marker that is significantly elevated in bronchoalveolar lavage fluid and serum in sarcoidosis patients versus those with IgG4-RD.[10] Additionally, preliminary evidence suggests that fluorodeoxyglucose-positron emission tomography (FDG-PET) scans of hilar lymph nodes may have diagnostic weight in distinguishing between sarcoidosis and IgG4-RD.[11]

IgG4-related disease generally responds quickly to systemic glucocorticoids, such that steroid therapy has become the standard for first-line treatment.[12] In a study of IgG4-RD patients initiated on glucocorticoids, eosinophilia, higher baseline IgG4-RD responder index, involvement of more than five organs, and dacryoadenitis were identified as the most prominent risk factors predictive of remission induction failure. Remission failure also varied greatly depending on which organ was involved.[13] A guidance statement on IgG4-RD acknowledged that temporary spontaneous remissions of the disease have been reported without treatment but will ultimately result in a relapsing-remitting pattern with progressive organ injury, sometimes re-emerging in a different site.[14] There is not much evidence to suggest that conventional steroid-sparing agents such as methotrexate are effective for IgG4-RD; however, data does show that B-cell targeting with rituximab is effective, and patients can be tapered quickly off of steroids once rituximab is initiated.[14,15]

4. Conclusions

Of note, our patient is also the first known case of presumed IgG4-ROD to have presented with secondary ocular hypertension. Though the IOP in his right eye was likely affected by the presence of rubeosis and hyphema, his left eye also demonstrated elevated IOP, suggesting an underlying trabecular dysfunction or alternate impairment of outflow related to inflammation or infiltration. This report therefore expands upon the spectrum of potential presentations of ocular inflammation in the setting of IgG4-related disease.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Patient consent

Consent to publish this case report has been obtained from the patient(s) in writing.

Declaration of competing interest

ET: Cylite Pty Ltd, Kowa Company Ltd, EyePoint Pharmaceuticals. The following authors have no financial disclosures: JLC, MM, BVN.

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References

1. Tanaka S, Kobayashi T, Nakanishi K, et al. Evidence of primary beta-cell destruction by T-cells and beta-cell differentiation from pancreatic ductal cells in diabetes associated with autoimmune chronic pancreatitis. *Diabetes Care*. 2001;24(9):1661–1667.
2. Uchida K, Masamune A, Shimosegawa T, et al. Prevalence of IgG4-related disease in Japan based on nationwide survey in 2009. *Internet J Rheumatol*. 2012:358371.
3. Goto H, Ueda S, Nemoto R, et al. Clinical features and symptoms of IgG4-related ophthalmic disease: a multicenter study. *Jpn J Ophthalmol*. 2021. https://doi.org/10.1007/s10384-021-00847-3.
4. Goto H, Takahira M, Azumi A, et al. Diagnostic criteria for IgG4-related ophthalmic disease. *Jpn J Ophthalmol*. 2015;59:1–7.
5. Derzko-Dzulynsky L. IgG4-related disease in the eye and ocular adnexa. *Curr Opin Ophthalmol*. 2017;28:617–622.
6. Tsui E, Goldberg N, Pillai C, et al. Multimodal imaging OF IGG4-RELATED papillitis and retinal disease. *Retin Cases Brief Rep*. 2019. https://doi.org/10.1097/ICB.0000000000000902.
7. Mavrommatis MA, Avila SA, France R. IgG4-related ophthalmic disease presenting as meningitis and panuveitis. *Case Reports in Ophthalmological Medicine*. 2019:5653282.
8. Michel L, Clairant R, Néel A, et al. Association between IgG4-related disease and sarcoidosis. *Thorax*. 2011;66:920–921.
9. Tsushima K, Tanabe T, Yamamoto H, et al. Pulmonary involvement of autoimmune pancreatitis. *Eur J Clin Invest*. 2009;39:714–722.
10. Komatsu M, Yamamoto H, Yasuo M, et al. The utility of serum C-C chemokine ligand 1 in sarcoidosis: a comparison to IgG4-related disease. *Cytokine*. 2020 Sep;133:

155123. https://doi.org/10.1016/j.cyto.2020.155123/Epub/2020/May/21. Erratum in: Cytokine. 2020 Jun 26;:155171. PMID: 32447247.
11. Ozawa Y, Yamamoto H, Yasuo M, et al. A comparison of the features of fluorine-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) between IgG4-related disease with bilateral hilar lymphadenopathy and sarcoidosis. *Nagoya J Med Sci*. 2020 Feb;82(1):101–111. https://doi.org/10.18999/nagjms.82.1.101. PMID: 32273638; PMCID: PMC7103870.
12. Khosroshahi A, Stone JH. Treatment approaches to IgG4-related systemic disease. *Curr Opin Rheumatol*. 2011 Jan;23(1):67–71. https://doi.org/10.1097/BOR.0b013e328341a240. PMID: 21124087.
13. Wang L, Zhang P, Wang M, et al. Failure of remission induction by glucocorticoids alone or in combination with immunosuppressive agents in IgG4-related disease: a prospective study of 215 patients. *Arthritis Res Ther*. 2018 Apr 10;20(1):65. https://doi.org/10.1186/s13075-018-1567-2. PMID: 29636109; PMCID: PMC5894179.
14. Khosroshahi A, Wallace ZS, Crowe JL, et al. Second international symposium on IgG4-related disease. International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheumatol*. 2015 Jul;67(7):1688–1699. https://doi.org/10.1002/art.39132. PMID: 25809420.
15. Carruthers MN, Topazian MD, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. *Ann Rheum Dis*. 2015 Jun;74(6):1171–1177. https://doi.org/10.1136/annrheumdis-2014-206605. Epub 2015 Feb 9. PMID: 25667206.