CASE REPORT

IgG4-related disease presenting as posterior scleritis and vitritis, progressing to multifocal orbital involvement

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SUMMARY

IgG4-related disease (IgG4-RD) is a rare, chronic inflammatory condition that may involve nearly every organ system. Originally identified as a cause of autoimmune pancreatitis, its characteristic histological and clinical features have been found in a wide variety of inflammatory presentations, including the eye and orbit. Here we describe an example of a case of IgG4-RD initially presenting as scleritis and vitritis, with further progression to multifocal bilateral orbital involvement. Tissue biopsy of an orbital mass was highly characteristic of IgG4-RD histology and a rapid clinical response to corticosteroids was observed. This case highlights IgG4-RD as a rare cause of intraocular inflammation that may progress to involve the orbit.

BACKGROUND

IgG4-related disease (IgG4-RD) is a recently described chronic, multisystem inflammatory condition, with a protean clinical presentation.¹ First described in association with autoimmune pancreatitis,² the condition has expanded to incorporate several previously distinct inflammatory conditions.³⁻⁴ This growing list includes IgG4-related orbital disease (IgG4-ROD), an uncommon cause of adnexal benign lymphoproliferative disorders, predominantly affecting the lacrimal gland.⁵ All these manifestations are unified by consistent histological findings of a dense lymphoplasmacytic infiltrate of IgG4-secreting plasma cells,⁶ and are often associated with a raised serum IgG4, and a rapid response to systemic corticosteroids.⁷

We present a case of a scleral, infiltrative lesion which demonstrated radiological, clinical and histological evidence of IgG4-RD. To our knowledge, this is the first example of IgG4-ROD demonstrating initial primary ocular involvement with progression to multifocal orbital disease.

Case presentation

An 82-year-old Caucasian woman presented with reduced vision in the left eye, pain on eye movement and a central scotoma. External examination demonstrated no evidence of extraocular disease. She had undergone uncomplicated left cataract surgery and intraocular lens implant 2 weeks previously, and her past medical history includes long-standing polymyalgia rheumatica, asthma and hypertension.

Figure 1 Images of ocular and orbital IgG4 diseases. (A) and (B) Optomap and optical coherence tomography images demonstrating initial serous retinal detachment. (C) T2-weighted image demonstrating hypointense scleral thickening on initial presentation (arrow). (D) T2 image demonstrating progression, with multifocal hypointense lesions within the left globe and adjacent to the right lamina papyracea (arrows).

INVESTIGATIONS

On examination of her left eye, her Snellen visual acuity was 4/60, with improvement with pinhole to 6/24. There was evidence of mild vitritis and scleritis, with choroidal thickening in association with a choroidal exudative detachment (figure 1a & b). The left eye was without hypopyon, conjunctival injection or anterior chamber leucocytes. B-mode ultrasound demonstrated fluid within sub-Tenon's space (T-sign), indicating the presence of scleritis. MRI of the brain and orbits demonstrated thickening of the left sclera (figure 1c), with no orbital lesions identified at this stage.

An initial diagnosis of a left posterior scleritis was made and oral prednisolone (45 mg once a day) was initiated. This resulted in rapid remission of pain and resolution of the vitritis, choroidal thickening and subretinal fluid, with improvement of visual acuity to 6/18.

On taper of oral corticosteroids 3 months later, the patient presented with a recurrence of scleritis and vitritis, with further visual loss to counting fingers arising from an exudative retinal detachment involving the macula. Full blood count, leucocyte count, erythrocyte sedimentation rate and C reactive protein were normal. Testing for antineutrophil cytoplasmic antibodies, antinuclear antibodies,

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Figure 2 Histopathology of IgG4-related orbital disease. (A) H&E, x 40 and (B) H&E, x 400. The orbital fibrofatty tissue is extensively infiltrated by inflammatory cells, which consist of scattered aggregates of mixed T and B lymphocytes, scattered macrophages and abundant polytypic plasma cells (kappa and lambda immunostains not shown). A moderate number of eosinophils are present. There is focal fibrosis showing a whorled (storiform) pattern. (C) The abundance of plasma cells is confirmed by CD138 immunostaining, x 200. (D) Immunostaining for IgG4. Forty per cent of the IgG+ plasma cells are IgG4+. There were >100 IgG4+ plasma cells per three high power fields. This biopsy specimen therefore meets criteria for IgG4 disease.

rheumatoid factor and ACE were normal or negative, as was a CT chest for hilar lymphadenopathy. Tuberculosis and fungal peripheral venous blood cultures were negative.

MRI of the left orbit demonstrated an increase in scleral thickening, with a homogenous, T2 hypointense mass extending from the subretinal space into the intraconal orbit, involving the optic nerve sheath and extraocular muscles (figure 1d). This lesion demonstrated intermediate T1 signal and minimal restricted water movement on diffusion-weighted imaging, inconsistent with a hypercellular neoplasm. New extraconal masses of identical signal characteristics were noted bilaterally, located along the lamina papyracea.

Positron emission tomography demonstrated mild-to-moderate enhanced fludeoxyglucose (FDG) uptake within each lesion, including both intraocular and extraocular masses, but with no evidence of FDG uptake elsewhere in the body. CT and MRI imaging also demonstrated no evidence of systemic spread.⁸

A diagnostic transcaruncular biopsy of the left extraconal mass demonstrated histopathological features positive for IgG4 disease. This included a dense lymphoplasmacytic infiltrate, storiform fibrosis, >40% IgG4+/IgG ratio and in excess of 30–40 IgG4+-positive cells within a high powered field (figure 2). Serum IgG4 level was 28 mg/dL. There was no malignant infiltrate identified.

Differential diagnosis

- ▶ Intraocular lymphoma
- ▶ IgG4-RD
- ▶ Ocular sarcoidosis
- ▶ Granulomatosis with polyangiitis (Wegener's granulomatosis)

- ▶ Churg-Strauss syndrome
- ▶ Choroidal melanoma with extrascleral spread
- ▶ Non-specific orbital inflammatory disease

TREATMENT

After histological diagnosis of IgG4-RD, immunosuppressive therapy with prednisolone 40 mg and methotrexate 15 mg was initiated. Prednisolone was subsequently reduced to 5 mg once a day.

OUTCOME AND FOLLOW-UP

Repeat MRI conducted 1 month post histological diagnosis and steroid re-introduction demonstrated resolution of both ocular and orbital masses. Her visual acuity in the right eye is 6/6 and remains at light perception in the left eye.

DISCUSSION

Reports of intraocular IgG4-RD consist of at least six separate cases,^{9–14} of which one demonstrates inferior rectus involvement,¹³ and none describe progression to multifocal orbital disease. Scleritis is the presenting feature in five reports,^{9–13} where rapid improvement after the introduction of corticosteroids and disease recurrence after initial steroid reduction are consistent with previous descriptions of systemic IgG4-RD.¹⁵ Treatment with an additional steroid-sparing immunosuppressive agent, usually methotrexate, is sometimes employed,^{9 10 13} and there is one description of the use of rituximab,¹² which is a biological immunotherapy more frequently used as a second agent in IgG4-RD.¹⁶

In common with histopathology reported with other systemic presentations of IgG4-RD, this case demonstrated a dense lymphoplasmacytic infiltrate and storiform fibrosis. In common with other cases of IgG4-RD, we did not detect obliterative phlebitis on biopsy,^{17 18} although this is a significant histological feature in autoimmune pancreatitis.⁶ From previous cases of intraocular IgG4-RD, three report a lack of obliterative phlebitis.^{9 11 14}

A raised serum IgG4 level (>135 mg/dL) was not detected in this patient. Although this is the most common laboratory test performed to diagnose IgG4-RD, a raised serum IgG4 is not present in up to 30% of patients, indicating a reduced sensitivity.¹⁹ This finding may be attributed to the small volumes of tissue involved in scleritis and orbital disease. Our case therefore fulfils the diagnostic criteria for 'probable' IgG4-RD, based on the histological findings of a marked plasma cell infiltration with ratio of ≥40% IgG4/IgG-positive cells and >10 IgG4-positive plasma cells per high powered field (figure 2), as per the most

Learning points

- ▶ IgG4-related disease (IgG4-RD) should be included in the differential diagnosis of inflammatory orbital mass and should be considered as a rare cause of scleritis.
- ▶ IgG4 ocular and orbital diseases display histological and radiological features consistent with IgG4-RD elsewhere within the body.
- ▶ IgG4-related orbital disease is steroid responsive, but additional steroid-sparing immunosuppressive therapy may be required.
- ▶ Early diagnosis and treatment has the potential to halt further visual impact.

recent classification systems for both systemic and ophthalmic disease.^{20 21}

This case illustrates that IgG4-RD may present initially as a highly steroid-sensitive posterior scleritis with the potential to progress to involve multiple ocular tissues simultaneously and bilaterally. Of these, vitreous and choroidal involvements are rarely reported in IgG4-RD but may accompany a severe posterior scleritis.

Contributors GLR was responsible for data collection and analysis and produced the manuscript. JHN and SA were involved in the recovery of the biopsy specimens and provided manuscript review. SS was the primary care provider for the patient and provided final review of the manuscript.

Competing interests None declared.

Patient consent Obtained.

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