IgG4 disease: a revised diagnosis of sarcoidosis after 36 years of treatment

Introduction

IgG4-related disease is a recently recognized systemic disease that has numerous clinical presentations and is characterized by IgG4-positive plasma cell tissue infiltration. This article presents a case of a 63-year-old man with an enlarging right supra-orbital mass that had been present for 36 years. This had previously been diagnosed as sarcoidosis and the mass had continued to grow despite glucocorticoid therapy. Multiple lesions were found on his hard palate and false vocal cords when he developed new symptoms and biopsies of these lesions revealed thickly encapsulated nodules of lymphoid tissue. He continued to deteriorate and only after specialist immunohistochemical staining for IgG4 was the diagnosis finally made. He was subsequently started on glucocorticoids and immunomodulation which resulted in improvement of his symptoms and no new lesions developing.

This case illustrates an important presentation of this elusive disease and reiterates the importance of maintaining a high-index of suspicion when encountering similarly difficult presentations.

Discussion

IgG4-related disease is characterized by IgG4-positive plasma cell tissue infiltration, often with high serum IgG4. It was first described by Kamisawa et al (2003) who identified that a subset of patients with autoimmune pancreatitis had extra-pancreatic manifestations. Numerous other tissues have since been identified as being involved in this multi-system disease and the list is constantly expanding (Kamisawa et al, 2006). It can present with an enigmatic myriad of seemingly unconnected symptoms and remains a major diagnostic challenge unless specifically considered.

The diagnosis of IgG4-related disease requires careful histological analysis of biopsy specimens for dense lymphoplasmacytic infiltrates in an irregular whorled pattern, eosinophil infiltration and obliterative phlebitis (Zen and Nakanuma, 2010). Elevated IgG4 concentration in tissue or serum samples may increase one's suspicion of IgG4-related disease, but it is not a specific diagnostic marker and should be interpreted with caution if the histological appearances are atypical (Strehl et al, 2011).

This case highlights the importance of considering this elusive and novel disease. It has numerous presentations, affects multiple organ systems and is easily mistaken for

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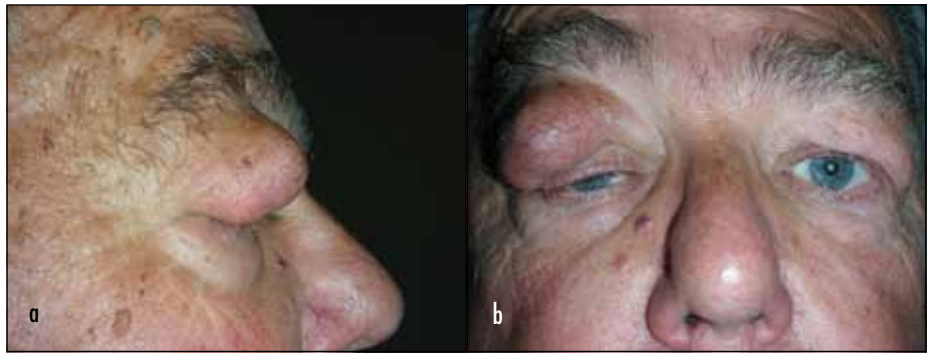
Figure 1. a. Frontal and (b) lateral view of orbital mass at presentation.



Case Report

This case describes a 63-year-old man, with a slowly enlarging right supra-orbital mass present for 36 years. He originally presented at the age of 27 years, when positive Kveim testing and orbital biopsy suggested sarcoidosis. He received long-term glucocorticoids that reduced the mass growth, but it continued to enlarge and slowly encroached upon his visual field measuring 2.5 cm in diameter and extending 3 cm beyond the orbital rim (*Figures 1a* and *b*). Visual acuity and eye movements were unaffected and there was no proptosis or alteration of periocular sensation. On subsequent review the diagnosis of sarcoidosis was questioned as there was no evidence of pulmonary sarcoidosis on imaging and the orbital mass was highly atypical of extrapulmonary sarcoidosis.

The steroids were therefore tapered and excision biopsy performed (*Figure 2a*) within the month, during which the supra-orbital nerve was sacrificed as it coursed through the centre of the mass and appeared intimately involved. Histology revealed a thickly encapsulated nodule of lymphoid tissue with mature plasma cells and inconclusive immunohistochemical-staining. Discussion at the regional lymphoma multidisciplinary team meeting concluded that it likely represented an inflammatory pseudo-tumour.

Over the next year he developed hoarseness of voice, dysphagia and upper jaw pain. False vocal cord and large hard palate lesions were discovered and further biopsies again confirmed a reactive lymphoid process (*Figure 2b*). He continued to experience symptoms from the enlarging lesions and was referred for tertiary centre review 18 months after his first biopsy. IgG4-related disease was diagnosed after biopsies revealed dense lymphoplasmacytic infiltrates and >50/high-power-field IgG4-positive plasma cells; serum immunoelectrophoresis confirmed a 12-fold increase in the IgG4 subset. He was started on steroids and methotrexate and made an excellent recovery with no recurrence of the head or neck masses (*Figure 3*).

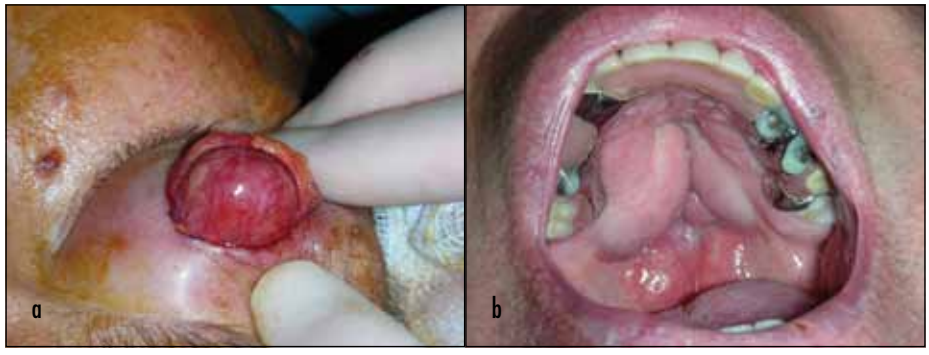


Figure 2. Appearance of (a) orbital and (b) hard palate masses.

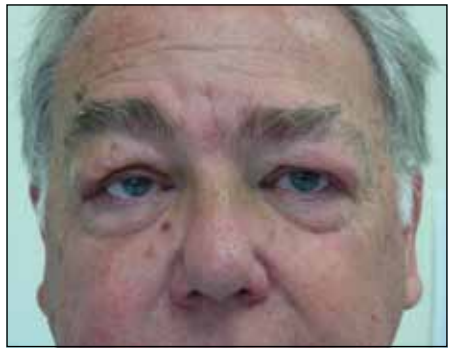


Figure 3. Postoperative appearance with no recurrence of orbital mass.

alternative diagnoses. The prognosis remains uncertain, but efficient multidisciplinary team working is pivotal. Long-term glucocorticoids, with or without immunomodulation, remain the mainstay of management at present (Khosroshahi and Stone, 2011) although systematic evaluation of their relative efficacies is required. **BJHM**

Kamisawa T, Funata N, Hayashi Y et al (2003) A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* **38**(10): 982–4
Kamisawa T, Nakajima H, Egawa N, Funata N, Tsuruta K, Okamoto A (2006) IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. *Pancreatology* **6**(1-2): 132–7
Khosroshahi A, Stone JH (2011) Treatment approaches to IgG4-related systemic disease. *Curr Opin Rheumatol* **23**(1): 67–71
Strehl JD, Hartmann A, Agaimy A (2011) Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. *J Clin Pathol* **64**(3): 237–43
Zen Y, Nakanuma Y (2010) IgG4-related disease: a cross-sectional study of 114 cases. *Am J Surg Pathol* **34**(12): 1812–19

LEARNING POINTS

- This case reminds the clinician to have a high index of suspicion for this novel, elusive disease when presented with a patient with unexplained symptoms.
- Specialist IgG4 staining needs to be requested on samples sent for histopathological analysis.
- Serum immunoglobulin electrophoresis may be of benefit in the diagnosis of this disease.

Norwegian scabies

An 87-year-old woman from a residential home presented with a 2-week history of worsening generalized pruritus. Her past medical history includes asteatotic eczema, recurrent urinary tract infections, and breast cancer.

Examination showed a generalized dry skin with scaling and erythematous macular rash not involving the oral or eye mucosa. She was started on emollients and topical steroids with little improvement.

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Over 2 weeks, the condition progressed with development of crusted hyperkeratotic lesions (*Figure 1*) on her palms, soles, nails, scalp and ears, and an erythematous, scaly macular eczematous rash on the trunk with associated fever.

Infection screen showed blood eosinophilia and blood cultures were positive for meticillin-resistant *Staphylococcus aureus*. Direct microscopy of skin scrapings from her palms showed *Sarcoptes scabiei* mites. Skin biopsy also showed *Sarcoptes scabiei* mites on the left palm and diffuse inflammatory infiltrate on the trunk. A computed tomography scan of the chest, abdomen and pelvis ruled out any underlying solid organ malignancy. She dramatically improved on treatment with teicoplanin and topical permethrin (*Figure 2*). Ivermectin was used during follow up to achieve cure. **BJHM**

Figure 1. Before treatment.

Figure 2. After treatment.