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SHORT COMMUNICATION

Idiopathic sclerosing inflammation of the orbit: A case of steroid-responsive disease in a patient with autoimmune hemolytic anemia

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PURPOSE. *Idiopathic sclerosing orbital inflammation (ISOI) has been categorized by some authors as a unique clinicopathologic entity, separate from the heterogenous group of disorders known collectively as nonspecific orbital inflammation. Histologic similarity and clinical association with other fibrosclerosing conditions has been shown. The authors present a case of ISOI in conjunction with autoimmune hemolytic anemia.*

METHODS. *A 59-year-old woman with a history of hemolytic anemia had left upper lid swelling, periocular pain, proptosis, and restriction of ocular motility. Magnetic resonance imaging (MRI) showed a homogenously enhancing lateral orbital mass. Biopsy revealed dense fibrous connective tissue with a paucicellular infiltrate, consistent with ISOI, and treatment with prednisolone 60 mg/day was instituted.*

RESULTS. *At 4-week review, the proptosis had settled and the patient regained full range of extraocular movements. At 14 months, the response was sustained and repeat MRI showed a 70% reduction in size of the mass.*

CONCLUSIONS. *The first known case of ISOI and hemolytic anemia is presented. Despite dense fibrosis histologically, steroid responsiveness can be encountered in cases of ISOI. An early, aggressive approach to management is recommended, and corticosteroids should be considered as a treatment option. (Eur J Ophthalmol 2005; 15: 263-6)*

KEY WORDS. *Idiopathic sclerosing orbital inflammation, Hemolytic anemia, Steroid, Histopathology*

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Case report

A 59-year-old woman had a 4-month history of a gradually enlarging left orbital mass. She complained of increasing left periocular pain and headache, redness, and diplopia. This was associated with left lid swelling, ptosis, proptosis, and restricted ocular motility in all directions of gaze.

Past medical history included indirect Coombs positive hemolytic anemia, associated with a positive cardiolipin and antinuclear autoantibody status, as well as hypertension, type II diabetes mellitus, and asthma.

Examination revealed visual acuities of 6/12 bilaterally. All extraocular movements of the left eye were restricted, especially in up and lateral gaze. Left upper periorbital swelling was evident with a mechanical ptosis, and 3 mm of axial proptosis. The remainder of the orbital and ophthalmic examination was unremarkable.

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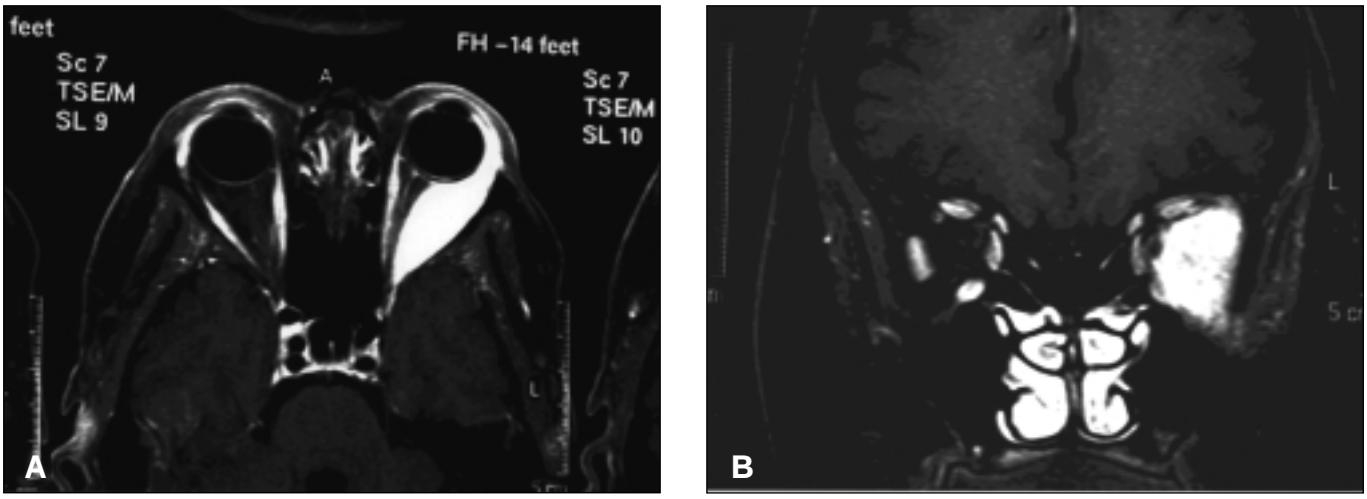

Fig. 1 - *Magnetic resonance imaging scan (T1 fat suppression, contrast enhancement).* **(A)** *Axial section showing homogenously enhancing lateral orbital mass extending to the apex.* **(B)** *Coronal section showing the mass involving the lateral rectus and lacrimal gland in the lateral orbit.*

Magnetic resonance imaging (MRI) revealed a homogeneously enhancing left lateral orbital mass, 4.5 x 1.5 cm in size, indistinguishable from the lateral rectus muscle (Fig. 1). Biopsy, via a swinging eyelid approach, revealed a dense fibrous stroma with paucicellular nonspecific lymphoid and plasma cell infiltrate, with cytologic analysis revealing a minimally atypical lymphoid population. Immunoperoxidase staining demonstrated a polyclonal population of kappa and lambda light chains. There were insufficient cells for flow cytometry. Bone marrow biopsy was normal, and computerized tomography of her chest and abdomen revealed no other abnormality.

Pathologic opinion was unclear at this stage whether the lesion was idiopathic sclerosing orbital inflammation (ISOI) or a sclerosing lymphoma. Hence, repeat biopsy was performed via a lateral orbitotomy, to obtain further tissue for analysis. Intraoperatively, the orbital mass was found to involve the lateral orbit and was composed of extremely fibrous, white, woody tissue. Histologic analysis revealed dense fibrous connective tissue with a mixed paucicellular infiltrate of lymphocytes, plasma cells, and very occasional eosinophils (Fig. 2). Polymerase chain reaction showed no evidence of JH (B-cell) rearrangement, and immunocytochemical analysis revealed no evidence of a monoclonal lymphoid population. Flow cytometry revealed raised levels of B-cell markers CD19 (56%) and CD20 (49%). The results were reviewed by two senior pathologists who confirmed the diagnosis of sclerosing orbital inflammation.

The patient was started on oral prednisolone 60 mg/day following the orbital biopsy. She was reviewed 1 week following this, and restriction in left extraocular movement had improved. The steroid was tapered slowly and she was reviewed again at 4 weeks following the biopsy. Again, remarkable improvement was seen, with no clinical evidence of proptosis and full extraocular muscle movements. Review 11 weeks after steroid treatment began showed no disease recurrence. A repeat MRI revealed that the orbital mass had decreased by 70% in size.

While on steroid therapy, the patient's hemoglobin level increased from 88 g/L to 124 g/L (Normal Range (R) 115–160) and her reticulocyte count decreased from 280 x 109 g/L to 126 x 109 g/L (R 20–100), indicating control of her hemolytic anemia. At last follow-up, 14 months later, there was no clinical evidence of recurrent orbital disease.

DISCUSSION

Over the past 20 years, ISOI has gained increasing recognition as a distinct clinicopathologic entity, separate from the heterogenous group of conditions classed as nonspecific orbital inflammation (NSOI) or orbital pseudotumor (1-3). However, the terminology surrounding sclerosing and other NSOI is still not clearly defined, with some authors referring to ISOI as sclerosing pseudotumor (4).

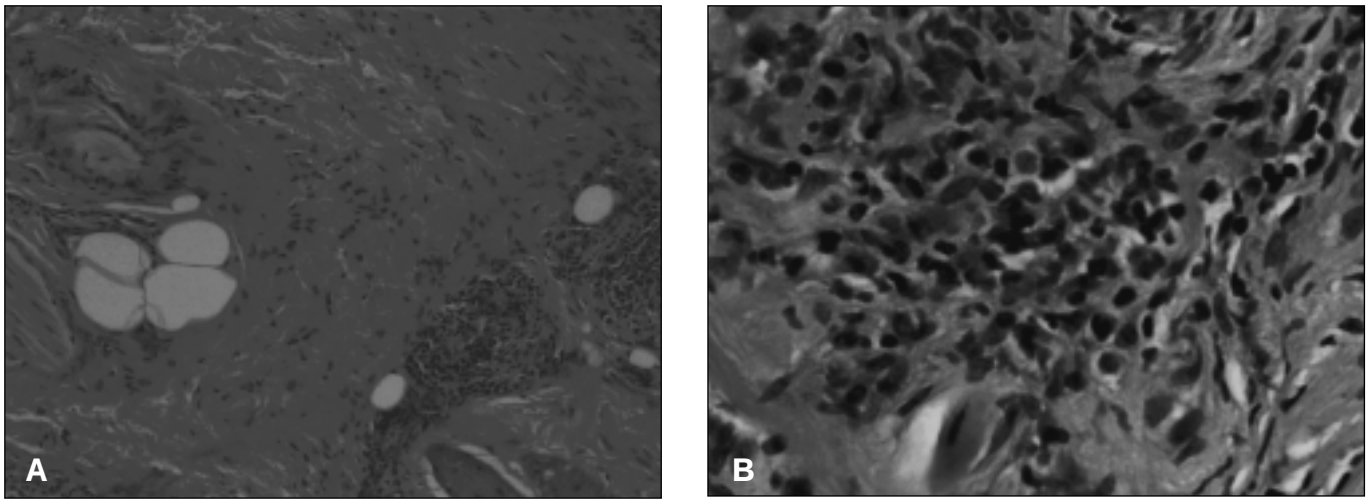

Fig. 2 - *Histologic specimen. Hematoxylin and eosin stain.* **(A)** *Orbital biopsy showing dense fibrous connective tissue and inflammation. Magnification x100.* **(B)** *Orbital biopsy showing infiltrate containing lymphocytes, plasma cells, and occasional eosinophils. Magnification x400.*

ISOI typically presents no later than cases of NSOI, which helps to negate alternate theories that sclerosing lesions were along a continuum with cases of NSOI, and represented the end stages of chronic inflammation (1).

It is unlike NSOI in that it tends to occur in a younger population, and is more likely to affect the orbital apex (3). Clinical features at presentation are typically orbital pain, headache, lid swelling, proptosis, and restriction of extraocular movements (1). Ptosis and a mild-to-significant reduction in visual acuity are also commonly seen (1).

Histologically, the disease is typified by dense, fibrous connective tissue, often with a paucicellular infiltrate consisting of lymphocytes, plasma cells, histiocytes, and eosinophils (5). Immunohistochemical analysis reveals a polyclonal lymphoid population, with an abundance of T-cells (6). The histologic appearance and immunohistochemical analyses of these lesions have more in common with idiopathic retroperitoneal fibrosis, and cases of multifocal fibrosclerosis, than NSOI (5).

ISOI has been described in conjunction with retroperitoneal fibrosis, mediastinal fibrosis, Reidel's thyroiditis (7), and sclerosing cholangitis (7, 8), lending further support to the theory that ISOI and multifocal fibrosclerosis share a common pathogenesis.

Autoimmune hemolytic anemia has been described in association with primary sclerosing cholangitis and a common pathologic process has been suggested (9, 10). This is the first case of autoimmune hemolytic anemia described in association with ISOI and, again, a common pathogenic process may be implicated. Recent immunohistochemical studies of ISOI specimens have revealed a predominance of T-cell populations, suggesting the underlying process is an immune-mediated one (5). The implementation of immunosuppressive agents such as azathioprine, methotrexate, and cyclosporine has been suggested as a theoretically more appropriate treatment strategy, but as yet, clinical evidence of their benefit has not yet been conclusive (1).

Typically, the disease is insidious, progressive, and difficult to treat. Intracranial extension has been described, and exenteration for a painful, blind eye is not uncommon (11). ISOI generally shows an incomplete or unsustained response to conventional treatment modalities, namely surgical excision, steroid therapy, or radiation therapy (3).

Numerous authors have described disease progression despite aggressive corticosteroid therapy (1, 3, 8, 11, 12). Steroid therapy has been shown to initially relieve symptoms and cause disease regression, but this result is generally not sustained (2). Adjunctive use of radiotherapy appears to stabilize the disease or improve results in some cases; however, relentless disease is also commonly seen, despite this (1, 6, 13). Chemotherapeutic agents have been suggested as potentially effective disease modifiers, and Rootman, reviewing 16 cases of ISOI, recommends first line treatment of azathioprine, cyclophosphamide, methotrexate, or cyclosporine, plus systemic corticosteroid (14). Results of the effectiveness of these agents, directed at T-cell and B-cell function, is not yet

compelling. ISOI disease progression has been halted by the use of radiotherapy and azathioprine (1, 6). Uy described ISOI progression despite systemic steroid and cyclophosphamide administration, resulting in exenteration (12). Rootman et al describe two cases treated with cyclophosphamide, plus systemic steroid and radiotherapy. One patient improved and stabilized, while the other continued to progress with further loss of vision (1).

Kennerdell states that fibrotic tissue seen histopathologically will not regress (15), and some authors share this intuitive view, opting not to trial steroid therapy in histologically dense, sclerotic lesions (4). Our case, despite a densely sclerotic appearance histologically, exhibited a dramatic and sustained response to systemic corticosteroid therapy only. This suggests that incongruity may exist between the histologic appearance of ISOI and its response to treatment, thus making estimates of responsiveness to various treatment modalities difficult and unpredictable.

Until the effectiveness of chemotherapeutic agents is proven further, corticosteroids should still be considered in the treatment of sclerosing orbital inflammation, prior to the institution of agents such as azathioprine, cyclosporine, or methotrexate.

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