EXTENDED REPORT

Idiopathic orbital inflammatory syndrome: Clinical features and treatment outcomes

B N Swamy, P McCluskey, A Nemet, R Crouch, P Martin, R Benger, R Ghabriel, D Wakefield

Br J Ophthalmol 2007;**91**:1667–1670. doi: 10.1136/bjo.2007.124156

See end of article for authors' affiliations

Correspondence to: Professor Peter McCluskey, Department of Ophthalmology, Liverpool Hospital, Liverpool NSW 2170, Australia; peter.mccluskey2@sswahs.nsw.gov.au

Accepted 1 June 2007
Published Online First 10 July 2007

Aim: To characterise the clinical and pathological features of 24 patients with biopsy proven Idiopathic Orbital Inflammatory Syndrome (IOIS).
Methods: Retrospective case series.
Results: The study included 14 men and 10 female patients, ranging in age from 14 to 75 years. The presenting symptoms and signs included pain (14/24), swelling/mass (19/24), diplopia (9/24), proptosis (15/24), extraocular muscle restriction (13/24), decreased vision (5/24) and ptosis (4/24). Histopathology was varied and included classical orbital pseudotumour (9/24), sclerosing orbital pseudotumour (13/24), vasculitic orbital pseudotumour (1/24) and granulomatous orbital pseudotumour (1/24). Treatments included oral steroids (19/24), intravenous steroids (1/24), methotrexate, azathioprine, mycophenalate and ciclosporin. Forty-two per cent of the patients had recurring episodes during the follow-up period, with 29% of patients requiring two or more treatment regimens to maintain remission. Two-thirds of patients (16/24) had complete resolution of their symptoms and signs. There was no correlation between the histopathological subtype, relapse rate or symptoms and resolution of signs.
Conclusion: Idiopathic Orbital Inflammatory Syndrome has variable clinical and pathological features. Although, in some patients, symptoms and signs resolve spontaneously, most require treatment with oral steroids and additional immunosuppressant drugs or radiotherapy. The clinical and pathological features do not correlate with treatment outcomes.

Idiopathic orbital inflammatory syndrome (IOIS), also known as orbital pseudotumour, is a heterogeneous group of disorders characterised by orbital inflammation without any identifiable local or systemic causes. It is a rare clinical entity and a diagnosis of exclusion.[1] There have been various classification systems proposed, but due to the highly variable clinical and pathological features of IOIS, none are universally accepted and used.[2–4] IOIS can affect any structure in the orbit, and the presentation can range from abrupt to insidious onset. Although IOIS is typically steroid-responsive, it is a difficult condition to treat, with many patients requiring multiple systemic immunosuppressant drugs and radiotherapy. Disease relapse is common.

The diagnosis of IOIS is often made on the basis of the clinical response to systemic corticosteroids. Significantly, many different orbital lesions, including thyroid eye disease and malignancy, may respond to corticosteroids, and so a histological diagnosis is considered important by most clinicians. The aim of this study was to characterise the clinical features, histopathology and treatment outcomes in patients with biopsy proven IOIS.

MATERIAL AND METHODS

The medical records of 98 patients with clinical diagnosis of IOIS or orbital pseudotumour diagnosed at the Sydney Eye Hospital between 1995 and 2005 were reviewed. The inclusion criteria included a confirmed histopathological diagnosis of IOIS and a minimum follow-up of 6 months to observe response to treatment. Seventy-four patients with diagnosis of IOIS but without a confirmed histopathological diagnosis were excluded from the review. Twenty-four patients had biopsy proven IOIS, and all of them met the minimum follow-up requirements. Approval for the study was obtained from the Sydney Eastern Sydney Illawarra Area Health Service Human Research and Ethics Committee.

The data extracted included age, gender, country of birth, signs and symptoms, surgical and radiological features, histopathological features, clinical course, treatment regimen and outcome. Follow-up information was collected from individual treating ophthalmologists. Due to the variable amount of follow-up, outcome measures in terms of relapses were reported as incidence rates (ie, relapse/person-years of follow-up).[5]

Clinical course was correlated with histopathology to delineate appropriate treatment regimens and prognosis. Statistical analyses were performed using SAS version 9 software (SAS, Cary, NC).

RESULTS

The 24 patients ranged in age from 14 to 75 years (mean 45.2 years); 14 were male, and 10 were female. The left eye was affected in 13 patients, right eye in 10 patients and both eyes in one patient.

The median duration of symptoms prior to presentation was 4 weeks (range 0.3–12 weeks). The patients presented with a range of signs and symptoms. A swelling/mass was the most common presentation followed by proptosis, pain, extraocular muscle restriction, diplopia, ptosis and decreased vision. Table 1 summarises the clinical signs and symptoms at presentation. Anatomically, orbital fat was the most commonly involved orbital structure followed by lacrimal gland and extraocular muscle. Table 2 summarises the different orbital structures involved at presentation. Most patients presented with unilateral disease (23/24), while one patient had bilateral involvement. All patients had an initial investigation by computed tomography (CT), and subsequently 46% (11/24) were examined by magnetic resonance imaging.

Abbreviation: IOIS, idiopathic orbital inflammatory syndrome

Table 1 Signs and symptoms at presentation

Sign or symptom	Percentage of patients with signs or symptoms
Pain	58.3 (14/24)
Swelling/mass	79.2 (19/24)
Diplopia	37.5 (9/24)
Proptosis	62.5 (15/24)
EOM restriction	54.2 (13/24)
Decreased vision/RAPD	20.8 (5/24)
Ptosis	16.7 (4/27)

EOM, extraocular movement; RAPD, reactive afferent papillary defect.

Table 2 Orbital site involved

Orbital site of pseudotumour	Percentage of patients
Lacrimal gland	54.2 (13/24)
Extraocular muscle	50.0 (12/24)
Orbital fat	75.0 (18/24)
Sclera	4.2 (1/24)
Optic nerve	20.8 (5/24)
Other*	8.3 (2/27)

*One patient had eyelid mass, and one patient had a medial canthal mass.

Histopathology

The classification system described by Mombaerts has been used in the current study, as it is widely accepted for classifying IOIS.[2]

In nine of the patients, the cellular infiltrate, the stromal component and the vascular changes were consistent with ''classical orbital pseudotumour'' (fig 1). This cellular infiltrate consisted of inflammatory cells, mainly of mature lymphocytes, admixed with plasma cells, neutrophils, eosinophils and occasionally macrophages and histiocytes. Consistent with classical orbital pseudotumour, there was an increase in the amount of connective tissue with variable amounts of tissue oedema and fibrosis. There was a mixture of chronic inflammatory cells surrounding the blood vessels. In 13 of the 24 cases, the diagnosis was that of ''idiopathic sclerosing orbital inflammation''. In these patients, connective tissue sclerosis and hyalinisation predominated with a paucity of inflammatory cells (fig 2). In one patient, the histopathological features were consistent with a ''granulomatous orbital pseudotumour'' with lesion characterised by histiocytic infiltration and multinucleated giant cells. In one case, the histology revealed a ''vasculitic orbital pseudotumour'' with a vasculitis of the small blood vessels the defining feature. Four patients who had been initially diagnosed as having classical orbital pseudotumour later developed the sclerosing subtype. Table 3 summarises the histopathological diagnoses.

One patient developed a retrobulbar haemorrhage after biopsy, and one further patient had a CSF leak following orbital decompression and biopsy, which subsequently required surgical repair.

Therapy consisted of observation alone, antibiotics, oral corticosteroids, intravenous corticosteroids and systemic immunosuppressive drugs. In a majority of the patients, oral steroids (19/24) were the initial treatment, and doses ranged from 50 to 100 mg/day. Seven patients required treatment with additional immunosuppressant drugs to control the inflammatory process. The drugs used included methotrexate, azathioprine, mycophenolate and ciclosporin. In five patients, there was resolution of the signs and symptoms without treatment, and in half of the patients the disease process was brought under control with the use of one medication. Nearly a third of the patients (7/24) needed two or more medications to bring the disease into remission (tables 4 and 5). Two patients had adjunctive radiotherapy (dose of 20 Gy in 10 fractions) to treat persistent, relapsing inflammation despite immunosuppressant drugs. Two out of 13 (15%) patients diagnosed as having ''sclerosing orbital pseudotumour'' needed two or more medications to induce remission; four out of nine (44%) patients diagnosed as having ''classical orbital pseudotumour'' needed two or more medications to control their disease.

The follow-up period was variable, with a range of 6–120 months (median 23 months). Ten patients suffered relapses within the follow-up period. The rate of relapse was 0.18/person-year. Surprisingly, the relapse rate for those with classical orbital pseudotumour was 0.29/person-year, and for those with sclerosing orbital pseudotumour 0.15/person-year. The patients with granulomatous pseudotumour and vasculitic pseudotumour had no relapses during their follow-up period.

Two-thirds of the patients (16/24) had complete resolution of their signs and symptoms; 6/9 (67%) of those diagnosed as having classical pseudotumour and 8/13 (62%) diagnosed as having sclerosing orbital pseudotumour. There was partial resolution of signs/symptoms in 17% of patients (4/24), while 17% (4/24) patients had no improvement in their symptoms/signs.

DISCUSSION

IOIS is a diagnosis that is made following careful investigations to exclude common orbital tumours, thyroid eye disease and systemic causes of inflammatory mass lesions.[6] IOIS accounts for approximately 10% of all orbital ''tumours''.[7 8] It is likely that the aetiology in IOIS is autoimmune in origin with viral, genetic and environmental factors proposed as possible trigger factors.[1 2 9–11]

The current study confirms that IOIS can present with a range of clinical manifestations, is typically unilateral developing over days to weeks, and has no gender, age or racial predilection in the Australian population. There is a mixture of infiltrative and inflammatory signs and symptoms, including: swelling, pain, proptosis, extraocular muscle restriction, diplopia, decreased vision and ptosis. Any orbital structure can be involved either focally or in a diffuse manner, with orbital fat, lacrimal gland and the extraocular muscles the common sites of involvement. Relapses are common during the course of the disease.

IOIS is often diagnosed on the basis of a rapid response to a trial of systemic corticosteroid treatment, as was the case in the 74 patients originally considered for inclusion in the study.[12] A rapid response to corticosteroids, although a useful diagnostic indicator, is not diagnostic. A number of studies have reported steroid unresponsive idiopathic inflammatory orbital tumours, and thyroid eye disease and malignant eye disease may respond to steroid therapy initially.[2] It is recommended that a biopsy be performed to confirm the diagnosis of IOIS, except in the case of pure myositic locations and posteriorly located tumours where there is a significant risk of damage to the optic nerve.[2] We included only biopsy proven cases in this study to correlate clinical and pathological features. It is not possible to identify the indications for biopsy in the group of patients initially considered for inclusion in the study. It is tempting to speculate that patients who underwent biopsy were those with either severe or atypical clinical features.

Initial investigation should include a careful history and complete physical examination followed by full blood count, ESR, CRP and radiology with a CT and/or MRI scan of the affected orbit. Further investigation depends on the individual clinical features. The indications for treatment of IOIS are threat to vision, pain or loss of function. There is often good

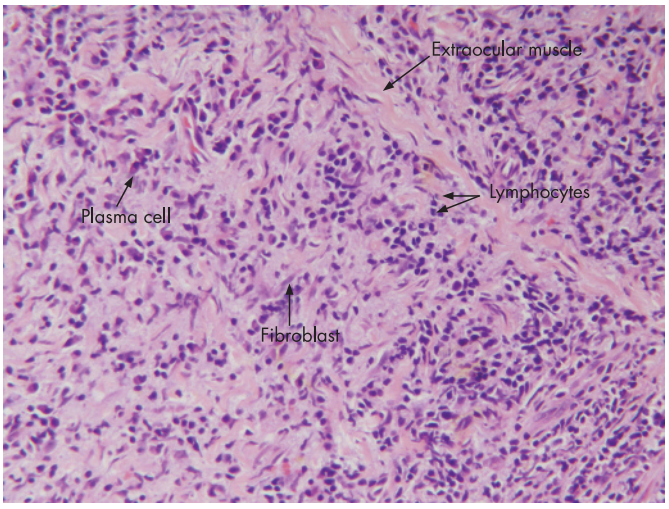

Figure 1 Classical idiopathic orbital inflammatory disease.

resolution of signs and symptoms with steroid therapy.[13] Additional immunosuppressant drugs and or radiotherapy are necessary when the response to steroids is unsatisfactory.[1 14] IOIS can be difficult to manage, with approximately a third of the patient needing two or more immunosuppressant drugs to control disease. Immunosuppressant drugs found to be effective in the treatment of IOIS include: azathioprine, methotrexate, mycophenolate and ciclosporin. There is no consensus on treatment protocol, and choice of therapy needs to be individualised by ophthalmologists and physicians with experience in using these drugs in ocular inflammatory disease.[15]

There is no agreement regarding a histopathological classification for IOIS. Some consider sclerosing orbital pseudotumour a distinct clinicopathological entity that may be related to systemic fibrotic disorders such as retroperitoneal fibrosis.[6 15–19] Others aver that while classical orbital pseudotumour lesions demonstrate a fibroinflammatory infiltrate, lesions with atypical histopathological patterns such as extensive sclerosis, vasculitis, granulomatous inflammation and tissue eosinophilia represent subgroups within the umbrella diagnosis of IOIS.[2 20] In keeping with this view, three patients in this study who had been initially diagnosed as having classical orbital pseudotumour later went on to to develop sclerosing orbital pseudotumour. Whether sclerosing orbital pseudotumour is a separate clinical entity or represents a ''healing phase'' of IOIS or is part of a systemic disease process, remains to be elucidated. This distinction is important for the clinician, as the disease progression, prognosis and treatment modalities may be different, depending on the histopathological diagnosis.

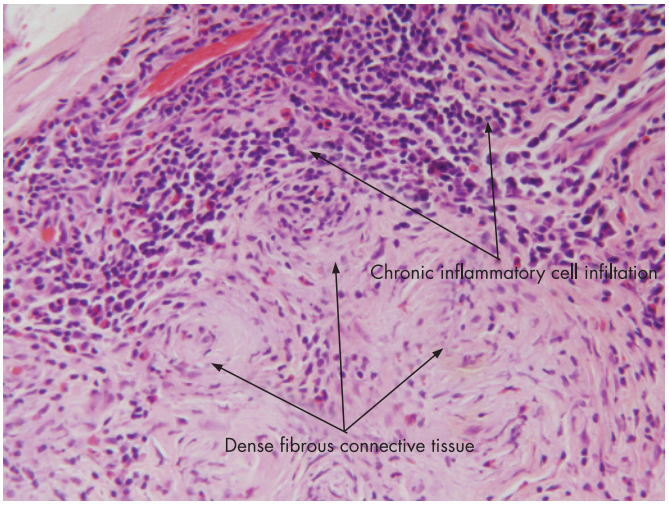

Figure 2 Sclerosing orbital inflammatory disease.

Table 3 Histopathological diagnosis

Histopathology	Percentage of patients
Classical orbital pseudotumour	41.2 (9/24)
Sclerosing orbital pseudotumour*	50.0 (13/24)
Granulomatous orbital pseudotumour	4.1 (1/24)
Vasculitic orbital pseudotumour	4.1 (1/24)
Eosinophilic orbital pseudotumour	0 (0/24)

*Three patients developed classical orbital pseudotumour in the first biopsy and subsequently diagnosed as having the sclerosing form in a repeat biopsy.

Table 4 Treatment received for the management of IOIS

Treatment received	Percentage of patients
Observation alone	20.8 (5/24)
Antibiotics	41.2 (10/24)
Steroid oral	79.2 (19/24)
Steroid intravenous	4.2 (1/24)
Other chemotherapeutic agent*	29.2 (7/24)

*Methotrexate, azathioprine, mycophenalate or ciclosporin.

Table 5 Number of drugs used to maintain remission

No. of drugs	Percentage of patients
0	20.8 (5/24)
1	50.0 (12/24)
2	25.0 (6/24)
⩾3	4.2 (1/24)

The present study findings are not consistent with the view that sclerosing and vasculitic orbital pseudotumours exhibit aggressive behaviour and have a poorer prognosis. In this case series, the rate of relapses among classical orbital pseudotumour was 0.29/person-year follow-up, and this was higher than those with a sclerosing orbital pseudotumour (0.15/person-year of follow-up). Additionally, clinical resolution was achieved in two-thirds of the patients, regardless of the histopathological classification.

This study has a number of significant limitations, as it was a small retrospective case series. The patients were selected from a tertiary referral hospital with resultant selection bias. Further, three-quarters of the patients initially considered for inclusion in the study did not have a biopsy to confirm the diagnosis and were excluded. It is likely that the patients who had a biopsy were patients with atypical or severe clinical features, and this may introduce a bias to the study population. The results of the study need to be interpreted with caution, given its retrospective design and the multiple potential types of bias inherent in such studies. The larger prospective study required to characterise the clinical and histopathological patterns involved in IOIS would be extremely difficult to perform, and management decisions continue to rely on data from small selective studies such as ours.

CONTRIBUTIONS OF AUTHORS

BS and PMc designed and conducted the study; BS collected and managed the data; BS and PMc analysed and interpretated the data,

and prepared the manuscript; PMc, AN, RC, PM, RB, RG and DW reviewed and approved the manuscript.

Authors' affiliations

B N Swamy, A Nemet, P Martin, R Benger, R Ghabriel, Sydney Eye Hospital, Sydney, Australia
R Crouch, D Wakefield, School of Pathology, UNSW, Sydney, Australia
P McCluskey, Department of Ophthalmology, Liverpool, Sydney, Australia

Funding/support: Nil. Financial disclosures: None

Competing interests: None declared.

REFERENCES

1 **Jacobs D**, Galetta S. Diagnosis and management of orbital pseudotumour. *Curr Opin Ophthalmol* 2002;**13**:347–51.
2 **Mombaerts I**, Goldschmeding R, Schlingemann RO, Koornneef L. What is orbital pseudotumour? *Surv Ophthalmol* 1996;**41**:66–78.
3 **Rootman J**, Nugent R. The classification and management of acute orbital pseudotumours. *Ophthalmology* 1982;**89**:1040–8.
4 **Fujii H**, Fujisada H, Kondo T, *et al*. Orbital pseudotumour: histopathological classification and treatment. *Ophthalmologica* 1985;**190**:230–42.
5 **Jabs DA**. Improving the reporting of clinical case series. *Am J Ophthalmol* 2005;**139**:900–5.
6 **Zborowska B**, Ghabrial R, Selva D, *et al*. Idiopathic orbital inflammation with extraorbital extension: case series and review. *Eye* 2006;**20**:107–13.
7 **Shikishima K**, Kawai K, Kitahara K. Pathological evaluation of orbital tumours in Japan: analysis of a large case series and 1379 cases reported in the Japanese literature. *Clin Exp Ophthalmol* 2006;**34**:239–44.
8 **Rose GE**, Wright JE. Exenteration for benign orbital disease. *Br J Ophthalmol* 1994;**78**:14–8.
9 **Kennerdell JS**, Dresner SC. The nonspecific orbital inflammatory syndromes. Survey of *Ophthalmology*, 1984;**29**:93–103.
10 **Yuen SJA**, Rubin PAD. Idiopathic orbital inflammation: ocular mechanisms and clinicopathology. *Ophthalmol Clin North Am* 2002;**15**:121–6.
11 **Mombaerts I**, Koornneef L. Current status in the treatment of orbital myositis. *Ophthalmology* 1997;**104**:402–8.
12 **Leone CR Jr**, Lloyd WC 3rd. Treatment protocol for orbital inflammatory disease. *Ophthalmology* 1985;**92**:1325–31.
13 **Mombaerts I**, Schlingemann RO, Goldschmeding R, *et al*. Are systemic corticosteroids useful in the management of orbital pseudotumours? [see comment]. *Ophthalmology* 1996;**103**:521–8.
14 **Orcutt JC**, Garner A, Henk JM, *et al*. Treatment of idiopathic inflammatory orbital pseudotumours by radiotherapy. *Br J Ophthalmol* 1983;**67**:570–4.
15 **Rootman J**, McCarthy M, White V, *et al*. Idiopathic sclerosing inflammation of the orbit. A distinct clinicopathologic entity. *Ophthalmology* 1994;**101**:570–84.
16 **Abramovitz JN**, Kasdon DL, Sutula F, *et al*. Sclerosing orbital pseudotumour. *Neurosurgery* 1983;**12**:463–8.
17 **Weissler MC**, Miller E, Fortune MA. Sclerosing orbital pseudotumour: a unique clinicopathologic entity. *Ann Otol Rhinol Laryngol* 1989;**98**:496–501.
18 **Vaglio A**, Salvarani C, Buzio C. Retroperitoneal fibrosis. *Lancet* 2006;**367**:241–51.
19 **McCarthy JM**, White VA, Harris G, *et al*. Idiopathic sclerosing inflammation of the orbit: immunohistologic analysis and comparison with retroperitoneal fibrosis. *Mod Pathol* 1993;**6**:581–7.
20 **Raskin EM**, McCormick SA, Maher EA, *et al*. Granulomatous idiopathic orbital inflammation. *Ophthal Plast Reconstr Surg* 1995;**11**:131–5.