Orbital involvement in multifocal fibrosclerosis


Abstract
Multifocal fibrosclerosis is a condition of unknown aetiology, characterised by fibrous lesions occurring at a variety of sites. Clinical variants include retroperitoneal fibrosis, Riedel's thyroiditis, sclerosing cholangitis, and mediastinal fibrosis. Orbital pseudotumour has been reported as a manifestation of this condition. Three patients with multifocal fibrosclerosis in whom orbital involvement was the dominant feature are described.

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A link between retroperitoneal fibrosis, Riedel's thyroiditis, and orbital pseudotumour was first suggested by Barrett,1 who noted a similarity in their pathological features. Coexistent orbital pseudotumour and Riedel's thyroiditis was reported by Andersen,2 and there have been five further case reports since.3-6 The term multifocal fibrosclerosis was introduced by Comings et al, who described two brothers with orbital pseudotumour and Riedel's thyroiditis. In addition, one brother had retroperitoneal fibrosis and the other had mediastinal fibrosis.6 There have been six subsequent case reports of orbital pseudotumour as a component of multifocal fibrosclerosis, four in association with retroperitoneal fibrosis,7-10 and two with sclerosing cholangitis.11,12 Other manifestations of the syndrome include Dupuytren's contracture,6 testicular fibrosis,13 subcutaneous fibrosis,14 vasculitis,15 and neurological involvement.16 Orbital involvement may lead to visual loss from optic nerve compression or rarely from serous detachment of the retina and retinal pigment epithelium.10

Materials and methods
Details of all patients attending the orbital clinic at Moorfields Eye Hospital have been entered into a computerised database over the past 10 years. The database was searched for all patients with a diagnosis of multifocal fibrosclerosis, or patients with orbital pseudotumour and involvement of other organs. Case records, photographs, and radiographs of all such patients were then reviewed by the authors.

Results
Three patients with a diagnosis of multifocal fibrosclerosis were identified. The case histories are as follows.

CASE 1
A 52-year-old man was referred to the orbital clinic with a diagnosis of dysthyroid eye disease. He gave a 4 year history of lower lid swelling and a 6 month history of gradual deterioration of vision in the left eye. He also complained of horizontal diplopia on left gaze. Chronic pancreatitis and sclerosing cholangitis had been diagnosed at the age of 35 and he had subsequently developed insulin dependent diabetes mellitus. His sister had developed the same syndrome at the age of 26 and the siblings had been reported in the literature.17

On examination he had a visual acuity of 6/18 in the left eye with a score of 1/17 Ishihara plates and 50% red desaturation. Visual function in the right eye was normal. He had bilateral lid swelling and proptosis with depression of the right globe (Fig 1). A firm mass was felt in the orbit above the right globe. Ocular motility was restricted in both eyes, particularly on elevation and abduction. There was a left relative afferent pupillary defect, examination of the fundus revealed choroidal folds and optic disc pallor. He had a scant, asymptomatic rash distributed over the skin of his face and trunk.

Humphrey field analysis showed global restriction in the left visual field but a normal right visual field. Thyroid function tests were normal (T4 99 mmol/litre, T3 1.1 mmol/litre, TSH 3.7 mU/litre). Computed tomography scan showed bilateral orbital masses but did not indicate swelling of extraocular muscles (Fig 2).

Biopsy was performed under general anaesthesia. Tissue was taken from the right lacrimal gland via a skin crease incision and a separate biopsy was taken via a superior fornix conjunctival incision. The right side was chosen because of greater accessibility of abnormal tissue, and concern about the effect of tissue swelling on an already compressed left optic nerve. Histology of both biopsies demonstrated masses of dense, hyalinised fibrous tissue in the presence of moderately severe diffuse lymphocyte and plasma cell infiltration (Fig 3). Eosinophils were also seen, being especially evident in the lacrimal gland specimen.

Figure 1 Case 1. Note the lid swelling and the right hypotropia. The skin rash is visible on the nose.
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Treatment with systemic steroids was considered but the patient gave a history of adverse effects, and the extensive fibrosis shown in the biopsies was not thought to be susceptible to anti-inflammatory treatment. Surgical decompression was also considered but was unlikely to be effective owing to the infiltrative and widespread nature of the lesion. Therefore, because the optic nerve compression was not progressive, conservative management was adopted.

Six months after the biopsy the vision remained stable with no change in left visual function. At this stage he developed a severe vasculitis of the skin which necessitated the use of oral steroids despite the history of adverse effects. Resolution of the vasculitis was accompanied by an improvement in his left visual acuity to 6/9, with a limited decrease in his proptosis. The patient was lost to further follow up.

CASE 2
A 66-year-old man presented with a 9 year history of irritation at the right medial canthus, and a 2 year history of proptosis. He suffered from hypertension and had undergone renal biopsy which revealed diffuse proliferative glomerular nephritis. Biopsy of a small, raised, erythematous lesion of the skin of his scalp revealed fibrosis with a leucocytic infiltrate, largely consisting of eosinophils.

On examination his visual acuity was 6/36 in the right eye and 6/9 in the left eye. He had a score of 5/17 Ishihara plates with the right eye, and a normal score with the left eye. The right globe had 15 mm of proptosis and external ocular movements were severely restricted in all directions of gaze on that side. A firm, non-tender mass was felt arising from the inferior orbital margin. There was a right relative afferent pupillary defect and a pale, cupped right optic disc.

Computed tomography scan showed a large orbital mass lying below and medial to the optic nerve (Fig 4). Orbital biopsy revealed fibrous tissue proliferation with a diffuse leucocytic infiltration consisting of lymphocytes, plasma cells, and some eosinophils.

Over the next 4 years he developed intractable pain. His vision gradually deteriorated to perception of light only. The proptosis increased and he showed signs of corneal exposure. A further biopsy showed identical histological features to the first.

Although the lesion was considered to be benign, right orbital exenteration was carried out because of the severity of the symptoms and the irreversible visual loss. His pain resolved and he remained well over a 4 year follow up period with no symptoms or signs of recurrence.

CASE 3
A 55-year-old man presented with a 2 year history of an asymptomatic lump above his right eye. He gave a history of retroperitoneal fibrosis, which had been confirmed by biopsy 3 years previously.

On examination his corrected visual acuity was 6/6 in each eye with normal colour vision on Ishihara plates. External ocular movements were normal. There was a firm mass in the upper outer quadrant of the right orbit which was fixed to the bony margin and non-tender (Fig 5). The globe was displaced downwards by 2 mm, but there was no proptosis. There were no abnormalities on fundus examination.

On histopathological examination of the orbital biopsy, bands of hyalinised fibrous tissue, separated by diffusely infiltrating inflammatory
cells, were conspicuous (Fig 5). Frequently they were arranged concentrically around obliterated small blood vessels and there was evidence of lacrimal gland involvement. Eosinophils were included in the leucocytic infiltration and focal aggregates of lymphoid cells were seen as well as more diffusely distributed cells.

A diagnosis of multifocal fibrosclerosis was made. No treatment was given and he was followed up for a period of 10 years, during which there was no change in visual function or in the size and appearance of the lesion.

Discussion

The three cases described illustrate the variety of clinical features that may occur in multifocal fibrosclerosis. The first patient had orbital pseudotumour, chronic pancreatitis, and sclerosing cholangitis. He also developed vasculitis of the skin, a recognised association.15

The second case had involvement of the orbit and skin, as well as renal disease, although the pathology of the renal disease did not suggest a fibrosclerotic process. The third case had orbital involvement associated with retroperitoneal fibrosis.

The reported cases of multifocal fibrosclerosis with orbital involvement are summarised in Table 1. The most frequently reported association is pseudotumour with Riedel's thyroiditis, but other organs can be involved. It is therefore important that the ophthalmologist is aware of the existence of this condition so that suitable treatment, where available, can be initiated without delay. This is particularly apposite in the case of ureteric obstruction from retroperitoneal fibrosis.

The histological diagnosis of multifocal fibrosclerosis depends on finding extensive deposition of hyalinised fibrous tissue, commonly arranged in more or less concentric whorls around extinct or attenuated blood vessels, in association with a chronic inflammatory cell infiltration that also tends to be perivascular. As such it is indistinguishable from the rather more common solitary orbital sclerosing pseudotumour. It differs, however, from the several categories of fibromatosis, including the childhood forms described in the context of the orbit18 and periorbital tissues,19 in being far less cellular and containing more mature collagen. Although conditions such as Erdheim–Chester disease20,21 and adult onset xanthogranuloma22 are also complicated by orbital fibrosis they can be discounted in the present situation because of absence of the characteristic foamy macrophages.

The aetiology of multifocal fibrosclerosis remains unknown. Methysergide administration can cause retroperitoneal fibrosis,23,24 but no cases of orbital pseudotumour associated with its use have been reported. A few cases in the literature have been familial, suggesting a genetic factor,6 and there is an association with HLA B27.25

There is nothing in the histological appearance of multifocal fibrosclerosis to differentiate it from most other forms of severe post-inflamatory orbital fibrosis and, consequently, it seems reasonable to assume that the process is mediated by inflammation. The invariable presence of lymphocytes and plasma cells, in the absence of neutrophil polymorphonuclear leucocytes, points to an insidious chronic

Table 1  Reported cases of multifocal fibrosclerosis involving the orbit

<table>
<thead>
<tr>
<th>Case report</th>
<th>Riedel's thyroiditis</th>
<th>Retroperitoneal fibrosis</th>
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The invariable presence of lymphocytes and plasma cells, in the absence of neutrophil polymorphonuclear leucocytes, points to an insidious chronic
Figure 5. Histology from case 3. Note the bands of hyalised fibrous tissue enclosing diffusely infiltrating inflammatory cells. (Haematoxylin and eosin, x190.)

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disorder which may be autoimmune, since no infectious agent or extraneous irritant has ever been isolated. Eosinophils, found in all three of the present cases, are a central feature of orbital fibrosclerosis cases in general, solitary as well as multifocal lesions. Noguchi et al suggested that toxic products of degranulated eosinophils, such as major basic protein, might be responsible for stimulating a fibrotic response. Recent studies, however, have shown that eosinophils can be a source of transforming growth factor β1 (TGF-β1) which serves, among other things, to promote fibroblast growth and collagen synthesis.

Ability to synthesise TGF-β1 appears to be restricted to eosinophils in fibrotic states such as hypereosinophilic syndrome, chronic inflammation of the upper airways, and the nodular sclerosing form of Hodgkin's disease. Eosinophils in non-fibrosing lesions do not secrete TGF-β1, and it may be that some local factor, possibly a T cell derived cytokine, is required to activate the process. Acute pseudotumour of the orbit responds dramatically to steroids, and they have been beneficial in the early, inflammatory stage of multifocal fibrosclerosis. However, the length of the history, and the histological appearances of dense fibrous tissue and hyalisation in our patients did not provide an encouraging basis for anti-inflammatory treatment. It is therefore interesting that the orbital pseudotumour of the first patient appeared to benefit from systemic steroids that were administered for vasculitis. The second case highlights the rare necessity of performing exenteration for intractable pain in benign orbital disease.


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