

Orbital Pseudotumour Masquerading as Wegener's Granulomatosis

Matthew Fenech, Thomas Fenech

Abstract

A twenty-two year old female patient presented with new onset bilateral hard orbital masses and progressively worse tear lake problems. Computed tomography of the orbits revealed poorly differentiated bilateral orbital masses. Laboratory investigation revealed ANCA positivity. Routine biochemical investigations were all within normal limits. CXR was also normal. Biopsy of the orbital masses revealed non-specific histological findings. An initial diagnosis of Granulomatosis with Polyangitis (GPA) was postulated. Oral steroids were given followed by a rapid response to steroid therapy. The working diagnosis of GPA was abandoned and a diagnosis of idiopathic orbital inflammation (IOI), or orbital pseudotumour was made owing to the benign, non-infective, inflammatory pathology with no evident systemic or local cause. Tailoring off of steroids resulted in repeated flare ups, resulting in the initiation of methotrexate therapy. The patient is in remission and is currently on combined steroid and methotrexate treatment. IOI is a diagnosis of exclusion and a rapid response to steroids serves as a diagnostic aid but is not in itself diagnostic.

Key words

Orbital Pseudotumour, Granulomatosis with Polyangitis, ANCA, Steroids

Background

Idiopathic orbital inflammation (IOI) or orbital pseudotumour is an uncommon, benign, non-infective, inflammatory pathology involving the orbital tissues. It is a diagnosis of exclusion after systemic and local causes have been thoroughly excluded, characterised by polymorphous lymphoid infiltrate with varying degrees of fibrosis. MR orbit is the single most important investigation. A diagnosis is usually clinched when a rapid response is seen to oral or systemic steroids. The pathological process underlying IOI remains unresolved, some postulating it is primarily an autoimmune process.

Case Presentation

A twenty-two year old female patient presented with bilateral orbital masses and persistent tear lake problems. There was associated proptosis but no involvement or impairment of any of the extra-ocular muscles movements. Humphrey Visual Field examination did not reveal any visual field defect. There was an extremely toxic tear lake secondary to the severe dacryoadenitis spilling inflammatory debris onto the front of the eye.

Masses were present in both lacrimal glands, especially on the right side, spilling down into the inferior part of the right orbit. Masses were woody hard with gross inflammation of the ocular surface overlying it. There was no corneal guttering or scleritis.

Serial MR Orbits were performed. The first revealed significant right preseptal and post-septal orbital change, which appeared to include and emanate from the region of the right lacrimal gland. The left lateral gland also appeared mildly prominent. A biopsy of the right lower orbital mass revealed fibroconnective tissue with a patchy chronic inflammatory infiltrate and no identifiable fat. The infiltrate included ill-formed lymphoid-follicles and a loose scattering of lymphocytes and histiocytes with only rare plasma cells and eosinophils. Occasional multinucleate giant cells were seen. There was no frank necrosis but ample nuclear dust was visible. There was no vasculitis and no evidence of underlying neoplasia. Findings were deemed to be non-specific but likely to be due to Granulomatosis with Polyangitis (GPA).

Matthew Fenech, MD*

Ophthalmic Department
Mater Dei Hospital
Msida, Malta
fenech.mat@gmail.com

Thomas Fenech, MBBS, FRCS, FRCOphth

Ophthalmic Department
Mater Dei Hospital
Msida, Malta
fenech.mat@gmail.com

**Corresponding Author*

Case Report

Laboratory investigation revealed elevated ANCA titres. Further breakdown of such titres revealed elevated P-ANCA patterns with grossly elevated Anti-Myeloperoxidase but insignificant Anti-protease 3 antibody levels. CRP, ESR, C3, C4 and anti-nuclear antibodies were never elevated and were always found within normal limits.

CXR revealed no evidence of pulmonary pathology.

The patient was started on IV steroids followed by oral steroids as an initial diagnosis of GPA was suspected. Rapid response to steroids was seen in the form of radiological and symptomatic improvement. Due to the non-specific histological findings and lack of systemic involvement, a diagnosis of GPA was abandoned and a diagnosis of IOI was adhered to.

Investigations

Routine laboratory and haematological investigations were normal including serum ACE, T3, T4 and TSH. CXR performed revealed no pathology. Serum ANCA levels were elevated. Further breakdown of such titres revealed P-ANCA patterns which are indicative of Anti-Myeloperoxidase antibody at 42.4, while Anti-protease 3 antibody was less than 2.0.

Imaging modalities used included computed tomography (CT) and magnetic resonance imaging (MRI). Usually, CT is the preferred imaging modality in IOI because of its good inherent contrast of orbital fat, muscle, bony structures and adjacent paranasal sinuses. MRI showed diffuse involvement of the lacrimal glands with associated infiltration of orbital fat. There were bilateral poorly-defined orbital masses. Both pre-septal and post-septal changes were seen. On T2-weighted imaging areas were hypointense in appearance with restricted diffusion. Such infiltrative changes favoured a diagnosis of IOI.

A decision was made to opt for a second opinion from specialists at the Moorfield's Eye Hospital London. A decision was made to perform biopsies of the left orbital mass in order to exclude an underlying malignancy or possible GPA, after the images from the MRI performed at Mater Dei Hospital were reviewed. Biopsy is not usually indicated for IOI but serves as a good diagnostic tool if a diagnosis has not been concretely established. Unfortunately, the histopathological spectrum of IOI is typically nondiagnostic.

Differential Diagnosis

IOI is diagnosed by a thorough clinical history and evaluation to rule out other causes of orbital disease. One must take note of similar episodes in the past and the onset of symptoms. Symptoms are rather acute in IOI but generally more subacute or chronic in

other pathologies. Trauma, infection and risk factors for immunological compromise must be excluded.

Infection was considered. The orbit is a common site for specific infections, usually spreading from adjacent sinuses or the face. It may also be a result of direct trauma. The patient was afebrile and routine investigations were unremarkable.

Thyroid orbitopathy must also be excluded. Laboratory investigations including T3, T4 and TSH were unremarkable. Onset of symptoms was rather acute, while in Graves' disease, a slower, more insidious course is usually apparent. Examination did not reveal any eye lid retraction, eyelid lag, extraocular myopathy. There was a mild element of proptosis. Radiological findings however were not consistent with thyroid orbitopathy. There was no evident enlargement of extraocular muscles, while conversely, orbital fat volume was reduced.

Wegener's Granulomatosis or Granulomatosis with polyangitis (GPA) was initially diagnosed secondary to the elevated serum ANCA levels. GPA is a necrotising granulomatous inflammation and vasculitis, effecting the respiratory and renal systems. Ophthalmic symptoms are usually acute in onset and may be unilateral or bilateral. Systemic work-up of our patient revealed no impairment of pulmonary or renal function. Further breakdown of ANCA levels revealed a grossly elevated P-ANCA level reactive against myeloperoxidase while a c-ANCA level reactive against proteinase 3 which was within normal limits. The anti-Proteinase3: Myeloperoxidase ratio was not elevated, making the serum ANCA level testing non-diagnostic. Furthermore, radiological changes were not classical of GPA, bar the mass lesions bilaterally. That being said, classical findings of GPA are present in less than a third of patients while ANCA is only found in 50-65% of patients with the limited form of GPA. A diagnosis of GPA was abandoned but ultimately could not be completely excluded.

The possibility of neoplasm must also be considered. Although this was excluded at biopsy.

Treatment

Corticosteroids are usually the mainstay of treatment usually providing rapid improvement of symptoms.

Such was the case with our patient. IV steroids were initiated after the biopsy was performed. IV steroids were given for 2 days followed by oral steroids, starting at a dose of 80mg per day, tailoring down accordingly over several months. Prednisolone treatment was stopped completely after 17 months. There was a significant resolution in both symptoms and radiological evidence. Methotrexate once weekly and 10mg Folic Acid daily were started after

Case Report

prednisolone was stopped.

The patient is currently still on methotrexate and undergoing regular follow up blood investigations. She is symptom free but occasionally still suffers from flare ups, consisting of orbital pain, a sensation of heaviness and conjunctival injection. Flare ups are less frequent and less severe ever since the prolonged use of methotrexate.

Outcome and Follow-up

Recurrence rates are high. Regular patient follow up is necessary to assess disease progression as well as treatment efficacy. Steroid therapy should be accompanied by close monitoring to assess for steroid related complications.

Stopping steroids typically results in a relapse rate of 60-80%, irrespective of the initial response to steroids. Response to steroids at relapse is typically not as dramatic as the initial response, commonly resulting in the use of other agents.

In our patient, follow up revealed near complete regression of masses bilaterally, with some residual disease on the right eye. There was no progression of orbital fat infiltration.

Serum ANCA levels also showed regression on follow up, further excluding the unlikely diagnosis of GPA.

Discussion

Idiopathic orbital inflammation (IOI) is a non-malignant, non-infectious orbital inflammation with no local or systemic cause. The disease may be confined to a single orbital structure, but more commonly effects multiple structures.¹ Any structure may be effected, with orbital fat, lacrimal glands and extraocular muscles being most commonly effected.²

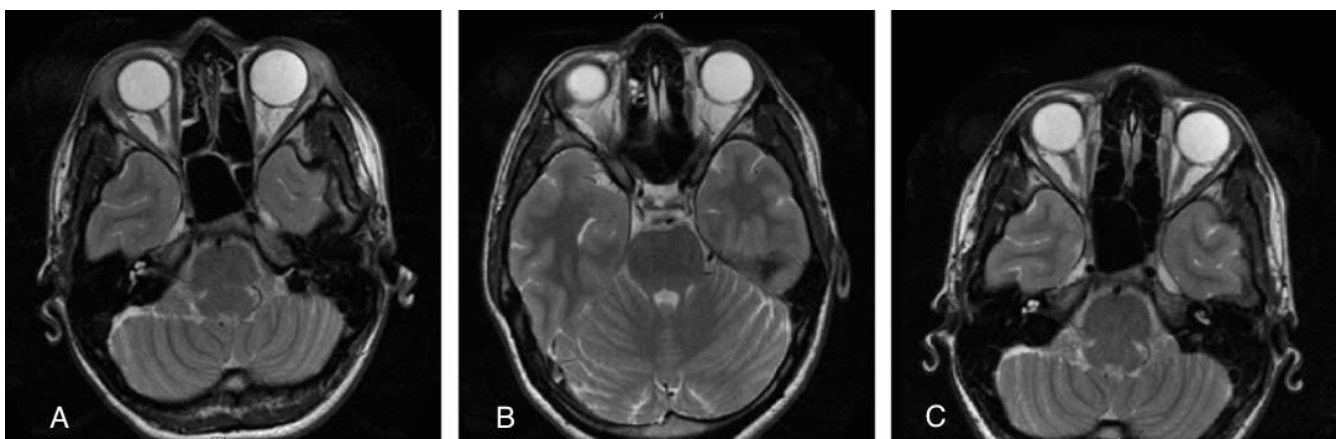
Onset is usually unilateral and acute, progressing over a few hours or days. That being said, bilateral disease is not uncommon and onset may be subacute or even chronic.³ There is no gender, age or racial predilection, presenting universally with a mixture of infiltrative and inflammatory signs and symptoms.⁴

Examination may reveal proptosis, chemosis, tenderness, peri-orbital swelling and impaired extra-ocular muscle function. Ultimately, presentation varies depending on the location and degree of inflammation, fibrosis or mass effect.⁵

The pathogenesis of IOI remains elusive and unclear. An immune-mediated response has been implicated as the most likely underlying cause. Infectious aetiologies have also been implicated, most commonly upper respiratory tract infections and Streptococcal pharyngitis. IOI is also strongly related to several rheumatological conditions including Crohn's disease, ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus and myasthenia gravis.⁶

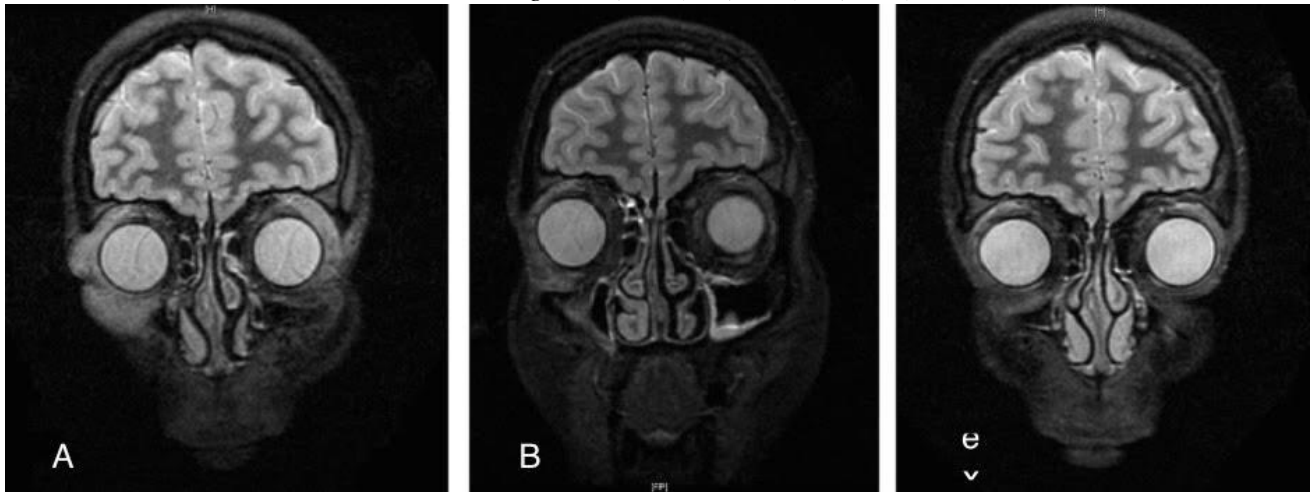
Laboratory investigation is usually followed by imaging studies. Classically, orbital pseudotumours may present as diffuse or localised orbital masses which is classically poorly demarcated and enhancing with contrast. The lacrimal gland is the most commonly involved structure usually showing diffuse enlargement with poorly defined margins. Other CT findings include diffuse infiltration of orbital fat, extraocular muscle enlargement, uveoscleral thickening and optic nerve thickening.⁷ MRI is more valuable in demonstrating soft tissue changes in IOI (*Figure 1, Figure 2*). T1 – weighted images show intense contrast enhancement of abnormal soft tissues.

Figure 1: MR Orbit; Axial T2 Sequence showing regression of orbital inflammation. A(2012), B(2013), C(2014)



Case Report

Figure 2: MR Orbit; Coronal Stir sequence showing regression of orbital inflammation with some residual disease in the lacrimal region. A(2012), B(2013), C(2014)



It is not uncommon that as a result of diagnostic uncertainty, a biopsy is performed. Classical IOI reveals an atypical histopathology with a fibro-inflammatory infiltrate.²

Before treatment is started, a thorough work up is required. If the work up is negative, treatment for presumed IOI may be initiated. In some patients, symptoms and signs may resolve spontaneously.⁵ In patients with mild clinical presentation, clinical progression may be monitored and non-steroidal anti-inflammatories may be started. In more moderate and severe disease, systemic corticosteroids are the cornerstone of management.³ Typically, 75% of patients show improvement of symptoms and radiological findings within 24-72 hours of initiating treatment. Steroids must be given for several months to ensure remission, ideally starting with a dose of 1-1.5 mg/kg body weight for 1-2 weeks followed by a gradual tapering down of the overall systemic dose.

A rapid response to steroids, although a useful diagnostic indicator, is not diagnostic. Several studies have shown steroid unresponsive IOI. Furthermore, even with treatment, 23% to 56% of patients tend to suffer recurrences, most commonly in cases showing bilateral disease. Recurrence is most likely the result of incomplete resolution of the initial presentation, typically resurfacing when treatment is tapered off.

Unfortunately, in cases which are refractory to both corticosteroids and radiation therapy, further treatment options are limited. Chemotherapeutic agents such as cyclophosphamide, cyclosporine or methotrexate have proven to be helpful.³

Following treatment, good visual prognosis may be expected. Response and recurrence rates are dependent on the degree of inflammation, dose and duration of corticosteroid treatment and ultimately the natural history of the disease. The clinical and histological features do not correlate well with the

final outcome.¹

Patient's perspective

The initial period was characterized by anxiety. The diagnosis was not certain and neither was the approach that was to be taken. The need for review by foreign specialists only increased her anxiety and did not help in what had been already difficult period.

Once a diagnosis was made, there was still uncertainty as to the possible response to therapy. She was pleased that steroid proved to be very successful initially but was left very frustrated by the fact that flare-ups did occasionally recur, even though they were not as severe as the initial presentation. A decision was made to start further treatment in the form of methotrexate. This was initially met with further anxiety as doubt on the certainty of the diagnosis began to resurface. However with reassurance and eventual stable response to the methotrexate, anxiety was resolved and she no longer has any issues with her treatment and response.

Learning Points/Take Home Messages

1. IOI is a diagnosis of exclusion.
2. Thorough history and examination is necessary in order to exclude concrete differential diagnosis.
3. Misdiagnosis may have serious implications considering the benign nature of this disease.
4. A rapid response to steroids serves as a diagnostic aid but is not in itself diagnostic.
5. Investment and research is needed to more accurately diagnose IOI. Currently, histological features are non-diagnostic, showing granulomatous and non-granulomatous inflammatory infiltrates.

References

1. Yuen SJ, Rubin PA. Idiopathic orbital inflammation: distribution, clinical features, and treatment outcome. *Arch Ophthalmol.* 2003;121:491–499.
2. Gordon LK. Diagnostic dilemmas in orbital inflammatory disease. *Ocul Immunol Inflamm.* 2003;11:3–15.
3. Jacobs D, Galetta S. Diagnosis and management of orbital pseudotumor. *Curr Opin Ophthalmol.* 2002;13:347–351.
4. Yuen SJ, Rubin PA. Idiopathic orbital inflammation: ocular mechanisms and clinicopathology. *Ophthalmol Clin North Am.* 2002;15:121–126.
5. Sirbaugh P. A case of orbital pseudotumor masquerading as orbital cellulitis in a patient with proptosis and fever. *Pediatr Emerg Care* 1997;13:337-9.
6. Weber AL, Romo LV, Sabates NR. Pseudotumor of the orbit: clinical, pathologic, and radiologic evaluation. *Radiol Clin North Am* 1999;37:151-68.
7. Karesh JW, On AV, Hirschbein MJ. Noninfectious orbital inflammatory disease. In: Tasman W, Jaeger EA, eds. *Duane's Ophthalmology.* 15th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2009:chap 35.